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The role of ACTN3, IGF-I, IGF-II and myostatin polymorphism on muscle phenotype.

Systematic Review

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Contents

Ich erkläre, dass ich die vorliegende Arbeit selbständig verfasst habe und nur die ausgewiesenen Hilfsmittel verwendet habe. Diese Arbeit wurde daher weder an anderen Stellen eingereicht noch von anderen Personen vorgelegt.

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Abstract

Subsequent work seeks to utilize available ACTN3, IGF-I, IGF-II and myostatin data to gain a better understanding of the polymorphisms in association with muscle phenotype. Several studies investigated the relationship of these genes in athletic and nonathletic cohorts. The aim of the review is to find similarities in the effects of these polymorphisms on muscle function or exercise adaptation. α-actinin is a major structural component of the Z-line, present in fast twitch muscle fibers. The presence of R and X alleles of ACTN3 has been reported to affect the spriniting and endurance abilities of elite athletes. While the other three growth factors (IGF-I, IGF-II and myostatin) are thought to be important regulators of muscle mass by influencing satellite cells. This critical evaluation of recent research on hand tries to explain this complex phenomena. The ACTN3 gene search resulted in the highest output of relevant studies. There was a range of responses among subjects which may be due to the training principle of individuality, that each subject responds different to the same quantitative and qualitative training stimuli. It is unknown, wheter the ACTN3 R577X polymorphism define`s the initial levels of power ability or it actually affects the response to training. It also turned out, that exercise performance is unlikely to be reducable to a single phenotypic trait. There seems to be an interaction of numerous genes and it might be plausible that other polymorphisms within the pathways could be involved in muscle metabolism. As found out for IGF-I pathways in muscular hypertrophy and strength response to strength training. But the IGF-I gene search delivered a small output of two studies, which might not be representable. This also applies to IGF-II gene. The two studies included in the review do not explain associations between early growth and grip strength, but there might be an influence on muscle mass and function in later life. Likewise, myostatin seems to be more related to muscle mass than it is to strength. Although most studies evaluated the relationship between myostatin and muscle mass rather than muscle strength, muscle mass does not always correlate directly with muscle strength and muscle mass cannot uniformly be explained by changes in muscle size.

Die folgende Diplomarbeit erhebt verfügbare Daten über ACTN3, IGF-I, IGF-II und Myostatin, um ein besseres Verständnis für die Polymorphismen im Zusammenhang mit dem muskulären Phenotypus zu gewinnen. Mehrere Studien untersuchten die Beziehung dieser Gene in Kohorten von Athleten und Nichtathleten. Das Ziel dieses Reviews ist es, Ähnlichkeiten in den Effekten dieser Polymorphismen mit Musklefunktionen oder Anpassung an sportliche Bewegung zu finden. α-actinin, vorhanden in schnellzuckenden Muskelfasern, ist ein wichtiger struktureller Komponent der Z-Linie. Das Vorhandensein von R und X Allelen wurde allgemein in Zusammenhang gebracht mit Schnellkraft und Ausdauerleistungsfähigkeit von Eliteathleten. Während angenommen wird, dass die anderen drei Wachstumsfaktoren (IGF-I, IGF-II und Moystatin) wichtige Regulatoren der Muskelmasse sind, indem sie Satellitenzellen aktivieren. Die vorliegende kritische Auswertung neuester Studien, versucht diese komplexen Phänomene zu erklären. Die ACTN3 Suche ergab die größte Menge an relevanten Studien. Es gab eine große Variation an Ergebnissen, was mit dem Trainingsprinzip der Individualität in Zusammenhang stehen kann. Demnach reagiert jeder Einzelne unterschiedlich auf die gleiche quantitative und qualitative Trainingsstimulation. Es ist unbekannt, ob ACTN3 das anfängliche Niveau der Kraftfähigkeit bestimmt, oder ob es tatsächlich die Reaktion auf Training beeinflusst. Eine weitere Feststellung ist, dass sportliche Leistung nur auf eine einzelne phenotypische Eigenschaft reduzierbar ist. Die Interaktion von mehreren Genen könnte verantwortlich sein und es scheint einleuchtend, dass mehrere Polymorphismen innerhalb dieser Pfade eine Auswirkung auf den Muskelstoffwechsel haben. Wie IGF-I Pfade in muskulärer Hypertrophy und Kraftreaktionen nach Krafttraining zeigen. Die Suche nach IGF-I ergab aber eine kleine Anzahl von zwei Studien, was nicht wissenschaftlich vetrtretbar ist. Dasselbe gilt für das IGF-II Gen. Die beiden in das Review eingeschlossenen Studien erklären nicht die Beziehungen zwischen embrionalem Wachstum und Armkraft, aber es dürfte ein Einfluss auf die Muskelmasse und Funktion im Erwachsenenalter vorhanden sein. Ebenso scheint Myostatin mehr im Zusammenhang zu stehen mit Muskelmasse als mit Kraft. Obwohl die meisten Studien den Zusammenhang zwischen Myostatin und Muskelmasse anstatt Muskelkraft evaluierten, korreliert Muskelmasse nicht immer direkt mit Muskelkraft und Muskelmasse kann nicht immer mit Veränderungen der Muskelgrösse in Zusammenhang gebracht werden.

Abbreviations

A_{2A} receptor	Adenosin 2A receptor
ActRIIA	Activin-receptor Type IIa
ActRIIB	Activin-receptor Type IIb
ABD	Actin-binding-domain
ACTN3	Alpha-actinin3
ACTN2	Alpha-actinin2
ADP	Adenosindiphosphat
ALS	Amyotrophic lateral sclerosis
ATP	Adenosintriphosphat
bHLH	Basic helix-loop-helix
BMI	Body mass index
PPP3R1	Calcineurin B
CA	Cytosin adenine
CANNTG	E box
CapZ	Capping protein muscle Z-line
CSA	Cross-sectional area
CK	Creatine kinase
DMD	Duchenne muscular dystrophy
DRP	Dynamin-related protein
DNA	Deoxyribonucleic acid
EPO	Erythropietin
ERK	Extracellular response kinase
FFM	Fat free mass
GDF8	Growth and differentiation factor 8

GH	Growth hormone
GSK	Glycogen synthase kinase
IBE-1	Eb-peptide fragment
IGFBP	IGF-binding protein
IGF-I	Insulinlike growth factor I
IGF-II	Insulinlike growth factor II
IGF-IR	IGF-I receptor
IGF-IIR	IGF-II receptor
IRS	Insulin receptor substrate
KE	Knee extension
LDHA	Lactate dehydrogenase A
LDHB	Lactate dehydrogenase B
LGfMS	Leuven Genes for Muscular Strength Study
M6PR	IGF-II/Mannose-6-phosphat-receptor
MAPK	Mitogen-activated protein kinase
MD	Muscular dystrophy
MGF	Mechano growth factor
MLCK	Myosin light chain kinase
MRF	Myogenic regulatory factors
MSTN	Myostatin
mRNA	Messenger ribonucleic acid
mtDNA	Mitochondrial deoxyribonucleic acid
MyD	Myeloid differentiation
MV	Muscle volume
MVC	Maximal voluntary contraction

MQ	Muscle quality
NMDA	N-methyl-D-aspartic acid
PI3K	Phosphatidylinositol-3-kinase
PIP_2	Phosphatidylinositol-4,5-biphosphatase
PKB	Protein kinase B
PT	Peak tourque
1-RM	1-repition maximum
RNA	Ribonucleic acid
SLR	Spectrin-like repeat
SNP	Single nucleotide polymorphism
ST	Strength training
TGFß	Transforming growth factor- ß
UTR	Untranslated region
Vo2max	Maximal oxigen uptake
WHAS	Women`s health and aging study

1 Introduction

The accommodation of the human body on environmental factors such as sports exercise has a considerable genetic basis. Skeletal muscle adaptations to exercise like changes in capillarization and muscle enzyme activities as well as fibre phenotypes and size, activate different levels of gene expression. These adaptation processes on the cellular level correspondingly influence the development of fatigue resistance by endurance training and the greater strength and size that results from a period of resistance training. The mechanisms responsible for the adaptation of cells and organs to exercise are characterized by genetic determinants. Looking at the DNA of a cell there is 99,9% identity between two human beings. Sometimes the mother cell template is incorrectly replicated and the DNA sequence of the individual changes. This mutations range from single nucleotide polymorphisms to deletions or additions of large chromosomal areas. Influenced by devergences in gene expression and function individual variations of exercise-related characteristics such as maximal oxygen uptake, muscle fibre composition, heart efficiency, power output, endurance or other traits occur. Polymorphisms, that mediate sports-related characteristics are the main subject of the study. The identification of such genetic loci informs about the mechanisms that regulate a phenotype. Molecular genetic research techniques allow to identify polymorphisms that are responsible for inherited variability in physical performance phenotypes. This may help to understand how exercise and genes can interact to modify a phenotypic trait or health outcome. The review on hand investigates studies corresponding to gene x phenotype interactions in concordance with anaerobic performances. The effects of ACTN3, IGF-I, IGF-II and myostatin polymorphisms on anaerobic phenotypes are in main focus. ACTN3 is a gene required for optimal muscle performance in endurance training. IGF-I is a growthfactor that plays an important role in resistance exercise by activatings satellite cells and influencing myogenic markers. The structure of IGF-I is very similar to the structure of IGF-II. Several of the features of IGF-I gene structure, expression, and regulation also apply to the IGF-II gene. In contrary myostatin functions as a negative growth regulator for skeletal muscle. Myostatin also influences satellite cell activation. The absence of myostatin results in a hypermuscular phenotype in a large number of different species. The genes are specified in Chapters 2 to 4.

This review establishes a correlation between outcomes on muscle phenotypes and the correlating genotypes underlaying the scientific questions: How do polymorphisms of ACTN3, IGF-I, IGF-II and myostatin influence anaerobic phenotype? Significances in gene activity may identify the link between genetic variation and athletic ability. Research questions are “What determines muscle mass?”, “What determines fast muscle fibers?” and “What determines slow muscle fibers?”. The signal transduction in relation to exercise plays a major role in this effects. The signal transduction pathways that upregulate protein synthesis and satellite cell proliferation after high intensity exercise will be discussed on Chapter 2, Chapter 3.5 and 4.1. The chapters below review the individual characteristics that determine the polymorphisms considered. In this chapters the focus is mainly concentrated on the intracellular molecular processes and how they represent an effect on muscle adjusting physical activity.

The variations of gene sequences und functions is highly investigated through the different species. This review is based on investigations made on human beings. It is interesting to note that there are some large differences between animals and humans, e.g. in rat muscles the protein turnover is much higher than in human muscles. Perhaps the differences are quantitative and do not result from different signaling processes. The evidence that a specific variation in genes influences physical performance is easily established in animal studies. Scientifics “knock out” the specific gene and observe the change in efficiency. The gene expression can be switched on or off in the whole organism or solely in a particular tissue such as skeletal muscle. Such an effect cannot be observed in human being, as shown on the Heritage- study of Bouchard. The study was designed to evaluate the role of genetic and non genetic factors in cardiovascular, metabolic and hormonal responses to aerobic exercise. Extensive data were gathered on 128 families before and after 20 weeks of supervised training. The families showed considerable individual differences in the response to regular exercise. This large variation occurred at all ages and at all levels of initial fitness and was similar for African-Americans and Caucasians and for women and men. There was 2.5 times more variance between families than within families for the gains in VO2 max and the maximal heritability reached 47%. However, families showing advantageous gene variants had better test results then others. In conclusion, human studies are necessary to verify findings on other models but they have to be descriptive and invasive.

Next to genetic characteristics environmental factors have strong influences on physical performance. The finnish cross- country skier Eero Mäntyranta represents an example. In 1964 he won Olympiagold although his body proportions have been disadvantageous for cross- country skiing. Due to a gene mutation he had exceptionally high levels of Erythropietin (EPO) circulating in his body. Reduced Erythropoietin- receptors enable easier docking of the hormone compared to wild forms. His body produced an enormous amount of red blood cells and was perfectly optimised to the viscous blood. Mäntyranta was the only successful competitive athlete in his familiy although similar high haemoconcentration was present in almost a quarter of his family members.

The discovery of the genes observed and its significance for the regulation of muscle growth has made sensational provides. In fact the scientific achievements have agricultural as well as therapeutical worth and are essential for the future of sports and exercise science. Popular- scientific articles give the impression that these genes give the starting point for genetic manipulation in purpose to improve performance in sports. In this case there would be a potential risk to the health of the athletes and science would risk the life of humans. Such investigations remain unnoticed, uncontrolled and untreated. The study on hand involves moral and ethical issues underlaying therapeutical purposes. The main reason of the study regards optimisation of sports exercise and specialisation of competitive athletes. Associations between polymorphisms and mitochondrial function in athletic performance may contribute to a better understanding of efficient ATP production and anaerobic glycolysis which can be considered in training stimulations across individual sports activities. Actually, we are looking at the results of a very complex myogenic system. Microarray studies have shown that the expression of hundreds of genes is changed in response to exercise in skeletal muscle. A combination of several gene variants is needed in order to understand this physiological processes according to heredity. Many other gene activities must be observed to get a better understanding

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1.1 Satellite cells

Muscle cells are long cylinders with multiple nuclei and cytoplasm consisting of still more long tiny fibers called myofibrils. These myofibrils are made of stacks of contractile units called sarcomers. Each sarcomere is a lattice of the proteins actin and myosin. According to the sliding- filament model of Huxley and Henson these protein filaments slide across one another to contract the sarcomere. The thinner actinfilaments shift along the big myosinfilaments in direction to the centre of the sarcomer without shortening or thickening (Stryer, 1996, S. 411- 438). Each molecule of myosin contains a globular subunit called the myosin head. The myosin heads have binding sites for the actin molecules and ATP. The activation of the muscle fiber causes the myosin heads to bind to actin. The thin filament draws a short distance past the thick filament and the linkages break in support with ATP. Subsequently the myosin head reforms farther along the thin filament (induced by ADP) to repeat the process. This sliding produces muscle contractions. This contraction is needed to provide the steady support for standing upright or to explosive power required to run a sprint- distance. To meet these constant and constantly changing demands, muscle has an intrinsic ability to adapt to different types of work by changing fibre type and muscle mass. There are for example different fiber types suited to long- lasting effort or quick bursts of strength. The force they generate can damage the muscle fiber unless it is channelled outward.

Dystrophin, the protein missing in Duchenne muscular dystrophy patients, conducts this energy across the muscle cell`s membrane, protecting the fiber (Hawke & Garry, 2001, S. 544). But muscle fibers are still injured by normal use. That is believed to be one way that exercise builds muscle mass and strength: Microscopic tears in the fibers caused by the exertion set off a chemical alarm that triggers tissue regeneration, which in muscle does not mean production of new muscle fibers but rather repairing the outer membrane of existing fibers and plumping their interior with new myofibrils. Manufacturing this new protein requires activation of the relevant genes within the muscle cell`s nuclei, and when the demand for myofibrils is great, additional nuclei are needed to bolster the muscle cell`s manufacturing capacity. Satellite cells, located between the basal lamina of the muscle and the sarcolemma of myofibers, answer this call. These satellite cells are pluripotent muscle-derived stem cells that promote postnatal muscle growth and repair. (Asakura, Seale,

Girgis- Gabardo & Rudnicki, 2002, S. 124; Hawke & Garry, 2001, S. 540; Adams, 2002, S. 1160; McCroskery, Thomas, Maxwell, Sharma & Kambadur, 2003, S. 1135).

The satellite cells reenter the cell circle and express myogenic markers (McCroskery et al. 2003, S. 1135). In this stadia they are also termed myoblasts. Some of their progeny fuse to existing muscle fibers or fuse together to form new myofibers during regeneration of damaged skeletal muscle (Hawke & Garry, 2001, S. 534). The total number of satellite cells remains constant over repeated cycles of degeneration and regeneration (McCroskery et al., 2003, S. 1135). The profile of gene expression of the quiescent satellite cell as well as their activated and proliferating progeny is largely unknown. Several satellite cell markers have been identified and are restricted to either the quiescent, activated, or proliferative state or are expressed more broadly. One group of this cell markers is the family of the myogenic regulatory factors (MRFs). This subset of the Basic helix- loop-helix (bHLH) family includes MyD, myf5, myogenin and MRF4 (Hawke, & Garry, 2001, S. 536). These markers seem to be qualified for the analysis of adaptation processes on resistance training. Psilander Damsgaard and Pilegaard (2003, S. S. 1038-1044) showed that myogenin, MyoD and MRF4 mRNA levels are transiently elevated in human skeletal muscle after a single bout of heavy resistance training, supporting the idea that the MRFs may be involved in regulating hypertrophy and/or fiber- type transitions (Psilander et al., 2003, S. 1038). Each of these myogenic bHLH proteins forms heterodimeric DNA binding complexes that include other bHLH proteins of the E2 gene family (E12 and E47) and bind a canonical DNA sequence, CANNTG (E-box), within enhancer elements of genes that encode terminal differentiation markers of the skeletal muscle lineage (Hawke & Garry, 2001, S. 536; Wyzykowsky, Winata, Mitin, Taparowsky & Konieczny, 2002, S. 6204). In addition it has been shown that these MRFs regulate the transcribtion of myosin- heavy chains (MHC) (Willoughby & Nelson, 2002, Myosin heavy- chain, S. 1262).

Myogenin for example interacts with the enhancer of the myosin light- chain and the muscle creatine kinase (Cserjesi & Olson, 1991, S. 4854).

The existence of satellite cells has been known since 1961 (Katz, 1961, S. 221-225). Within the last decade, biological researchers have begun to make remarkable strides regarding the role of satellite cells in muscle growth and regeneration. Many of these investigations have made significant findings relating to various growth factors like IGF-I and the stimulation of satellite cell proliferation and/or differentiation (Spangenburg & Booth, 2001, S. 533). Satellite cells respond to IGF-I by undergoing a greater number of

cell divisions, whereas a different growth- regulating factor, myostatin inhibits their proliferation (Hawke & Garry, 2001, S. 540).

2 ACTN3

One essential question in the physiological understanding of sports- related activities is how a muscle differentiates between glycolytic or oxidative muscle fibers. The health-related ACTN3 gene may give an answer. ACTN3, also named as Actinin or alpha 3 is located at chromosome 11q13-11q14. The gene is determined at nucleotide 1747 in exon 16, which leads to the replacement of an arginine codon by a stop codon. By absence of a DdeI restriction site the allele 577R (codon CGA) can be distinguished and the allele 577X (codon TGA) by its presence (Niemi & Majamaa, 2005, S. 965). Marked by a molecular mass of 94-103 kDa, the ACTN3 gene is one of four known loci, which encode α-actinin 1, α-actinin 2, α-actinin 3 and α-actinin 4. These proteins can be categorised into two broad groups: nonmuscle cytoskeletal (calcium- sensitive) isoforms and muscle sarcomeric (calcium-insensitive) isoforms. α-actinin 1 and α-actinin 4 are thought to play a role in anchoring actin as non-muscle/smooth muscle isoforms. Human skeletal muscle contains the two sarcomeric isoforms α-actinin 2 and α-actinin 3, but very few of the interactions investigated have been directly confirmed for α-actinin 3. The ACTN3 expression is highly specialised and limited to fast glycolytic type 2 fibres in skeletal muscle (100% type 2b and 50% 2a), while the related ACTN2 protein expression is present in all types of muscle fibers (Kremerskothen, Teber, Wendholt, Liedtke & Boeckers, 2002, S. 687-681; Macarthur & North, (2004), S. 786-895). Functional redundancy occurs when two genes perform overlapping functions so that inactivation of one of the genes has little or no effect on the phenotype. α-actinin 2 expression in skeletal muscle completely overlaps α-actinin 3 expression (Mills, Yang, Weinberger, Vander Woude, Beggs, Easteal & North, 2001, S.1336). Loss of the encoded protein α-actinin-3 in fast fibers compensates an upregulation of the protein α-actinin-2 (Macarthur, Seto, Raftery, Qinlan, Huttley, Hook, Lemckert, Kee, Edwards, Berman, Hardeman, Gunning, Easteal, Yang, & North, 2007, S. 1261). α-actinin-2 and α-actinin-3 differ in sequence adjacent to the actin-binding domain and have high sequence similarity and lack of significant functional differences as they form

ACTN3 homodimmers and heterodimmers in vitro and in vivo (80% amino acid sequence identity and 90% sequence similarity) (Beggs et al., 1992, S. 9284; Mills et al., 2001, S. 1336; Chan, Tong, Beggs & Louis, 1998, S. 134-139).

The α- actinins were first idenitified by Ebashi and Ebashi in 1965 (Ebashi & Ebashi, 1965, S. 7-12). α- actinins belong to a larger group of proteins referred to as the spectrin superfamily. Next to α- actinins this superfamily encodes a diverse group of cytoskeletal proteins including the α and ß spectrins, dystrophin and a protein called DRP (Beggs, Byers, Knoll, Boyce, Bruns & Kunkel, 1992, S. 9281-9288). The spectrins are located on the inner surface of the plasma membrane, where they play a role in maintaining cellular integrity and flexibility as components of the membrane cytoskeleton (Bennett, 1990, S. 1029-1065). This fact is also confirmed by binding studies reviewed by Mills, Yang, Weinberger, Vander Woude, Beggs, Eastal & North (2001, S. 1335). The research group suggests that the α-actinins play a role in thin filament organization and the interaction between the sarcomeric cytoskeleton and the muscle membrane. In addition it regulates the myofibre differentiation and coordination.

A major function of the α-actinin dimers is their actin filament cross-linking activity. (Abb.1) α–actinin-2 and -3 are structural components of the Z line that anchor the actin-containing thin filaments and stabilizes the muscle contractile apparatus (North, 2008, S. 384-394; Macarthur & North, 2004, S. 786; Mills et al., 2001, S. 1335). In smooth muscle α-actinin is found at dense bodies and dense plaques that have a similar anchoring function (Endo & Masaki, 1982, S. 1457-1468; Endo & Masaki, 1984, S. 2322-2332; Geiger, Dutton, Tokuyasu & Singer, 1981, S. 614-628). The α-actinins have various functional domains (North, 2008, S. 384-394). They consist of two calponin- homology domains (CH) at the N-terminus which confer the ability to bind actin (ABD- actin-binding-domain).(Baron, Davison, Jones & Critchley, 1987, S. 17623-17629; Beggs et al., 1992, S. 9281-9288; Dubreil, 1991, S. 219-226). The central rod domain consists of spectrin-like repeats (SLRs). The C- terminal region contains an EF- hand calcium- binding domain that may be functional, as in nonmuscle α-actinins and α-spectrins, or degenerate as in the muscle α-actinins and dystrophin (Blanchard, Ohanian & Critchley, 1989, S. 280-289; Macarthur & North, 2004, S. 786-895; Arimura, Suzuki, Yanagisawa, Imamura & Hamada, 1988, S. 649-655; Noegel, Witke & Schleicher, 1987, S. 391-396; Koenig, Monaco & Kunkel, 1988, S. 219-226).

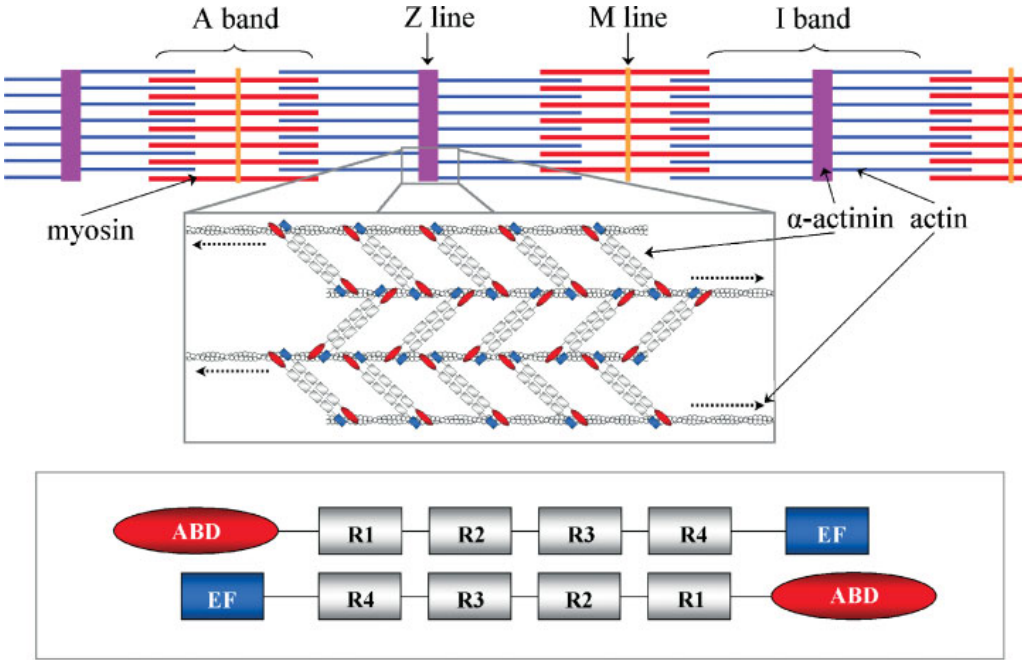

Abbildung 1: Localisation and domain structure of the sarcomeric α-actinins (Macarthur & North, 2004, S.787)

One of the proposed roles for this protein is a mechanical stabilizer of the sarcomer, while another possible function may be as an influencer of signaling and methabolic pathways, enabling a muscle fiber to differentiate towards a fast-twitch, glycolytic profile (Chan, Seto, MacArthur, Yang, North & Head, 2008, S. C903). The sarcomeric α- actinins have a strong affinity to bind to themselves. They form head-to-tail dimmers through interactions between their SLRs (Blanchard et al., 1989, S. 289; Flood, Rowe, Critchley, Gratzer, 1997, S. 431-435) This protein-protein interaction seems to be the primary function of the SLRs, in the formation of dimmers and in binding with a variety of structural and signaling proteins (Djinovic-Carugo, Gautel, Ylanne, & Young, 2002, S. 119-123). The most well characterised interaction of the α-actinins is with the thin filament protein actin. The sarcomeric α-actinins also bind to myozenin, the actin cross-linking protein myotilin, the massive proteins titin and nebulin, the thin filament capping protein CapZ, the intermediate filament proteins synemin and vinculin, and the sarcolemmal membrane proteins dystrophin and ß1 integrin (Mills et al., 2001, S. 1335; Papa, Astier, Kwiatek, Raynaud & Bonnal, 1999, S. 187-188; Salmikangas, Mykkanen, Gronholm, Heiska, & Kere, 1999, S.

1329-1336; Ohtsuka, Yajima, Maruyama, & Kimura, 1997, S. 65-67; Nave, Furst & Weber, 1990, S. 163-166). Through interactions with dystrophin and integrin the α-actinins participate in the two major protein complexes linking the sarcomere to the muscle fibre membrane (Hance, Fu, Watkins, Beggs& Michalak, 1999, S. 216-222, Otey, Pavalko & Burridge, 1990, S. 721-729). In addition MacArthur & North (2004, S. 788) clarify an α-actinin interaction with an array of signaling proteins, including the PDZ- LIM domain-containing proteins and a number of membrane receptors and ion channels, including the adenosine A_{2A} receptor, the NR1 and NR2B subunits of the NMDA glutamate receptor, the L-type calcium channel, and the Kv1.4 and Kv1.5 potassium channels. The researchers also describe an interaction with members of the calsarcin family, a group of proteins that localise to the Z line in striated muscle and bind to the Ca^{2+} and calmodulin- dependent protein phosphatise calcineurin. Calcineurin is an important signaling protein in skeletal muscle playing a role in the determination of muscle fibre type and in muscle hypertrophy (Olson & Williams, 2000, S. 510-519; Chin, Olson, Richardson, Yang, & Humphries, 1998, S. 2499-2509). The α-actinin interaction with metabolic enzymes, including the glycogenetic enzyme phosphorylase and the enzymes fructose-1,6-bisphophatase and aldolase is still unclear.

The interactions of the α-actinins with their binding partners are regulated in several ways. In non- muscle the binding appears to be controlled by calcium. Calcium- mediated inhibition of actin binding does not affect striated and smooth muscle α-actinin isoforms, due to sequence changes in the EFh region that eliminate their calcium-binding properties (Noegel et al., 1987, S. 396). Sarcomeric as well as cytoskeletal α-actinins are regulated by phosphatidylinositol-4,5-biphosphatase (PIP_2). PIP_2 increases the affinity for titin and inhibits binding to CapZ (Papa et al., 1999, S. 187-188; Young & Gautel, 2000, S. 6331-6340). The PIP_2 binding site of α-actinin is located between the ABD and the first spectrin-like repeat with recognisable similarity to the target region of titin (Macarthur & North, 2004, S. 788). MacArthur & North (2004, S. 786-793) declare a detailed summury of the PIP2 activity:

> „In the absence of PIP2, this N-terminal region acts as a pseudoligand for the C-terminal titin-binding site of the other α-actinin molecule in the dimmer, sterically blocking the interaction with titin. The binding of PIP2 to α-actinin relieves this self-inhibitory binding between α-actinin and titin, and presumably also modifies the binding affinity of α-actinin for both actin and CapZ."

The diverse array of known binding partners suggests that these proteins regulate functional important pathways in skeletal muscle, helping to maintain the integrity of both the contractile apparatus and the crucial link between the sarcomere and the plasma membrane, and potentially playing important roles in the communication between the sarcomeric machinery and other cellular pathways and in the regulation in muscle metabolism.

Observations made by Dixson, Michael, Forstner & Garcia (2003, S. 1-10) presented evidence that α- actinin 2 was the first of the four α- actinins to arise by gene duplication, followed by the divergence of α-actinin 3 and then α-actinin 1 and 4. This undermines the hypothesis that the expression pattern of the α-actinins has diverged during mammalian evolution. Gene duplication and alternative splicing have resulted in functional diversity. Some of the isoform diversitys of α-actinins are the result of transcription from different genetic loci. Biochemical studies identified a number of different α-actinin isoforms in various tissues and species including protists (Noegel et al. 1987, S. 391-396), intervertebrates (Fyrberg, Kelly, Ball, Fyrberg & Reedy, 1990, S. 1999-2011) and birds (Arimura, Suzuki, Yanagisawa, Imamura & 1998, S. 649-655, Beggs et al., 1992, S. 9281-9288). Alternative splicing occurs in both vertebrates and intervertebrates, but affects different regions of the transcript in the two lineages (MacArthur & North, 2004, S. 790). Sequence comparison of human and chicken skeletal muscle α-actinin genes suggest that human ACTN2 and ACTN3 have both evolved very slowly since their divergence more than 300 million years ago, implying strong functional conservation (North, Yang, Wattanasirichaigoo, Mills, Tong, Easteal & Beggs, 1999, S. 353-354). ACTN2 and ACTN3 are differently expressed in human and mouse as ACTN2 expression does not completely overlap ACTN3 expression in mouse postnatal skeletal muscle (North, 2008, S. 386). There is marked variation in the frequency of α-actinin-3 deficiency in different ethnic groups. 25% and 18% of people with Asian and European ancestry do not express α-actinin-3 (homozygous null for 577X) compared to less than 1% of a South African Bantu population. This raised the possibility that ACTN3 genotype confers a fitness advantage to humans under certain environmental conditions or at the extremes of performance (North, 2008, S. 384).

In 2003 Yang, MacArthur, Gulbin, Hahn Beggs, Easteal & North (2003, S. 627-631) demonstrated that the ACTN3 genotype influences elite athletic performance. Interestingly it turned out that the frequency of the null allele 577x in sprint and power athletes is

significantly lower, suggesting that α-actinin-3 is required for optimal muscle performance at high velocity (Macarthur, & North, 2004, S 894-895). In contrast a higher frequency of the null allele in endurance athletes suggests that this variant may provide an advantage for long-distance performance. This leads to the conclusion of MacArthur and North (2004) that „the R577x variant has been maintained in the human population for a significant period of our evolutionary history balancing selection, and that the frequency of this allele in some ethic groups may have been due to recent population-specific positive selection."

3 IGF-I and IGF-II

3.1 Insulin-like growth factor I (IGF-I)

Looking at the processes of activity- induced muscle adaptation, one crucial link is missing: How is the human body activating satellite cells as a response to increased loading meanwhile deciding whether a fast or a slow muscle fiber should be activated? A factor, that is taking part in this reactions has to accomplish specific properties. The factor has to operate locally in the activated muscle and must be produced there meanwhile muscle contraction. He also has to be able to activate satellite cells and influence myogenic markers. The insulinlike growth factor-I (IGF-I) seems to accomplish these processes and therefore could have an effect on hypertrophy (Adams, 2002, S. 1159- 1167, Machida & Booth, 2004, S. 337-340).

IGF-I is part of the growthfactors. In general the growth hormone (GH) or somatotropin (STH) is responsible for the growth- processes in the different tissues. Frequently GH has an effect on an account of somatomedins made in the liver. The aminoacidsequences of these somatomedins resemble 40 percent to insulin. That's why somatomedins are called insulinlike growth factors. There are three forms: somatomedin A or insulinlike growth factor-II (IGF-II), somatomedin B which is derived from vitronectin and somatomedin C which is the most important factor and another name for insulinlike growth factor-I. IGF-I and IGF-II are about the same size. IGF-I contains 70 amino acids and IGF-II 67 amino acid residues (Brissenden, Ullrich & Franke, 1984, S. 781-784).

The former hypothesis that IGF-I is produced in the liver could be defeated. It has long been appreciated that there is local control of growth because if a muscle is exercised it is that muscle that undergoes hypertrophy and not all the skeletal muscles of the body (McKoy, Ashley, Mander, Yang, Williams, Russell & Goldspink, 1999, S. 584). Today it is rather known that the major source of circulating IGF-I is the liver, but it is also produced in a wide variety of tissues such as skeletal muscle (Adams, 2002, S. 2509; Chew, Lavender, Clark & Ross, 1995, S.1939- 1945; Laron, 2001, S. 311-316). Although they are of similar size, muscle IGF-I isoforms are not completely homologous to the liver isoforms (McKoy et al., 1999, S. 584). Studies reporting the increase in amount of circulating IGF-I did not show any changes in muscle (Adams & McCue, 1998, S. 1718). This suggests that IGF-I is a locally produced growth factor that has endocrine and paracrine/autocrine modes of action. This is confirmed by the fact that the IGF-I production in muscle is regardless of the circulating GH (Eliakim, Moromisato, Brasel, Roberts Jr & Cooper, 1997, S. 1557-1561) and that locally infused IGF-I results in local muscle reactions (Adams & McCue, 1998, S. 1716- 1722). Several studies showed that an overload in skeletal muscle induces an increase in IGF-I expression accompanied by muscle hypertrophy (Adams & Haddad, 1996, S. 2509- 2519; Adams & McCue, 1998, S. S. 1716-1722; Yang, Alnaqeeb, Simpson & Goldspink, 1997, S. 613-622; Lee, Barton, Sweeney & Farrar, 2004, S. 1097-1104; Hawke & Garry, 2001, S. 540). This makes it propable for IGF-I to be concerned in hypertrophy processes.

Except IGF-I, the mechano growth factor could accomplish the criterias mentioned above. Chew et al. (1995) were the first, who identified this alternatively spliced IGF-I transcript in human liver. The mature 70-amino acid peptide has B,C,A and D domains. In addition there is an E- peptide which differs. By alternative splicing of IGF-I messenger RNA (mRNA) the E-peptide produces different proteins. If the splicing does not occur, IGF-IEa, the “normal” IGF-I peptide develops. Splicing indicates the insertion of 49 base pairs in the cDNA between the coding parts of D- and Ea- peptide. The inserted factor is called IGF-IEc- peptide. The predicted final residues of the Ec- peptide are frameshifted exon 6 codons ending in a frame stop codon. The predicted peptide sequences of Ec and Eb differ at the cleavage site of the Eb- peptide fragment (IBE1), which has been shown to have mitogenic activity. The Ec- peptide sequence is 73% homologous to the rat Eb- peptide sequence (Chew et al., 1995, S. 1939). Lately, Yang et al. could proof the production of IGF-IEa and IGF-IEb in skeletal muscle. Interestingly IGF-I was not found in non- loaded

muscle (Yang, Alnaqeeb, Simpson & Goldspink, 1996, S. 487-495). Following studies also found IGF-IEc mostly in mechanical stimulated muscle. So it was termed mechano growth factor (MGF) (Goldspink, 2002, S. 285- 290). Today MGF appears to be misnamed because it is not stimulated by mechanical signal it is expressed following muscle damage. There are two main muscle forms: one which is similar to the main IGF-I isoform produced in the liver (IGF-Ea) and another that is apparently designed for an autocrine/ paracrine mode of action (IGF-IEc or MGF). The liver IGF-I forms are induced by GH and the muscle IGF-I isoforms are induced by mechanical stress. (McCoy et al., 1999, S. 590; Yang & Goldspink, 2002, S. 156- 160; Laron, 2001, S. 311-316). The muscle IGF-I isoforms have different exons from the liver types and they are not glycosylated. Therefore they are smaller and have a shorter half life than liver IGF-I (Goldspink, 2000, S. 159-169). It seems that IGF-I is the key agent in the signaling pathways that allow individual skeletal muscles to adapt to increased loading. IGF-I appears to be able to stimulate and/or coordinate both the anabolic processes necessary to increase muscle protein and the recruitment of satellite cells, thereby providing new myonuclei and preserving the equilibrium between the number of myonuclei and the size of myofibers (Adams & McCue, 1998, S. 1721, Hawke & Garry, 2001, S. 540). IGF-I gene is differentially spliced in response to local muscle overload and damage. Initially, it is spliced to produce mainly MGF splice variants and this appears to initiate muscle satellite (stem) cell activation. Additionally, this provides the extra undamaged nuclei required for muscle fibre repair with some upregulation of protein synthesis. Thereafter, the splicing switches towards producing systematic IGF-I Ea, which upregulates protein synthesis over a longer time scale. This makes it clear that IGF-I and MGF must have different functions. Studies of Hill & Goldspink (2003, S. 409-418) showed that MGF was rapidly expressed and then declined within a few days following both types of damage. IGF-IEa was more slowly upregulated and its increase was commensurate with the rate of decline in MGF expression. It was also found that the kinetics of expression is different for these two IGF-I splice variants.

3.2 Insulin-like growth factor-II (IGF-II)

Skeletal muscle secrets somatomedin A which is named insulinlike growth factor-II (IGF-II). The structure of IGF-I and IGF-II is very similar. Several of the features of the IGF-I gene structure, expression, and regulation also apply to the IGF-II gene. Brissenden et al. (1984) assigned the IGF-II gene to chromosome 11p15. The short arm of chromosome 11 also encodes the c- Ha- ras1 oncogene and the lactate dehydrogenase A (LDHA) gene (Brissenden et al. 1984, S. 781-784). The short arm of chromosome 12 where IGF-I is localized, encodes the structurally related genes c-Ki-ras2 and the lactate dehydrogenase B (LDHB) gene (Tricoly, Rall & Scott, 1984, S. 784- 786; Holthuizen, Cleutjens & Veenstra, 1993, S. 77-89). The IGF-II gene is an imprinted gene with parental allele expressed and maternal allele silenced (Kaneda & Feinberg, 2005, S. 11236-11240). IGF-II spans 30 kb and comprises 9 exons (E1-E9) and 4 distinct promotors (P1-P4). Nonomura, Nishimura, Miki, Kanno, Yokoyama & Okuyama (1997, S. 2575- 2577) see the regulation of the IGF-II gene as extremely complex: „with the four promoters reported to be under differential, developmental, and regional controls." Transcripts initiated at the P2, P3, and P4 promoters display monoallelic paternal activity predominating most embryonic non-hepatic tissues. These three promotors are preconnected to exons E4, E5 and E6. IGF-II transcripts from the P1 promotor are induced from both parental alleles (Nonomura et al., 1997, S. 2575). P1, which is preconnected to E1, mostly controls the postnatal expression of liver IGF-II (Pagter- Holthuizen, Jansen & van Schaik, 1987, S. 259- 263). Exons 7,8 and 9 contain a long 3`non- translated region. These exons encode prepro IGF-II protein containing a carboxy-terminal peptide of 89 amino acids and a signal peptide of 24 amino acids. (O`Dell & Day, 1998, S. 768-769). O`Dell & Day (1998, S. 767- 768) define the IGF-II structure: „Exons 1 to 6 are non- coding and form alternative 5`- untranslated regions (UTRs) of different RNA molecules which are expresses from the four promotors in a tissue- and development- specific way". Adults show activity of P2 to P4 only in non-hepatic tissues while the activity is switched off in liver (Pagter- Holthuizen et al. 1987, S. 259; Reeve, 1996, S. 470-475). In rodent animals the IGF-II gene spans 12 kbp and is also close to the insulin gene. (Holthuizen et al., 1993, S. 77). In rats the gene is situated at chromosome 1 (Soares, Turken & Ishii, (1986), S. 737), while in mice the gene is localized at chromosome 7 (Rotwein & Hall, 1990, S. 725). Since the promoter P1 is missing in rats and mice, the IGF-II transcription is adjusted postnatally (Rotwein & Hall, 1990, S. 729-

731; Humbel, 1990, S. 445-462). Contrary to the missing P1 promoter in roden animals, prenatal human IGF- II serum concentrations are low during birth and increase meanwhile age of infancy (Zapf, Walter & Frosch, 1981, S. 1329). As a consequence of the IGF-II gene structure in the different species, different IGF-II-mRNAs at a length from 1,8 kb to 7,5 kb can be transcribed (Rotwein, 1991, S. 31-38). Furthermore, the simultaneous production of several IGF-II transcripts in one cell occurs through differential splicing. This has been shown by colorectal cancer cells (Lahm, Amstad & Wyniger, 1994, S. 452-459). Next to the A- and B- domain, that is characteristic for Insulin as well as the IGFs, the IGFs have an additional C- domain that is present in proinsulin. The C- domaine in proinsulin is proteolytically cleaved during structural maturation (O`Dell & Day, 1998, S. 768). The D-domain does not exist in insulin. This domain located on the C- terminal end has the greatest variability in the different species (Rotwein, 1991, S. 31-38).

The effects of IGF-II were discused contrary. IGF-II, generally occurs at higher concentrations prenatally, and is usually considered to be a fetal growth factor, with IGF-I contributing more to postnatal growth (LeRoith & Roberts, 2003, S. 127-137). Recently, DeChiara, Efstratiadis & Robertson (1990, S. 78-80) showed that a germ-line disruption of the IGF-II gene by homologous recombination results in mice with an IGF-II deficiency which are phenotypically smaller. IGF-II is awarded a growthfactor in the development of the central nervous system and a fetal growth factor in rodent (DeChiara et al., 1990, S.78-80). Although the role of IGF-II and the mechanisms by which it functions remain obscure, it has been reported that IGF-II mediates anabolic effects in skeletal muscle, such as amino acid and glucose uptake, and suppresses degradation of proteins (Florini, 1987, S. 577-598). It has been shown that IGF-II is induced during muscle regeneration in rodents. Time course studies by Levinovitz, Jennische, Oldfors, Edwall & Norstedt (1992, S. 1227-1234) showed that IGF-I and IGF-II were present during muscle regeneration. The expression of IGF-I exceeds that of IGF-II. This suggests that the regulation and function of these growth factors are different during muscle regeneration. The IGF-II gene is also activated in a number of different types of tumors, but the mechanism of activation is completely unknown.

3.3 IGF- receptors (IGF-IR and IGF-IIR)

Peptidehormones perform their biological effects through specific receptors named IGF-I-receptor (IGF-IR) and IGF-II-receptor (IGF-IIR), better known as IGF-II/Mannose-6-phosphat-receptor (M6PR). (Abb. 1) Most of the biological IGF- signals like their anabolic and mitogenic effects mediate about the IGF-IR (Butt, Firth & Baxter, 1999, S. 256-262). The IGF-I receptor is able to bind IGF-I with a ten to fifteen times higher affinity than IGF-II and has structural similarities and properties with the insulin receptor (Germain-Lee, Janicot & Lammers, 1992, S. 413-417). Moreover the insulin receptor binds the IGFs with low affinity (Ballard, Ross, Upton & Francis, 1988, S. 721-726; Casella, Han & D`Ercole, 1986, S. 9268-9273; Delaine, Alvino, McNeil, Mulhern, Gaugin, DeMeyts, Jones, Brown, Wallace & Forbes, 2007, S. 18886-18894; O`Gorman, Weiss, Hettiaratchi, Firth & Scott, 2002, S. 4287-4292; Rechler & Nissley, 1986, S. 152-159; Roth & Kiess, 1994, S. 31-38).

By means of ligand binding a specific tyrosine kinase activity and a protein phosphorylation cascade activates other intracellular second messenger systems (O´Dell & Day, 1998, S. 767-771). The substances formed in the signalcascades are responsible for cell-responses like apoptoses or changes in cell-mobility and intrude in the regulation of the cell cycle as well as gene expression (DeMyets, 1994, S. 135-148). In this manner IGF-IR acts as a key agent in the IGF- signaling pathways containing not only transforming and growthstimulating, but also antiapoptosic and mytogenic qualities (Baserga, Hongo & Rubini, 1997, S. F105-F126; Baserga, Resnicoff, D`Ambrosio & Valentinis, 1997, S. 65-98; Butt, Firth & Baxter, 1999, S. 256-262; Grothey, Voigt & Schober, 1999, S. 166-173; LeRoth & Roberts, 2003, S. 127-137). Unlike IGF-II, IGF-I and Insulin bind with low affinity to IGF-IIR (Braulke, 1999, S. 242-246). IGF-IIR is a membrane associated receptor of approximately 220kDa (O´Gorman et al., 2002, S. 4287-4294). The M6P receptor is involved in transporting IGF-II from the Golgi apparatus to the lysosomes where IGF-II and extracellular enzymes are proteolytically reduced (O`Dell & Day, 1998, S.767-771; O´Gorman et al., 2002, S. 4287-4294). He may compete with IGF-IR for IGF-II targeting lysosomal enzymes for internalisation and degradation of IGF-II (Abb. 2). The type II receptor is also found in the circulation, cleaved from the cell surface receptor. IGF-IIR binds a significant amount of IGF-II particularly in the foetal circulation and may function as an IGF-II- specific binding protein (Gelato, Rutherford, Stark & Daniel, 1989,

S. 2935-2943). IGF-IR and IGF-IIR have been identified in embryonic and foetal tissues and the high density of both receptors in placenta suggests that a paracrine release of IGF peptides may influence placental growth and function, with consequent influence on foetal development (O´Dell & Day, 1998, S. 770). The IGF-II concentration in plasma is up to 100 times higher than that required for its effect in vitro. A consequence of association with specific IGF-binding proteins (IGFBPs) (O´Dell & Day, 1998, S. 770). Unlike to Insulin the IGFs are not circulating in serum. They are able to bind to six characterized binding proteins with high affinity named IGFBP-1,-2,-3,-4,-5 and -6 which are found in the circulation and extracellular fluids (Sara & Hall, 1990, S. 591-614).

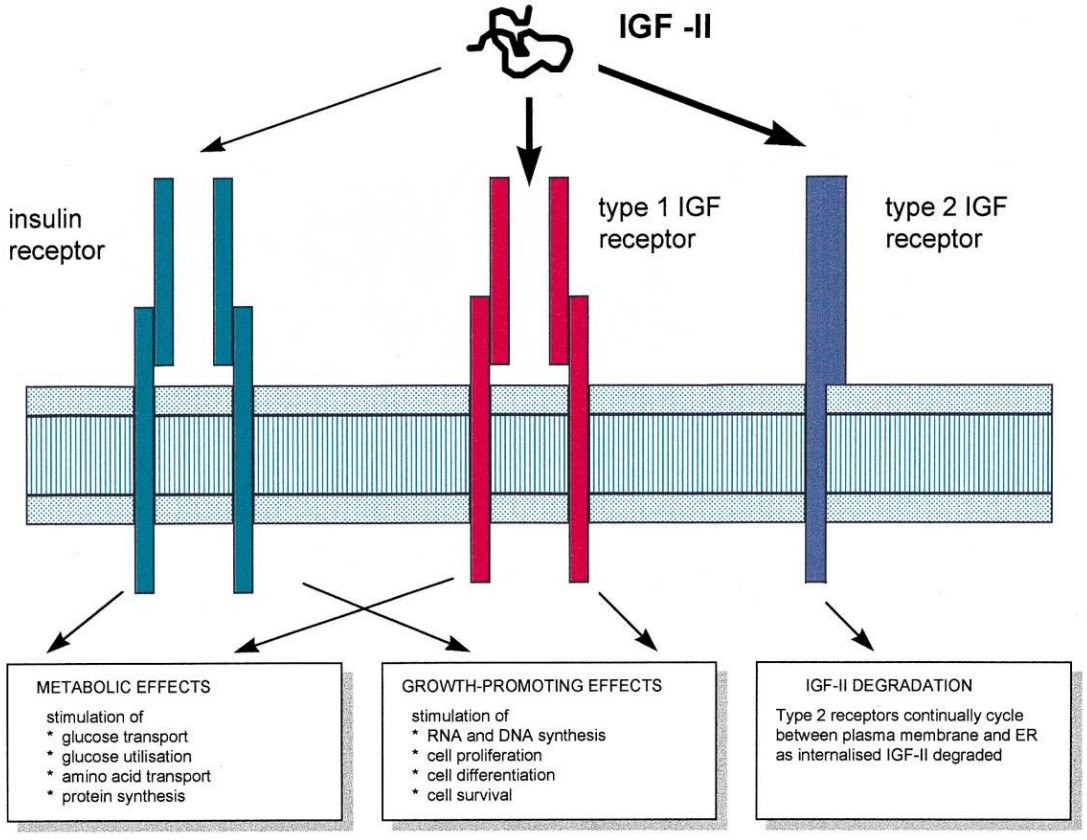

Abbildung 2: Interaction of IGF-II with receptors (O`Dell & Day, 1998, S.769)

3.4 IGF binding proteins (IGFBP)

The IGFBPs influence IGF action positively and negatively. Human IGFBP genes are localised on different chromosomes with various lenghts:

Bindungsprotein	Chromosom	Länge (kb)
IGFBP-1	7q	5,5
IGFBP-2	2q	32,0
IGFBP-3	7q	8,9
IGFBP-4	17q	15,3
IGFBP-5	2q	33,0
IGFBP-6	12	4,7

(Ehrenborg, Zazzi, & Lagercrantz, 1999, S. 376-380; Hwa, Oh, & Rosenfeld, 1999, 761-787)

IGFBPs consist of four exons, that are coding the respective domains, except IGFBP-3 which is the only one binding protein that contains an additional untranslated fifth exon in the 3`end. The N- terminal and the C-terminal domain are highly conservated containing the IGF- binding sites. The IGFBPs have been isolated and characterized from several mammalian species, and at least one binding protein, IGFBP5, has been identified in non-mammalian vertebrates (Upton, Chan, Steiner, Wallace & Ballard, 1993, S. 29-32). This suggests that modulation of IGF action by specific binding proteins is important in vivo (James, Jones, Busby & Clemmons, 1993, S. 22305-22312). Some of the binding proteins are membrane associated and some are soluble. Specific proteases can regulate the degredation of the IGFBPs. The IGFBPs bind IGF with different affinity. In general membrane-bound forms enhance IGF action by attracting IGFs to the region of the receptor and the soluble forms are inhibitory (O´Dell & Day, 1998, S. 770). IGF binds to as many as 10 distinct serum proteins, but in adults 90% of the circulating IGFs are complexed with IGFBP-3 (Borst, De Hoyos, Garzarella, Vincent, Pollock, Lowenthal & Pollock, 2001, S. 651). It is unclear if IGFBP-3 is the primary carrier of IGF-I in skeletal muscle, but there is evidence that it does exist there (Hand, Kostek, Ferrell, Delmonico, Douglass, Roth, Hagberg & Hurley, 2007, S. 1678).

3.5 The IGF- signaling pathways

The IGF-I receptor phosphorylates tyrosine, an amino acid in its structure which is essential for starting the downstream signaling cascade (Spurway & Wackerhage, 2006, S. 198). Then the autophosphorylated receptor attracts scaffolding proteins by protein-protein interaction which facilitate the activation of specific signal transduction pathways. One pathway activated by IGF involves Ras- Raf signaling to extracellular response kinases (ERKs)

The activities of the pathways are conditional (Adams, 2002, S. 1160). There are reports that both ERK and PI3K activity act in concert in some cell types and both may be required for the differentiation of myoblasts (Mehrhof, Muller, Bergmann, Li, Wang, Schmitz, Dietz & von Harsdorf, 2001, S. 2088-2094; Yu, Roshan, Liu & Cantley, 2001, S. 32252-32258). In contrast other reports show that activity of one pathway may actually inhibit the other (Rommel, Clarke, Zimmermann, Nunez, Rossmann, Reid, Moelling, Yancopoulos & Glass, 1999, S. 1009-1013; Samuel, Ewton, Coolican, Petley, McWade & Flotini, 1999, S. 55-64; Zimmermann & Moelling, 1999, S. 1741-1744). The processes of cellular proliferation and differentiation are generally thought to be exclusive (Adams, 2002, S. 1161). In a number of cell types, activation of one of the two primary signaling pathways associated with ligation of growth factor receptors will generally inactivate portions of the other (Abb. 3 vs Abb. 4). Spurway & Wackerhage (2006, S. 199) suspect that the ERK pathway, which is associated with tyrosine kinase activity of the IGF-IR, as probably more related to muscle fibre phenotype regulation than to growth. As shown on Abbildung 3 the phosphorylation targets of ERKs include transcription factors and additional protein kinases.

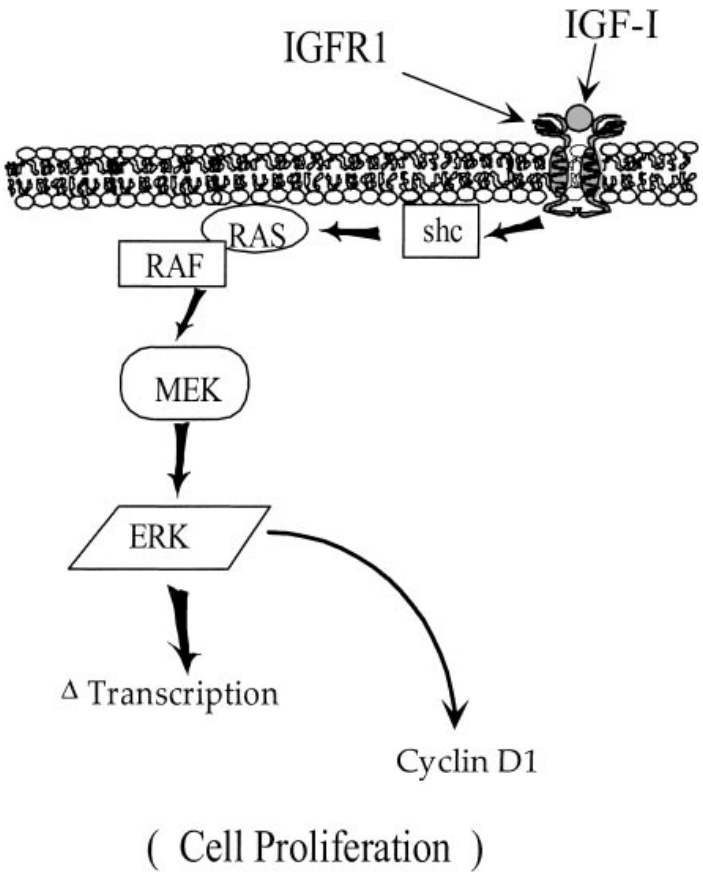

Abbildung 3: The Ras-ERK signalling cascade (Adams, 2002, S. 1160)

(MAPK/ERK kinase; Raf, MAPK kinase kinase; Ras protein, member of the Ras GTPase family; Shc, SH2- containing collagen-related proteins (couples IGFR1 tyrosine kinase to Ras)

Insulin receptor substrate (IRS) proteins are the scaffolding proteins that regulate the activation of the PKB pathway in response to IGF-1, IGF-2 and insulin. These four IRS isoforms (IRS 1-4) are phosphorylated at tyrosine residues by active IGF-1/ insulin receptors (Spurway & Wackerhage, 2006, S. 202). Phosphorylated IRS attract phosphatidylinositol-3-kinase (PI3K) to the receptor which is essential for the activation of PKB further downstream. IRS-1 seems to be most important for IGF-1- stimulated muscle growth, as these isoforms control growth and glucose metabolism. PI3K phosphorylates regulatory peptides (phosphatidylinositols- PtdIns) that can be phosphorylated and dephosphorylated just like proteins. PI3K uses ATP to phosphorylate PIP2 to PtdInsP3 (PIP3). PIP3 than binds to PIP3- dependent protein kinase-1 (PDK1) and protein kinase B (PKB) proteins and stimulates their translocation from cytosol to the cell membrane (Abb.4). PDK1 is able to phosphorylate PKB at Thr 308 (Spurway & Wackerhage, 2006,

S. 202). There are three PKB isoforms: PKBα (Akt1), PKBβ (Akt2) and BKPγ (Akt3). Once phosphorylated, Akt can act on a broad spectrum of subtrates that can influence cell survival, proliferation and protein synthesis (Vivanco & Sawyers, 2002, S. 489-501). mTOR phosphorylation by Akt leads to mTOR activation and the subsequent activation of S6K1. Activation of the Akt/mTOR pathway may also promote muscle growth by inhibiting glycogen synthase kinase (GSK)-3β, α serine/threonine kinase that can block translation that is iniciated by eukaryotic initiation factor-2B and may reduce protein synthesis (Tidball, 2005, S. 1905). Numerous observations support the likely importance of the Akt/mTOR/S6K pathway as promoting muscle growth. Akt1 phosphorylation and expression are elevated during muscle hypertrophy and reduced during atrophy (Bodeine, Stitt, Gonzalez, Kline, Stover, Bauerlein, Zlotchenko, Scrimgeour, Lawrence, Glass & Yancopoulos, 2001, S. 1014-1019).

The intracellular pathways that subserve IGF-IR ligation also represent potential points for interactions between IGF-I induced responses and those initiated by other mediators. There is evidence that there are interactions between the calcineurin and IGF-I signaling pathways in skeletal muscle. Whether calcineurin is part of a mechanical signal transduction pathway that modulates skeletal muscle growth or adaptation remains unclear. However, many observations are consistent with the hypothesis that mechanical loading increases IGF-I release and IGF-I can stimulate Ca^{2+} influx and therby activate calcineurin (Perrone, Fenwick-Smith, & Vandenburgh, 1995, S. 2099-2106; Tidball, 2005, S. 1904). Signaling via the calcineurin/nuclear factor of activated T-cell pathway produces a shift towards a slower phenotype (Type I) in muscle but can also increase muscle mass. This may show evidence that mechanical loading and IGF-I could affect muscle through overlapping signaling pathways.

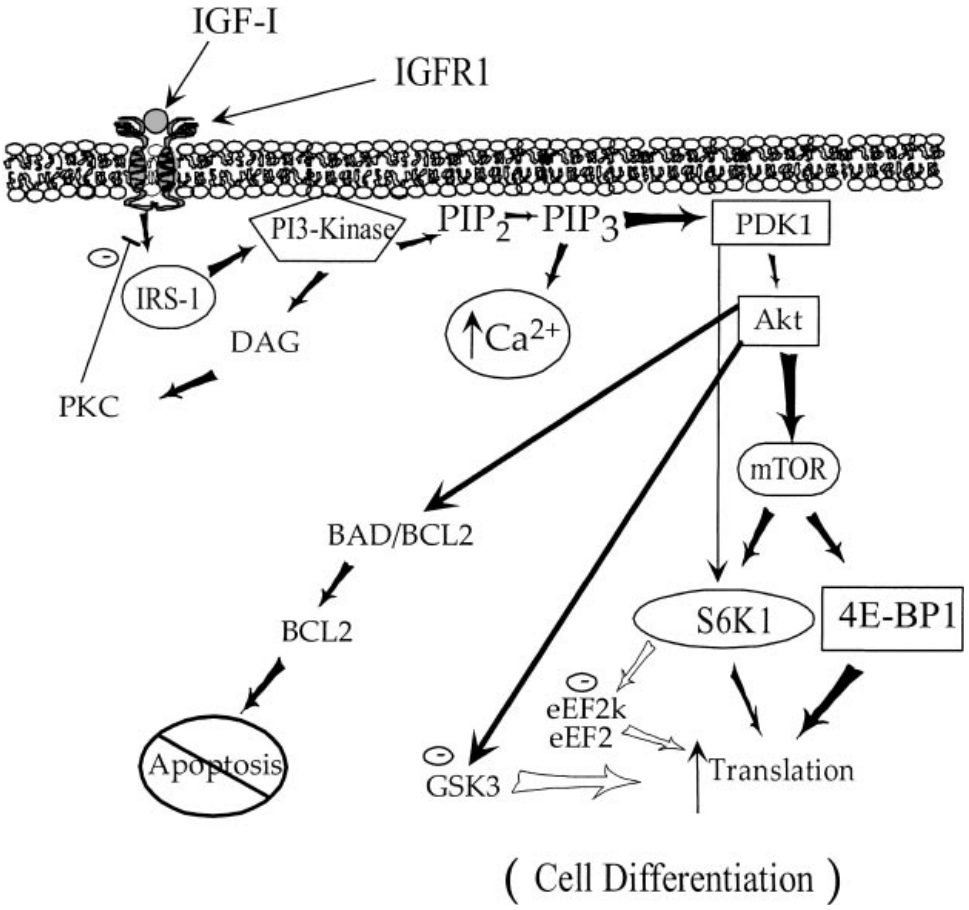

Abbildung 4: The IRS-PI3K signalling cascade. Also shown is the pathway for protection from apoptosis and that which mediate increased cytoplasmic calcium levels. (Adams, 2002, S. 1161)

(Act, protein kinase B: BAD, proapoptotic regulator of programmed cell death; Bcl2, regulator of programmed cell death, promotes cell survival; DAG, diacylglycerol; 4E-BP1, eukaryotic initiation factor 4 binding protein; eEF2, eukaryotic elongation factor-2 (k=kinase); GSK3, glycogen synthase kinase 3; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; PI3-kinase (PI3K), phosphotidylinositol 3-kinase; PIP2, phosphatidylinositol 3,4-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PDK1, PI3K-dependent kinase; PKC, protein kinase C; S6K1, p70 S6 kinase)

4 Myostatin

In skeletal muscle little is known about the control of tissue size. Over 40 years ago, Bullough (1962, S. 307-342) recognised that tissue size is controlled by the activities of negative growth regulators that he dubbed chalones. According to this hypothesis, individual tissues secrete distinct chalones. They circulate throughout the body and act to inhibit the growth of the tissue producing the specific chalone. It has been shown that skeletal muscle might utilize this general type of regulatory mechanism to control tissue mass and myostatin appears to be the key mediator of this loung-sought colone (Lee, 2004, S. 62).

Myostatin (MSTN), formerly known as growth and differentiation factor 8 (GDF8) is a member of the transforming growth factor- ß superfamily (TGF-ß) (Rodgers, Roalson, Weber, Roberts & Goetz, 2007, S. E371-E372). The superfamily comprises over 35 members that play an essential role in growth and differentiation of embryonic development and regulation of tissue homeostasis in adults (Rios, Fernandez-Nocelos, Carneiro, Arce & Devesa, 2004, S. 2795-2803). The myostatin protein sequence has all the hallmarks present in other family members (Lee, 2004, S. 62). The protein is produced as an inactive dimeric precursor that undergoes two proteolytic processing events resulting in a 26-kDa N-terminal propeptide signal sequence, a dibasic proteolytic processing site, and a 12.5-kDa C-terminal fragment that is the major myostatin ligand and the biological active species. (McPherron, Lawler & Lee, 1997a, S. 83-90; Thomas, Langley, Berry, Sharma, Kirk, Bass & Kambadur, 2000, S. 40235-40243; Lee, 2004, S. 61-86; Bradley, Yaworsky & Walsh, 2008, S. 2119-2124). The myostatin sequence in the C-terminal region shows significant homology to other family members. (Abb. 5) Together with the highly related protein GDF-11, myostatin defines a distinct subgroup within the larger superfamily (McPherron et al.,1997a, S. 83-84; Gamer, Wolfman, Celeste, Hattersley, Hewick & Rosen, 1999, S. 222-232; Lee, 2004, S. 61-62). The propeptide plays an important role in regulating the activity of the C-terminal dimmer. Following proteolytic processing, the propeptide and the C- terminal dimmer remain in a latent complex. Activation of latent myostatin can occur by proteolytic cleavage of the propeptide by members of the BMP-1/tolloid family of metalloproteinases (Lee, 2004, S. 67), which causes dissociation of the latent complex. Interestingly, it has been shown that one member of the BMP-1/tolloid family, TLL-2 is expressed specifically in skeletal muscle during embryogeneses (Scott,

Blitz, Pappano, Imamura & Clark, 1999, S. 28-300). Next to propetide there are other binding proteins that are capable of regulating myostatin activity in vitro, including follistatin (Lee, 2004, S. 61-67; Zimmers, Davies, Koniaris, Haynes & Esquela, 2002, S. 1486-1488), FLRG (Hill, Davies, Pearson, Wang & Hewick, 2002, S. 40735-40741) and Gasp-1 (Hill, Qiu, Hewick, Wolfman, 2003, S. 1144-1154). FLRG and GASP-1 seem to be involved in regulatoring the activity of the myostatin C-terminal dimmer extracellularly (Hill et al., 2002, S. 40735-40741).

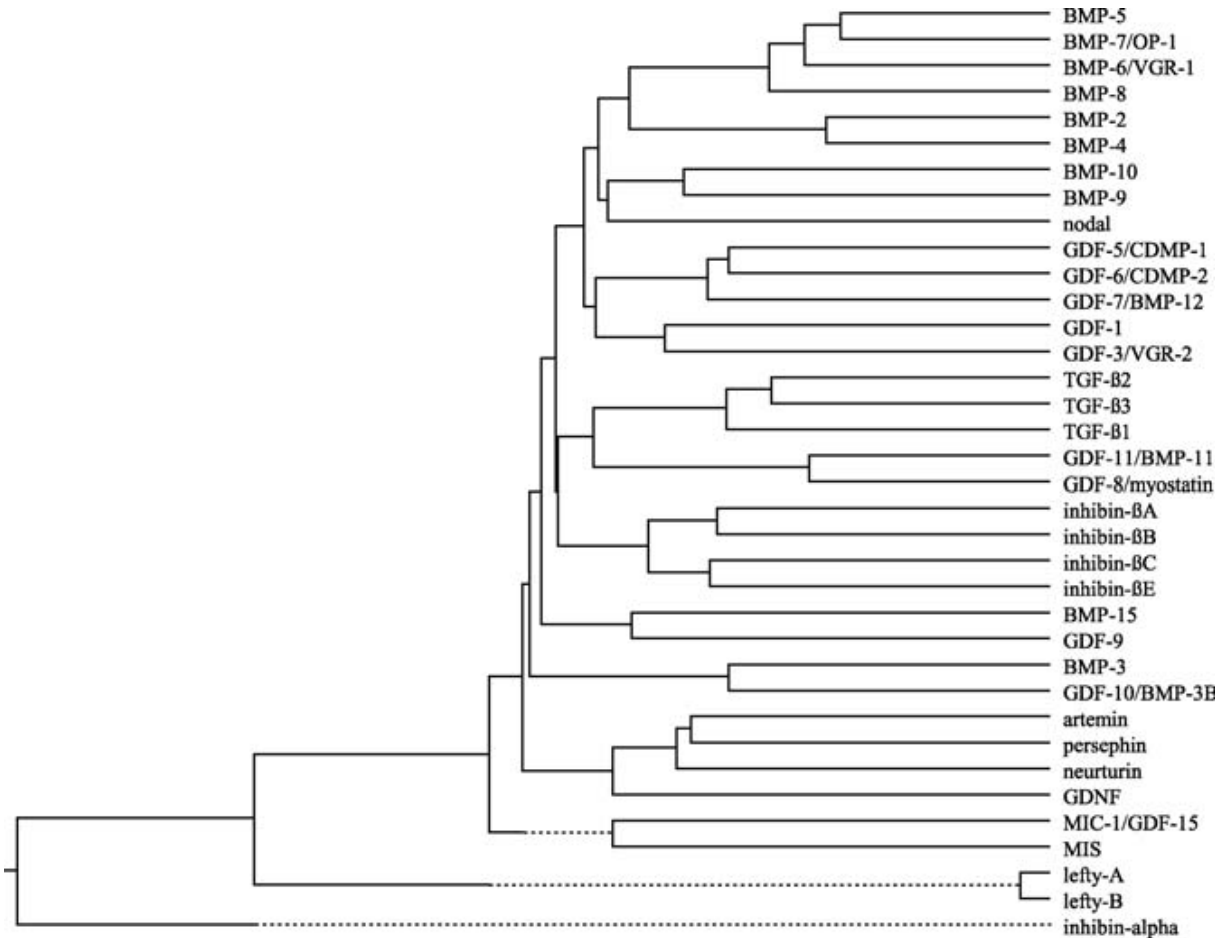

Abbildung 5: Sequence comparisons of members of the TGF-ß superfamily (Lee, 2004, S. 62)

During embryogenesis, myostatin expression is detected in the myotome compartement of developing somites and acts to regulate the final number of muscle fibers that are formed. In adult tissues, myostatin protein is produced by skeletal axial and paraxial muscle, circulates in the blood, and acts to limit muscle fiber growth (Lee, 2004, S. 63). These findings suggest that myostatin may play two distinct regulatory roles: one during early development and a second during adult homeostatic processes. The myostatin expression is restricted exclusively to cells of the skeletal muscle lineage (McPherron et al., 1997a, S. 83-90). Although to a lower extent, myostatin expression has been detected in adipose tissue (McPherron et al., 1997a, S. 83-90; Lee, 2004, S. 63), mammary gland (Ji, Losinski, Cornelius, Frank, Willis, Gerrard, Depreux & Spurlock, 1998, S. R1265-R1273), cardiomyocytes, purkinje fibers of the heart (Sharma, Kambadura, Matthews, Somers, Devlin, Conaglen, Fowke & Bass, 1999, S. 1-9), and hemopoietic cells (Fernandez, Rios, Arce, Diaz, Alonso, Perez, Bello & Devesa, 2002, S. 323-326).

Myostatin functions as a negative regulator for muscle growth, such that the absence of myostatin results in a hypermuscular phenotype in a large number of different species (Wagner, 2005, S. 2519-2524; Roth, Martel, Ferrell, Metter, Hurley & Rogers, 2003, S. 706-709). The function of myostatin was elucidated by gene targeting studies in mice (McPherron & Lee, 1997b, S. 12457-12461). In this “mighty mice” the gene encoding myostatin has been knocked out. Homozygous inhibition of the myostatin gene in mice produces a considerably increase in skeletal muscle mass, resulting from a combination of muscle cell hyperplasia and hypertrophy (McPherron et al., 1997a, S. 83-90; McPherron & Lee, 2002, S.595-601; Lin, Arnold, Della-Ferra, Azain, Hartzell & Baile, 2002, S. 701-706). „Every skeletal muscle examined appears to be affected by the mutation, and males and females are affected proportionately” (Lee, 2004, S. 63). Significantly, heterozygous mice are also affected, albeit to a lesser degree, suggesting that the effect of myostatin is dose dependent.

Naturally occurring mutations of the myostatin gene produce the compact phenotype in mice (Szabo, Dallman, Muller, Patthy, Soller & Varga, 1998, S. 671-672). In contrast, systematic overexpression of the myostatin gene leads to a wasting syndrome characterized by extensive muscle loss (Schuelke, Wagner, Stolz, Hübner, Riedbel, Kömen, Braun, Tobin & Lee,2004, S. 2682-2689).

4.1 The myostatin signaling pathway

The mechanism of this regulatory factor encompasses an autocrine/paracrine regulatory loop by undergoing a complex signaling pathway (Abb. 6). There is considerable evidence that myostatin signals by a mechanism similar to that of other TGF-ß-related ligands. Myostatin signals through a TGF-ß/activin/nodal-like pathway by binding to and activating a receptor heterodinamic complex composed of the type II receptor ActRIIB together with a type I receptor partner of either ALK4 or ALK5, that is expressed by myogenic stem cells and proliferating myoblasts (Rebbapragada, Benchabane, Wrana, Celeste & Attisan, 2003, S. 7230-7242). The activated receptor triggers multiple intracellular signaling cascades including the SMAD and MAPK pathways that activate the AKT and p21/Rb pathways and inhibit expression of the myogenic regulatory factors (Bradley et al., 2008, S. 2119). The phosphorylisation of Smad2 and Smad3 propagates the intercellular signal that ultimately leads to activation of TGF-ß-responsive promotors (Rebbapragada et al., 2003, S. 7230-7242).

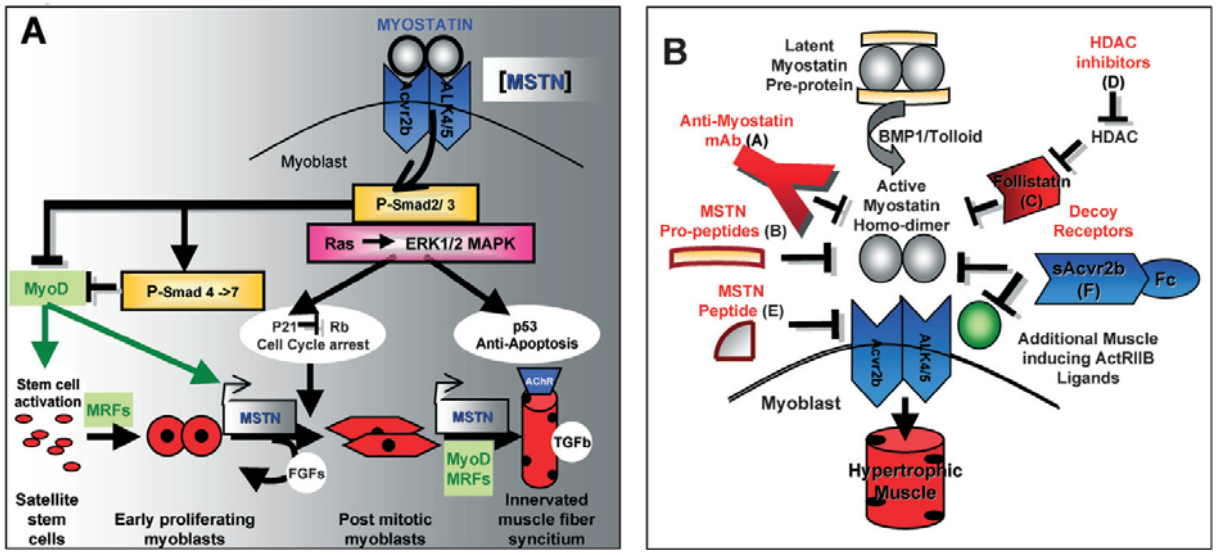

Abbildung 6: The complex myostatin system (Bradley et al., 2008, S. 2120)

Myostatin and GDF-11 are the newest members of a growing list of ligands that appear to be capable of signaling through activin type II receptors. GD-11 is capable of binding both ActRIIB and ActRIIA, and it appears that GD-11 binds more strongly to ActRIIB than toActRIIA (Oh, Yeo, Lee, Schrewe, Whitman & Li, 2002, S. 2749-2754). The fact that Myostatin and GDF-11 have a relatively widespread expression pattern and that some of these ligands, including myostatin itself, circulate systematically, arises the key question how specifity of signaling is achieved. For myostatin, one possible mechanism might be selective activation of the latent complex of the target side. An attractive hypothesis is that the BMP-1/tolloid proteinases are activated only at sites and times at which suppression of muscle growth is desired (Lee, 2004, S. 61-86).

An alternative mechanism is selective utilization of coreceptors in order to engage the type II receptor. In a study of Lee and McPherron (Lee & McPherron, 2001, S. 9306-9311) the receptor binding affinity of myostatin that has been determined for COS-1 cells transferred with ActRIIB is somewhat lower than typical affinities reported for other TGF-ß family members and their cognat type II receptors. This raises the possibility that a receptor component for myostatin, such as a coreceptor, may have been limiting in COS-1 cells.

Another possibility for achieving specifity of signaling is restricted expression of the appropriate type I receptors. Only those cells expressing both the activin type II receptors and the appropriate type I receptors would be capable of transducing the myostatin signal (Lee, 2004, S. 61-86). The type I receptor can enhance the affinity of the ligand for the type II receptor (Attisano & Wrana, 2002, S. 1646-1647).

Finally, there is considerable genetic data showing that the nuclear protein c-ski, which normally functions to block myostatin signaling by blocking activities of Smad proteins normally activated by myostatin, (Lee, 2004, S. 73) is a potent regulator of muscle growth . C-ski is capable of interacting with and blocking the activity of Smad 2,3 and 4 (Luo, Stroschein, Wang, Chen & Martens, 1999, S. 2196- 2197; Stroschein, Wang, Zhou & Lou, 1999, S. 771-774; Akiyoshi, Inoue, Hanai, Kusanagi & Nemoto, 1999, S. 35269-352677).

Several studies have demonstrated that myostatin is capable of blocking both proliferation (Thomas et al., 2000, S. 40235-40243; Taylor, Bhasin, Artaza, Byhower & Azam, 2001, S. E221-E228; Joulia, Bernardi, Garandel, Rabenoelina, Vernus & Cabello, 2003, S. 263-275) and differentiation (Rios, Carneiro, Arce & Devesa, 2001, S. 561-566; Joulia et al., 2003, S. 263-275) of myoblasts during development by regulating MyoD expression. This

suggests that a major target for myostatin signaling in adult animals is the cell cycle and in special the satellite cell. „Studies with isolated satellite cells demonstrated that myostatin is capable of up- regulating p21 expression, down- regulating Cdk2 expression, and inhibiting cell proliferation" (Lee, 2004, S. 73). Myostatin mutant mice have been shown to have an increased number of satellite cells per unit length and a higher proportion of activated satellite cells than muscles of wild-type mice. McCroskery et al. (2003, S. 11135-1147) clarifys an increase in the proliferation rate of fast and slow fiber- specific satellite cells in lack of myostatin. The same study demonstrated that myostatin is expressed in satellite cells and regulates satellite cell quiescence. In the absence of myostatin there is increased self-renewal of satellite cells, possibly by increased proliferation of satellite cell-derived myoblasts. Increased activation of satellite cells, and subsequent enhanced proliferation with delayed differentiation of myostatin- null myoblasts could be the primary reason for the increased postnatal muscle growth and hypertrophy in myostatin-null mutations (McCroskery et al., 2003, 1144-1145). It seems likely that other cells are also capable of responding to myostatin. Overexpression of myostatin in adult mice has been shown to induce a dramatic systemic wasting syndrome (cachexia) characterized by extensive loss of muscle. As mentioned before this was accompanied by loss of adipose tissue mass (Lee, 2004, S. 75). This raises the possibility that myostatin may also have direct effects on adipocytes. Alternatively, the effects on muscle mass and fat stores may reflect the activity of some other mediator of cachexia whose activity is induced by myostatin.

Whether there is direct signaling on adipocytes or an indirect effect, mice lacking myostatin have a reduction in total body fat, which is particularly pronounced in older animals (Lin et al., 2002, S. 705; McPherron & Lee, 2002, S. 12457). That makes it clear that myostatin can influence fat metabolism and adipocyte function. This leads to the speculation that circulating levels of myostatin change under different environmental conditions or different physiological states, such as physical activity, illness, pregnancy or age. These changing levels alter the metabolic homeostatic balance between fat storage and muscle growth.

4.2 The ancient gene

Mutations in the myostatin gene have been shown to be responsible for the double-muscling phenotype in cattle. This phenotype defines three breeds of cattle named Belgium Blue, Piedmontese and Austuriana de los Valles. Investigations of a larger number of double- muscled breeds identified at least seven different mutations, including premature stopcodons, frameshift mutations and point mutations at highly conserved amino acid residues (Grobet, Martin, Poncelet, Pirottin, Brouwers, Riquet, Schoeberlein, Dunner, Menissier, Massabanda, Fries, Hanset & Georges, 1997, S. 71-74; Kambadur, Sharma, Skith & Bass, 1997, S. 910-915; McPherron & Lee, 1997b, S. 12457-12459; Cappucio, Marchitelli, Serracchioli, Nardone & Filippini, 1998, S. 51; Marchitelli, Savarese, Crista, Nardone, Marsan & Valentini, 2003, S. 392-395).

Genetic analysis of the Belgian Blue revealed that this trait segregated as a single locus on bovine chromosome 2 with a semidominant mode of inheritance (Lee, 2004, S. 61-86). Together with mapping studies this shows that the human myostatin gene is located homologous to the mutation in the bovine myostatin gene of the double muscling locus (Grobet et al., 1997, S. 71-74; Kambadur et al., 1997, S. 910-915; McPherron & Lee, 1997, S. 12460). Actually, the gene is located in band 2q32.2. The predicted myostatin protein sequences in the C-terminal domain are identical among humans, mice, rats, chickens, turkeys and pigs. The predicted protein sequences in fish are significantly diverged from those of other vertebrates, indicating that myostatin function has been remarkably well conserved through evolution (Rios et al., 2004, S. 64). It is the profound metabolic consequences resulting from altered myostatin activity that explain the extraordinary degree to which myostatin has been conserved through evolution (Lee, 2004, S. 61-86). It is known that the circulating levels of myostatin protein in humans are lower than in mice (Schuelke et al., 2004, S. 2622-2628; Zimmers et al., 2002, S. 1486-1588), raising the possibility that the balance of the relative roles played by myostatin and by these other regulators may have shifted further away from myostatin in humans compared to mice (Lee, 2007, S. 789). In this respect it will be essential to determine the identity of other ligands that cooperate with myostatin, to develop the best possible strategies for manipulating this pathway for the treatment of human patients with muscle wasting and muscle degenerating diseases. Myostatin blockade might be beneficial for a variety of primary and secondary myopathies including muscular dystrophy (MD) like Duchenne

MD (DMD) or Becker`s MD, amyotrophic lateral sclerosis (ALS), sarcopenia, limb girdle muscular dystrophie, ageing and muscle loss due to chronic infections (e.g. HIV) or immobilization. Additionally, it might prove to be useful for the management of systematic metabolic disorders such as obesity and type II diabetes (Li & Murthy, 2001, S. 593-605).

5 Methods

5.1 Objectives

1. To examine the effects of ACTN3, IGF-I, IGF-II and myostatin polymorphisms on anaerobic phenotypes.

2. To perform a systematic review in this area.

5.2 Types of studies

All abstracts were reviewed by the following inlcusion criterias:

a.) Does the study include genotype analysis of ACTN3, IGF-I, IGF-II or myostatin polymorphism?

b.) Does the study include observations on human muscle tissue phenotype?

5.3 Types of participants

The participants were healthy adult men and women from all kinds of races without age limit. The investigations were made for athletics and nonathletics separately. Athletics were defined as participating in competitions of national or international elite level.

5.4 Types of interventions

Two main analyses were undertaken:

1.) Genotype was compared to exercise intervention.

2.) Genotype was compared in observational studies.

Interventions were defined as resistance/strength/power/weight formed with concentric/eccentric or isometric action and training/exercise.

5.5 Types of outcome measures

Primary outcome measures:

Studies were included if the participants genotype and the effect on muscle phenotypes was measured.

Secondary outcome measures:

Measurements on muscle strength values characterized by 1-repetition maximum, maximal power output by cross- sectional area, fiber type distribution, lean body mass, muscle volume, muscle quality & peak tourque were extracted.

5.6 Identification of studies

Three electronic databases (Elektronische Zeitschriftenbibliothek MedUniGraz, Österreichische Zeitschriftendatenbank, Pubmed) were searched from September 2008 to February 2009 using seventeen text words in all relevant combinations: ACTN3, α-actinin-3, anaerobic, exercise, genotype, GDF8, growth differentiation factor 8, IGF-I, IGF-II, Insulinlike growth factor, muscle, myostatin, phenotype, polymorphism, R577X, strength, training. The search maschine www.google.com was also used. Hand search included the

reference lists of all retrieved publications and the “Human gene map for performance and health-related fitness phenotypes” from 2000 to 2008.

5.7 Assessement of study quality

Quality assessment and internal validity of the included trials are summarized in Tabelle 1-3. The levels of evidence vary from cross section studies (9 study) to cohort studies (5 studies), case- controll trials (14 studies) and randomised controlled trials (9 studies).

Author	Year	Probands	Parameters	Intervention	Results	Levels of evidence
Clarkson, P. M.et al.	2005	157 subjects: 78 men (n=78) & women (n=79) age: 19-22	- genotype analysis of ACTN3 & MLCK - CK - Mb - dynamic (1- RM) & isometric strength (MVC)	- 2 sets of 25 max. eccentric contractions of nondominant arm elbow flexor (3s contraction followed by 12s rest) seperated by 5 min rest period - 3 max. MVC (3s contraction 1 min rest) on force transducer	**1.) Body composition:** RX (n=78) > XX (n=41) > RR (n=35) - no relationship of age, BMI or sex 1.) **baseline CK activity:** - RX (126.6 +/- 6.6) > XX (99.1 +/- 9.1) (P=0.035) - RR (106.2 +/- 9.9) = RX (126.6 +/- 6.6) - variation attributable to ACTN3 genotype: 3.5% **2.) Effect on muscle strength:** - no association with baseline strength or change in strength - no association with blood proteins after exercise	cross-section study
Clarkson, P. M.et al.	2005	602 subjects men (n=247) & women (n=355) age: 18- 40	- genotype analysis by TaqMan assay - muscle size via MRI (CSA of biceps brachii) - dynamic (1-RM) & isometric strength (MVC) before and after exercise training - height - CSA - body mass and age as covariants - subset of ethnic groups	- 12-wk ~45- 60 min of progressive elbow/flexor/extensor resistance training of nondominant arm (biceps preachercurl, biceps concentration curl, standing biceps curl, overhead triceps extension, and triceps kickback) 2s concentric & 2s eccentric - weeks 1-4: 3 sets 12 rep. of 12-rep. max. weight - weeks 5-9: 3 sets 8 rep of 8 rep max weight	RX (n=263) > RR (n=176) > XX (n=164) (43.5% : 29.3% : 27.2%) Allele frequencies: X=0.489 R=0.511 *Men:* RX (n=114) > RR (n=68) > XX (n=65) (46.2% : 27.5% : 26.3%) Allele freqgencies: X=0.493 R=0.506 *Women:* RX (n=148) > RR (n=108) > XX (n=99) (41.7% : 30.4% : 27.9%) Allele frequencies: X=0.487 R=0.513 **1.) Effect on muscle strength:** - no association between RX genotype & muscle strength in men	cross-section study

				- weeks 10-12: 3 sets 6 rep of 6 rep. max. weight	- sign. between RX and strength in women (validated in ethnic subpopulations) - *women baseline MVC:* RX (69.7 +/-1.8) >RR (67.9 +/- 2.1) > XX (61.5 +/- 2.2) (adjusted to baseline body mass & age by analysing of covariance) RX (70.6 +/- 1.9) > RR (96.8 +/- 2.3) > XX (61.5 +/- 2.3) (adjusted for biceps CSA & age) - *Absolut change in 1-RM:* women: XX (8.7 +/- 0.4) > RX (8.0 +/- 0.3) > RR (7.2 +/- 0.4) - *Relative change in 1-RM:* XX (68.5 +/- 3.6) > RX (63.9 +/- 2.9) > RR (55.5 +/- 3.5) - relative increase in in both strength measures women > men ($P<0.05$) - men > baseline biceps, muscle size, 1-RM, MVCgain & absoulte gains in muscle size & strength women > relative isometric strength (MVC) (22 vs. 16%) & sign.; > relative 1-RM strength than men (64 vs. 40%) - 2.1 % of variability in absolute difference in 1-RM strength, 1.8% of variability in relative difference in 1-RM & 2.2% of variability in baseline MVC strength are attributable to ACTN3 genotype	

Vincent, B. et al.	2007	90 healthy young men age: 18-29	- genotype- analysis by TaqMan SNP (DNA extraction & SNP genotyping) - fiber type composition by immunohistochemistry - biopsy of right vastus lateralis - quadriceps CSA - %body fat, fat mass & fat free mass - physical activity questionnaire (h/wk) - Phase I: Relationship of R577X & muscle strength (n=90) -Phase II: 1.) Comparing of fiber type distribution & strength between RR (n=22) & XX (n=22) 2.) muscle α-actinin 2/3 protein content	- static & dynamique tourges of knee-extensor muscles (2 max. isometric extensions (5s) at 45° knee flexion as static torque; dynamic tourques at 100, 200, 300 and 400°/s as registered tourque (45°) during one extension movement; eccentric torque as 1 max. knee extension contraction, while knee flexion was forced at an angular velocity of 100°/s)	**1.) Body composition** XX: n=19 RX: n=40 RR: n=26 XX : RX : RR = 0.24 : 0.44 : 0.31 Allele frequencies: X=0.47 R=0.53 **2.) Effect on fiber type composition:** 577XX (n=21) 577RR (n=22) Type I: 55+/-3 50+/-2 Type II: 35 +/-2 37+/-2 Type IIx: 9+/+1 14+/+2 (P<0.05) I : II : IIx = 52 : 36 : 12 (%) - IIx fibers > 5% in RR than XX (P=0.04) - Relat. Surface area by IIx: RR > XX (P=0.03) - no sign. diff. in surface area for I & IIa **3.) Effect on muscle strength:** *Absolute tourque:* 577XX (n=22) 577RX (n=40) 577RR(n=28) 211+/-6 207+/-4 195+/-5 *Eccentric tourque:* 219+/+7 215+/-3 212+/-4 *Relative Tourque (300°/s):* 0.26+/-0.03 0.28+/-0.02 0.043+/-0.02 (P=0.04) *Relative dynamic power:* XX < XX (wild type) *Maximal tourque:* similar in groups for static & dynamic co- & eccentric contractions **4.) Protein content** RR > XX (80%) *Staining intensity:* RR = XX (large variation in subjects)	cross-section study

					α-actinin3 protein content: RR: IIX > IIa (>10; n=11) *α-actinin3 average red fibers* IIx > IIa (~17%) (P= 0.04)	
Delmonico, M. J. et al.	2007	157 healthy y Caucasian men (n=71) & women (n=86) age: 50- 85	- genotype analysis by EDTA- anticoagulated blood samples - Body Composition by DXA - MV by CT in trained & untrained thighs - PP & PV at baseline & following ST - 1-RM before & after ST - BMI - %fat & FFM - baseline values & change or drift in control leg, - medication use (diuretics, ACE inhibitors, hormone replacement therapy & antiinflammatories/pain reducers)	- ~ 10 weeks 3times/wk unilateral ST of knee extensors of right leg < 75 yrs: 5 sets > 75 yrs: 4 sets	**1.) Body composition:** *Men:* RR (n=29) > RX (n=27) > XX (n=15) *Women:* RX (n=33) > RR (n=33) > XX (n=24) **2.) Effect on muscle strength:** - men before 307 (88); after 388 (98) > women before 160 (47); after 1189 (205) - MV > in men before 1758 (268); after 1916 (303) (9.0 +/- 1%) - MV > women before 1085 (208); after 1180 (205) (8.8 +/- 1%) women: *Absolute PP:* XX (242 +/- 10) > RX (210 +/- 10) > RR (200 +/- 11) (age & baseline covaried) *Absolute MPQ:* XX (2.2 +/- 0.1) > RR (2.0 +/- 0.1) > RX (1.9 +/- 0.1) (age & baseline covaried) *Relative MPQ:* XX (2.1 +/- 0.1) > RR (1.9 +/- 0.1) > RX (1.8 +/- 0.1) (age & baseline covaried) *Absolute peak movement:* XX (4.8 +/- 0.2) > RX (4.5 +/- 0.2) > RR (4.3 +/- 0.1) (covaried for age & baseline) *Relative peak movement:* XX (4.2 +/- 0.1) > RX (3.8 +/- 0.1) & RR (3.8	cross-section study

					+/- 0.1) *men:* -no differences in any of baseline muscle function measures *<u>untrained leg:</u>* *Absolute PP change:* men: RR > RX > XX (p< .05) women: RR > RX > XX (no sign.) *Relative PP change*: women: RR > RX > XX (RR : XX p=.02) (adjusted for age & changes) sign. within group increases: RR (p=.007) RX (p=.03) men: no differences in change (only RR: p=.01)	
Norman, B. et al.	2009	120 moderately well-trained men (n=61) & women (n=59) age: 19-32 (BMI: < 30 kg/m²; > 3-4 yrs of training; training h/wk: > 2-10	- genotype analysis by QIAamp - muscle biopsies from vastus lateralis - fiber type composition (I, IIa, IIb, IIc) - leisure time sports activities questionnaire - FFW - average power output - PP & MP - FI -MVC	- 2 bouts of exercise with 20 min rest between - 30-s exercise on cycle ergometer max. speed; resistance: 7.5% of body mass subset of 21 men 12 RR & 9 XX: - knee angle: 90-180° - maximal contraction: 30, 60, 90, 120, 180 & 300°/s - muscle fatigue on isokinetic exercise - 30 maximal concentric KE (90° to full extension at	**1. Body composition:** XX (n=23) = RR (n=23) > RX (n=17) - no sign. diff. in age, physical status or activity level **1.) Fiber-Type composition** - no sign. differences in fiber type composition in genotypes *Men:* 577XX (n=12) 577RX (n=9) 577RR (n=16) I: 52+/-14 54+/-10 49+/-17 IIa: 31+/-15 36+/- 6 39+/+14 IIb: 16+/-10 9+/- 5 12+/-13 *Women:* 577XX (n=11) 577RX (n=8) 577RR (n=7) I: 59+/- 8 62+/-13 66+/- 7	randomised controlled trial

				120°/s) - isometric contraction: 110°, 4-6s	IIa: 34+/-10 31+/-13 25+/- 8 IIb: 7+/- 8 7+/- 6 8+/- 5 - women > I (P=0.014) than men - women < IIb (P=0.026) *Value:* I: IIa : IIb 0.73 : 0.79 : 0.49 - Type I fibers proportion training h/wk: r=0.377; P=0.0005 (positive correlation) - Type I: sign.: training status (P=0.011) & sex (P=0.001), no effect of genotype (P=0.816) - Type II: sign.: sex (P=0.024), no effect of training status (P=0.166) & genotype (P=0.712) **2.) Effect on muscle strength:** - weight: RR (n=12) > XX (n=9) - FFW: RR > XX - no sign. diff. in absolute MVC related to body mass - no sign. diff. in fatigability RR : XX **3.) mRNA expression** RR 6.98 +/- 5.5 AU > XX 0.40 +/- 0.4 AU (P<0.001) *ACTN3 expression (11 RR):* negative corr. between ACTN3 & 5typeI positive corr. between ACTN3 & 5Type IIb	

Tabelle 1: ACTN3 nonathletics with intervention

Author	Year	Probands	Parameters	Results	Levels of evidence
San Juan, A. F. et al.	2006	23 healthy women age 61-80 - moderately active lifestyle	- genotype analysis by enzymatic digestion of amplicons with DdeI - blood analysis - anthropometric measurements - graded exercise test - bench press test (1-RM) - functional test sit-stand test for lower body & 1 mile walk test for functional endurance - gas exchange - peak oxygen uptake - V02max - peak power output - ventilatory threshold	**1.) Body composition:** (RX & RR) (n=18, 78%) > XX (n=5, 22%) - no sign. difference between XX & (RX + RR) - deficiency of XX does not effect health status, longevity & aerobic fitness - no sign. differences in ventilatory threshold (VO2max at VT: (RX & RR) 12.0(0.8) > XX 11.5(1.1), Vo2Peak: (RX + RR) 20.7(1.3) > XX 18.4(2.0), 1-mile walk test: XX 980(43) > (RX + RR) 932(18), sit- stand test: (RX + RR) 9.5(0.3) > XX 9.1 (0.3)	randomised controlled trial
Moran, C. N. et al.	2007	992 adolescent greeks: men (n=525) & women (n=467) 2 age groups: 11- & 12, 17- & 18; classified in: men: 124 inactives , 157 mildly actives (2-4 h/ week), 97 intermediatly actives (4-6 h/week) & 134 highly actives (6 h/week)	genotype analysis by TaqMan SNP assay - Body composition (BMI, triceps & subscapular skinfolds); *power/strength related phenotypes*: handgrip strength, sitting bb throw, vertical jump, 40m sprint & agility run; *endurance- related phenotype*: shuttle run test & a proxy for aerobic	**1.) Body composition:** RR=34%, RX=48%, XX=18% Allele frequencies: X=0.42 R=0.58 **2.) Effect on muscle strength:** - sign. effect of genotype & 40m sprint in men P=0.003 - men: RR (5.92) > XX (6.13); RX (6.00) > XX (6.13) (not sign.) - no association between RX & strength/power phenotypes - no association with RX & shuttle run results (no influence on endurance performance) - no association with RX & body composition	cross-section study

		women: 205 inactives, 117 mildly actives, 76 intermediately actives & 54 highly actives	capacity/Vo2 max - health questionnaire	- no association in female subjects - no effect of physical activity level alone, nor any interaction between genotype & physical activity level (RX P=0.019; physical activity level P=0.205; interaction: P=0.265) - no interaction between genotype & age (RX, P=0.018; age: P<0.001; interaction: P=0.344 - lower (faster) group of sprint time: RR is overrepresented (OR=1.7; 95%CI 1.1-2.5; P=0.013 XX is under-represented (OR=0.3; 95%CI 0.1-0.7; P=0.003 - higher (slower) quartile group: RR is not sign. under-represented (OR=0.7; 95%CI 0.4-1.1; P=0.090), - XX sign. over-represented (OR=1.6; 95%CI 0.9-3.0; P=0.098)	
Delmonico et al.	2008	*Health ABC cohort:* 1367 subjects: men (n=726)& women (n=641) (in the 5yr follow-up study there was a loss of n= 372); *2nd cohort:* a subset of the MrOS Study 1152 white men 65 yrs or older	- genotype analysis by TaqMan assay *ABC study:* - midthigh CSA of right leg at baseline & 5 yrs after - isokinetic knee extensor muscle tourque at baseline & 5 yrs after (60°/s on right leg) - muscle quality defined as MT/midthigh muscle CSA at baseline & after 5 yrs	**1.) Body Composition:** *ABC study:* (RX= 777 (50%) > RR= 473 (30%) > XX=301(19%) (x^2=0.32, df=1, p=.570) men: RX (n=384) > RR (n=234) > XX (n=144) women: RX (n=330) > RR (n=186) > XX (n=125) - sign.difference in men between genotype groups only for phys.act. (RR > XX > RX; P=.020) - no differences in other charcteristics in men, no differences in participant characteristics in	cohort study

			- PLL by self-reported walking ¼ mile or climbing 10 steps without resting (2 consecutive 6 mo intervals) - physical performance at baseline & after 5 yrs using EPESE SPPB:5 chair stands, test of gait speed & standing balance - 400m walk *MrOS study:* - FFM by dual-energy x-ray absorptiometry - grip strength in both hands - Leg power (9 measurements on each leg) - Leg power quality as power/thigh FFM - time to complete a walking course over 6m - 5 chair- stand test without using arms	women *MrOS study (men>65yrs):* RX=551 (48%) > RR= 361(31%) > XX=240 (21%) (x^2=1.23, df=1,p=.540) - RX < RR < XX (P=0.39) - no other baseline characteristic differences between genotype groups **2.) Effect on muscle strength:** *ABC study:* - no adjusted differences between genotype groups in men & women for phenotypes - sign. difference across genotypes for adjusted increases in 400m walk-time (P=.030) (XX > RR (P=.008) & RX (P=0.75) - no sign. difference in women in 400m walk-time *incident PLL risk in men & women:* - RR (35%) < XX (hazard ratio=0.65; 95%CI=0.44-0.94) *MrOS study:* - no adjusted differences between genotype groups for any phenotype - no sign. differences between genotype groups for age-related adjusted changes in muscle or performance phenotypes in m & w	
McCauley T. et al.	2008	79 activ but not-strength-trained UK Caucasian men (University students): age: 20.1 +/- 2.2 body mass: 75.3+/-11.1kg	- genotype analysis by PCR - blood samples - height - body mass - skinfold thickness - muscle function test on	- no differences between ACTN3 & knee extensor isokinetic tourque (ANOVA 0.64< P < 0.99) or relat. tourque any velocity (240:30 deg s; RR 60 +/- 6% RX 58 +/-4% XX 60 +/-6% ANOVA P=0.19) - no differences between ACTN3 & time course	cohort study

		height: 1.79+/-0.06m, BMI: 23.2+/-3.9kg, FFM: 57.1+/-8.4kg	knee extensors on both legs voluntary (3 or 4 max. voluntary contractions, 3s duration with 3s rest) - electrically stimulated measuring contractile properties: TPT, HRT, peak RFD (3 twitches analysed with 30s rest)	of twitch or peak RFD (RR 4493 +/- 1241 Ns; RX 4748 +/- 1344 Ns XX 4611 +/- 1226 Ns; ANOVA P=0.65 -isometric strength was independent of ACTN3 (RR 599 +/- 81 RX 619 +/-92 N XX 606 +/-103 N; ANOVA P=0.66	
Walsh, S. et al.	2008	848 subjects age: 22-90 men (n=454) & women (n=394)	- genotype analysis by DANN - knee extensor shortening & lengthening peak tourque values using isokinetik dynamometry - FFM by DEXA - Body mass - Height;	**1. Body composition:** men: RX (n=213) > RR (n=161) > XX (n=80) women: RX (n=174) > RR (n=167) > XX (n=53) - women XX : RR; XX : (RR & RX) < levels of body mass, BMI, fat mass and FFM (P< 0.05); **2.) Effect on muscle strength:** - Knee extensor peak tourque; age & height as covariate: women XX < RX shortening: 30°/s P=0.003; 180°/s P=0.007 lengthening: 30°/s P=0.004; 180°/s P=0.004 - XX : RR similar but not all comparisons sign shortening: 30°/s P=0.073; 180°/s P=0.091 lengthening: 30°/s P=0.144; 180°/s P=0.036 - no sig. diff. in men - Knee extensor peak tourque; FFM differences covaried in place if height: XX > (RX + RR) shortening peak torque at 30°/s P=0.049 5.) *subanalysis women* > 50 yrs (age & height	randomised controlled trial

				as covariates) XX < (RX & RR) KE shortening 30°/s XX (78.4 +/- 4.1 N*m) vs. (RX + RR) (89.1 +/- 1.6 N*m) P=0.015; 180°/s XX (55.6 +/- 2.9 N*m) vs. (RX + RR) (61.3 +/- 1.1 N*m) P=0.07 KE lengthening 30°/s XX (112.4 +/- 6.9 N*m) vs. (RX + RR) (127.3 +/- 2.6 N*m) P=0.046 180°/s XX (109 +/- 6.6) vs. (RX + RR) (127 +/- 2.5 N*m) P=0.012 - FFM differences covaried in place if height: strength values no longer differed sign. between genotype groups - no significant differences in men > 50 yrs	

Tabelle 2: ACTN3 Nonathletics without intervention

Author	Year	Probands	Parameters	Results	Levels of evidence
MacArthur D. G. et al.	1999	- Caucasian control group (n=152), - elite (national level) sprint athletes (n=83) - elite endurance athletes (n=183)	- genotype frequencies by amplifying a 291 bp region spanning exon 16 using PCR	**1.) Body composition:** *Control:* RX (n=78; 0.51) > RR (n=46; 0.30) > XX (n=28 (0.18) *Endurance:* RX (n=59; 0.32) > RR (n=59; 0.32) > XX (n=47; 0.26) *Sprint:* RX (n=41; 0.49) > RR (n=37; 0.45 > XX (n=5; 0.06) - hiqhly significant differences in ACTN3 genotypic frequencies between elite sprint athletes and controls, with the frequency of the XX genotype approximately threefold lower in sprint athletes compared to controls, and more than four- fold lower in sprinters compared to endurance athletes Endurance (n=183) > Control (n=152) > Sprint (n=83) - the endurance group displayed a higher frequency of the XX genotype than controls, but this difference was not statistically significant	case controll trial
Yang, N. et al.	2003	- white elite athletes at Australian international level (n=429): 14 different sports: - elite Sprint athletes (n=107) men (n=72) & women (n=35); - endurance athletes (n=194) (122 men (n=122) & women (n=72); - 128 athletes were excluded; - 436 unrelated white controls (150 blood	- genotype analysis by log-linear modeling approach (described by Hutley & Wilson)	**1.) Body composition:** controls (n=436): RX 226(52) > RR 130(30) > XX 80(18) sprint (n=107): RR 53(50) > RX 48(45) > XX 6(6) endurance (n=194): RX88(45) > RR 60(31) > XX 46(24) *men:* controls (n=134): RX 73(54) > RR 40(30) > XX 21(16) sprint (n=72): RR 38(53) > RX 28(39) > 6(8) endurance (n=122): RX 63(52) > RR 34(28) > XX 25(20) *women:* controls (n=292): RX 147(50) > RR 88(30) > XX 57(20) sprint (n=35): RX 20(57) > RR 15(43) > XX 0(0) endurance (n=72): RR 26(36) > RX 25(35) > XX 21(29) Allele frequencies: contr: X 44% R 56% sprint: X 28% R 72% endu: X 46% R 54%	cross-sectional study

		donors, 71 healthy children, 215 healthy adults): men (n=134) & women (n=292)		*men:* contr: X 43% R 57% sprint: X 28% R 72% endu: X 46% R 54% *women:* contr: X 45% R 55% sprint: X 29% R71% endur: X 47% R 53% **2.) Effects on genotype:** - genotype profiles of control group did not differ (x^2= 0.19;P= .996) - no significant allele or genotype frequency differences between elite athlete group as whole and controls - subset of athletes in sprint and endurance showed strong evidence of allele frequence variation (x^2=23;P=.001) - significant allele frequency differences between sprint & controls for both m (x^2==14.8;P<.001) & f (x^2=7.2;P<.01) - sprint < XX (6% vs. 18%); no f sprint and Olympians were XX - sprint > RR (50% vs. 30%) & < RX (45% vs. 52%) compared with controls - Endurance > XX (24%) than controls (18%) - allele frequencies in sprint & endurance deviated in opposite directions and differed from each other in both m (x^2=13.3; P<.001) & f (x^2=5.8;P=<.05) 8.) f sprint > RX than RR (20 vs. 15) & f endurance RX < RR (25 vs. 26); nor effect in m - f endurance RX < than f controls (35% vs. 50%) - ACTN3 577R allele provides advantage for power & sprint athletes	
Li-Ling Chiu et al.	2005	259 elite Taiwanese olympic game level athletes from 19	- genotype analysis by PCR-RFLPon exon 16 (577R had	**1. Body composition:** IND (n=125) (RR+RX) 107(86) > RX 66(53) > RR 41(33) > XX 18(14)	cross-section study

		different sports classified in - individual sports (IND) men (n=71) & women (n=54) -team sports (TEAM) men (n=62) & women (n=72) - controls (n=603) (CON) Taiwanese general population men (n=361) & women (n= 242)	205 and 85 bp fragments, 577X PCR had 108, 97 and 85 bp fragments)	Allele fregencies: X 102(41) R148(59) men (n=71) (RR+RX) 59(83) > RX 37(52) > RR 22(31) > XX 12(17) Allele frequencies: X 61(43) R81(57) women (n=54) (RR+RX) 48(89) > RX 29(54) > RR 19(35) > XX 6(11) Allele frequencies: X 41(38) R67(62) TEAM (n=133) (RR+RX) 99(74) > RX 63(47) > RR 36(27) > XX 34(26) Allele frequencies: X 131(49) R135(51) men (RR+RX) 50(81) > RX 33(53) > RR 17(27) > XX 12(19) Allele frequencies: X 57(46) R 67(54) women (n=71) (RR+RX) 49(69) > RX 30(42) > RR 19(27) > XX 22(31) Allele frequencies: X 74(52) R 68(48) CON (n=603) (RR+RX) 485(80) > RX 294(49) > RR 191(32) > XX 118(20) Allele frequencies: X 530(44) R676(56) men (n=361) (RR+RX) 299(83) > RX 182(50) > RR 117(32)> XX 62(17) Allele frequencies: X 306(42) R 416(58) women (n=242) (RR+RX) 186(77) > RX 112(46) > RR 74(31) > XX (56(23) - no linkage association in genotypes of ACTN3 and ACE genes in CON - distribution of ACTN3 and ACE genotypes not sign. diff. between athletes and CON. - Females had significantly lower ($p<.05$) frequency of ACTN3 577X genotype in IND (11%) compared to CON (23%) and TEAM (31%).	

				- non of athletes exhibited both ACTN3 577XX and ACE DD genotypes	
Niemi A.-K. & Majamaa, K.	2005	- finnish elite track & field athletes (n=141) (endurance athletes n=52, sprinters n=89) including 3 pairs of twins (endurance athletes n=2, sprinters n=1) & 5 pairs of siblings (endurance n=1, sprinters n=1); - anonymous Finish control subjects (n=1060); subgroup of top athletes (endurance n=20, sprinters n=23)	- MtDNA haplogroup & subhaplogroup analysis	**1.) Body composition:** top endurance: RR 10(50%) > RX 7(35%) > XX 3(15%) endurance: RR 20(50%) > RX 16(40%) > XX 4(10%) control: RX 55(~46%) > RR 54(45%) > XX 11(~9%) sprinter: RR 35(~51%) > RX 27(~40%) > XX 6(~9%) top sprinter: RX 12(~52%) > RR 11(~49%) **2.) Effects on genotype** - frequencies of mtDNA haplogroups differed between endurance & sprint (P=0.039) - frequencies of haplogroups J & K > among sprinters - none endurance belonged to haplogroup K, frequency of haplogroup K was 9.0% in sprinters - none endurance belonged to haplogroup J2 - 4 endurance belonged to haplogroup I, but none of the sprinters - spinters: < frequency of 577XX genotype & < 577RR than endurance (stratisfied in subsets= inverse correlation) - association between haplogroup J & longevity (subhaplogroup J2 more frequent in very ald than among controls - haplogroup K is associated with longevity	cross-sectional study
Lucia, A. et al.	2006	102 Caucasian (European ancestry) elite endurance	- genotype analysis by EDTA - Vo2max	**1.) Body composition:** controls: RR: 28.5%; RX: 53.6% and XX:17.9% cyclists: RR: 28.0%; RX: 46.0% and XX: 26.0%	case-controll trial

		athletes: - unrelated male spanish top- level cyclists (n=50) age: 26.9 +/- 0.4 - Olympic- class spanish male middle-distance runners (n=52) age: 26.8 +/- 0.6 yrs - control group of healthy, sedentary, unrelated male Caucasians (n=123) (European descent) age: 19- 50	- VE - ventilatory equivalent for oxygen & carbon duioxide - endtidal partial pressure of oxygen & carbon dioxide	runners: RR: 25.0%; RX: 57.7%; XX: 17.3% - distribution frequency of R and X alleles similar in the 3 groups Allele frequencies: controls: X= 44.7% R=55.3%; cyclists: X= 49% R=51%; runners: X=46.1% R=53.9% - all 3 genotypes were present in 7 cyclists who finished Tour Vuelta or Giro in top-3 position - no sign. diff. found in Vo2max, VT & RCT between RR, RX & XX within groups - no differences were found in indices of endurance performance (VO2peak or ventilatory thresholds) between athlete carriers of each R577X genotype.	
Paparini, A. et al.	2007	Caucasian males (n=144): - unrelated healthy subjects from northern, central & southern Italy (n=102), - Italian endurance athletes (n=42) (rowing at Olympic level)	- real-time PCR genotyping of R577X & Q 523R plymorphisms, verified by traditional PCR-RFLP approach	**1.) Body composition:** ACTN3Q523R: *male athletes (n=42):* RQ 25(59.52) > QQ 9(21.43) > RR 8(19.05) Allele frequencies: Q 0.51 R 0.49 *male controls (n=102):* RQ 48(47.06) > QQ 31(30.39) > RR 23(22.55) Allele frequencies: Q 0.54 R 0.46 ACTN3R577X: *male athletes (n=42):* RX 25(59.52) > RR 9(21.43) > XX 8(19.05) Allele frequencies: X 0.49 R 0.51 *male controls (n=102):* RX 48(47.06) > RR 32(31.37) > XX 22(21.57) Allele frequencies: X 0.45 R 0.55	case-controll trial

				2.) Effects on genotype: - haplotype distribution confirmed the presence of linkage disequilibrium between the polymorphisms, both in the Italian general population and athletes (respectively: x^2 = 54.4, P<0.001 & x^2 = 24.5, P<0.001) - no sign. diff. in haplotype distributions between controls & athletes (X=1.323; P<1) - controls: homozygous subjects (21.6%) was deficient for Actn3. No significant differences were observed in athletes (19.05%) - concordance between PCR-RFLP and real-time PCR results was 100 and 93% for polymorphisms Q523R and R577X	
Saunders, C. J. et al.	2007	- Caucasian male triathletes (n=457) who completed South African Ironman - 3 subgroups based on performance: Fast Triath (n=152), Mid Triath (n=152) & Slow Triath group (n=153), - healthy Caucasian male controls (n=143) from Cape Town area	- genotype analysis by EDTA vacutainer tube, - age - height - weight - BMI - overall time - swim time - bike time - run time - south africanborn	**1.) Body composition:** *frequency of 577XX genotype in fastest triathletes:* RR 35.5% RX 47.4% RX 17.1% *frequency of R577X genotypes in fastest triathletes:* RR31% RX 45% RX 24% **2.) Effects on genotype:** - fast group sign. younger, weighted less & had lowest BMI - no sign. diff. in genotype (P=0.486) or allele frequencies (P=0.375) within fastest, middle or slowest & control group - no sign. linear trend for distribution between the 4 groups (P=0.091) - no genotype effects on any physiological variable nor the split & overall performance - no association of the R577X polymorphism with endurance performance	case-controll trial
Yang, N. et al.	2007	- East African cohort (n=198) - Ethiopian controls:	- genotype analysis (buccal swab samples, TaqMan	**1.) Body composition** <u>*Ethiopians:*</u> *general control (n=105):*	case-controll trial

		general Ethiopian (n=105), Arsi province (n=93) - Ethiopian elite endurance athletes (n=76) - Kenyan controls (n=158) - Kenyan elite endurance runners (n=284) - Nigerian cohort (n=120): 60 controls & 62 power athletes	SNP Assay)	RR 46(44 = RX 46(44) > XX 13(12) Allele frequencies: X 72(34) R138(66) *Arsi control (n=93):* RX 47(50) > RR 37(40) > XX 9(10) Allele frequncies: X 65(35) R 121(65) *total control (n= 198):* RX 93(47) > RR 83(42) > XX 22(11) endurance runners (n=76): RR 35(46) = RX 35(46) > XX 6(8) Allele frequencies: X 47(31) R 105(69) <u>*Kenyans*</u>: *control (n=158):* RR 133(84) > RX 23(15) > XX 2(1) Allele frequencies: X 27(9) R 286(91) *endurance runners (n=284):* RR 212(75) > RX 69(24) > XX 3(1) Allele frequencies: X 75(13) R 493(87) <u>*Nigerians:*</u> *control (n=60):* RR 50(83) > RX 10(17) > XX 0(0) Allele frequencies: X 75(13) R 493(87) *power athletes (n=62):* RR 54(87) > RX 8(13) > XX (0) Allele frequencies: X 8(6) R 116(94) *Japanese (n=97):* RX 57(59) > XX 23(24) > RR 17(17) **2.) Effects on genotype:** - XX: absent in Nigerians, extremely low in Kenyans (~1%), higher in Ethiopians (11%) - Japanese > XX (24%) in line with other Asian - Ethiopian endurance athletes did not differ from general	

				population (P=0.69) or Arsi region ((P=0.72) - Kenyan endurance differ from Kenyan control group (P=0.036) tendency towards differences in genotype frequency (P=0.063) - endurance: no increase in XX, exces of heterozygotes (24%), deficiency of homozygotes relative to controls (15%) - sign. diff. in X allele female Kenyan athletes compared to conrols (P=0.09) - no differences between Nigerian control subjects & Nigerian power athletes (P=0.62) - α-actinin-3 deficiency is not a major influence on performance in African athletes	
Ahmetov, I. et al.	2008	- Russian endurance-oriented athletes (n=456) (regional or national competitive standard) - 4 subgroups: highly elite (n=30) elite (n=90) sub-elite (n=105) average (n=222) - associations between genotype & data from Russian Cup Rowing Tournament: highly & elite athletes (n=54) & female rowers (n=20); 1211	- genoype analysis (mouthwash samples, PCR digested with BstDEI) - data from Rusian Cup Rowing Tournament	**1.) Body composition:** *totals (n=456):* RX 55 > RR 39.3 > XX 5.7 (P< 0.0001) Allele frequencies: X 33.2 R 66.8 men (n=293): RX 52.9 > RR 40.3 > XX 6.8 (P<0.01) Allele frequencies: X 33.3 R 66.7 women (n=163): RX 58.9 > RR 37.4 > XX 3.7 (P<0.01) Allele frequencies: X 33.1 R 66.9 *biathlon (n=40):* RX 55 > RR 42.5 > XX 2.5 (P=0.1) Allele frequencies: X 30 R 70 *cc skiing (n=98):* RX 49 > RR 45.9 > XX 5.1 (P=0.019) Allele frequencies: X 29.6 R 70.4 *race walking (n=21):* RX 52.4 > RR 33.3 > XX 14.3 (P=0.95)	case-controll trial

		controls: men (n=532) & women (n=679) (citizens from Russia)		Allele frequencies: X 40.5 R 59.5 *road cycling (n=34):* RX 52.9 > RR 47.1 > XX 0 (P=0.049) Allele frequencies: X 26.5 R 73.5 *rowing (n=187):* RX 62.6 > RR 32.1 > XX 5.3 (P=0.0002) Allele frequencies: X 36.6 R 63.4 *swimming 0.8- 25 km (n=42):* RR 52.4 > RX 30.9 > XX 16.7 (P=0.059) Allele frequencies: X 32.1 R 67.9 *triathlon (n=34):* RX 64.7 > RR 35.3 > XX 0 (P=0.038) Allele frequencies: X 32.3 R 67.7 *controls (n=1211):* RX 49 > RR 36.5 > XX 14.5 (P=1.00) Allele frequencies: X 39 R 61 *men controls (n=532):* RX 47 > RR 36.3 > XX 16.7 Allele frequencies: X 40.2 R 59.8 *women controls (n=679):* RX 50.6 > RR 36,7 > XX 12.7 Allele frequencies: X 38 R 62 **2.) Effects on genotype:** - biathletes (P=0.034), cross-country skiers (P=0.0097) road cyclists (P=0.01), rowers (P=0.0003) & triathletes (P=0.01): < XX compared to controls (14.5%) - none of highly elite athletes had XX (P=0.016) (XX < in elite, subelite & average athletes) - ACTN3 genotype distribution in men & women sign. diff. compared to men & women controls, XX under-represented in both sexes compared to controls (men: 6.8% vs. men	

				controls: 16.7%; P<0.0001; women: 3.7% vs. women controls 12.7%; P=0.0004) Association study: - from 54 rowers, only 3 had XX (showed the slowest rowing times compared to RX & RR) - no significant differences in competition results of RR & RX	
Drzhevskaya, A. M. et al.	2008	- power-oriented male & female athletes (n= 486) subdevided in highly elite, elite, sub-elite & average - 1,197 healthy unrelated controls of Moscow	genotype analysis from mouthwash samples	**1.) Body composition:** athletes: RX 53.9 > RR 39.7 > XX 6.4 (P=0.0001) Allele frequencies: X 33.3 R 66.7 (P=0.004) men: RX 55.9 > RR 37.7 > XX 6.4 (P=0.0001) Allele frequencies: X 34.3 R 65.7 (P=0.021) women: RX 48 > RR 45.5 > XX 6.5 (P=0.067) Allel frequencies: X 30.5 R69.5 (P=0.034) controls: RX 49 > RR 36.8 > XX 14.2 Allele frequencies: X 38.7 R 61.3 men: RX 46.8 > RR 36.8 > XX 16.4 Allele frequencies: X 39.8 R 60.2 women: RX 50.7 > RR 36.8 > XX 12.5 Allele frequencies: X 37.8 R 62.2 - < XX (6.4 vs. 14.2%; P<0.0001) & X allele (33.3 vs. 38.7%; P=0.0004) in athletes compared to controls **2.) Effects on genotype:** - decreasing linear trend of XX with increasing athlete level - X allele frequencies in men (34.3 vs. 39.8%; P=0.021) &	case-controll trial

				women (30.5 vs. 37.8%; P=0.034) were different to controls - XX underrepresented in both sexes compared to controls (men: 6.4 vs. 16.4%; P<0.0001; women: 6.5 vs. 12.5%; P=0.067)	
Muniesa A. C. et al.	2008	- nonathletic controls (n=123) - professional cyclists (n=50) - Olympic-class runners (n=52) - World-class rowers (n=39) (medalists in the World championships, lightweight category).	- power – endurance sport - genotype analysis by EDTA	**1.) Body composition:** rowers: RX 43.6% > RR 33.3% > XX 23.1% cyclists: RX 46% > RR 28% > XX 26% runners: RX 57.7% > RR 25% > XX 17.3% controls: RX 53.7% > RR 28.5% > XX 17.9% **2.) Effect on genotype:** - no sign. genotype distributions; ACE < (P<0.05) in rowers (10.3%) than in total (22.3%)	case-controll trial
Papadimitriou et al.	2008	- elite Greek track & field athletes (n=101) men (n=73) & women (n=28) at international level – 2 subgroups of power & endurance athletes - unrelated healthy Caucasian Greek controls (n=181)	- genotype analysis	**1.) Body composition:** *power athletes (n=73):* RR 47.49 > RX 35.62 > XX 16.44 (P<0.02) Allele frequencies: X 34.2 R 65.8 *sprinters (n=34):* RR 73.53 > RX 17.65 > XX 8.82 (P<0.001 compared with con) Allele frequencies: X 17.6 R 65.8 *endurance (n=28):* RR 50> RX 25 & XX 25 Allele frequencies: X 37.5 R 62.5 *controls (n=181):* RX 55.8 > RR 25.97 > XX 18.23 Allele frequencies: X 46.1 R 53.9 **2.) Effects on genotype:**	case-controll trial

				- Differences in frequencies of alleles (p=0.017) & genotypes (p=0.016) between elite power & controls - power had lesser frequency of X than controls (more prominent in sprinters) - all Olymic/European-level-sprinters had at least 1 R allele (None had XX) - sprinters: < XX (8.82% vs. 18.23%) & > RR (73.53% vs. 25.97%) (P=0.0001) - increased XX in elite endurance group compared to sprinters & control - Olympic/European endurance level had RR 57% - no sign. diff. in frequencies of alleles (p=0.252) or genotypes (p=0.238) between endurance & controls or between power & endurance for allele & genotype comparisons	
Roth, S. M. et al.	2008	- black & white elite bodybuilders & strength athletes (n=75) predominantly male - control group of 2 subgroups (n=876): white group (n=668) men (n=363) & women (n=305) black group (n=208) men (n=98) & women (n=110) age: 19 - 90 - Baltimore longitudinal Study of	- genotype analysis	**1.) Body composition:** *athletes:* RX 62.6 > RR 30.7 > XX 6.7 (P=0.005) *control:* RX 45.6 > RR 38.1 > XX 16.3 *white athletes:* RX 65.4 > RR 25.0 > XX 19.9 (P=0.018) *white controls:* RX 47.5 > RR 32.6 > XX 19.9 *black athletes:* RX 56.5 > RR 43.5 > XX 0 (P=0.10) *black controls:* RR 55.8 > RX 39.4 > XX 4.8 **2.) Effects on genotype:** - deviation in total athletes (P=0.001), white athletes (P=0.01) & black athletes (P=0.06)	case-controll trial

		Aging		- no sign frequency differences between m & w within controls - athletes: < XX (6.7%) compared to controls (16.3%; P=0.005) - XX < in white athletes (9.7%) compared to controls (19.9%; P=0.018) - no black athlete with XX - no differences in allele frequency between bodybuilders & powerlifters - controls: > RR compared to athletes	
Santiago, C. et al.	2008	- male elite soccer players (n=60) age: 17-32; participating in the spanish first (n=18), second (n=27) and third division (n=15); Vast majority (96.7%) of Caucasian origin-Spanish (91.7%) & non-Spanish European (5%); - 102 Spanish world-class male endurance athletes (n=102) age: 19-38: 50 professional cyclists and 52 Olympic-class runners; - Control group of	- genomic DNA extracted from peripheral EDTA treated anticoagulated blood obtained according to standard phenol/chloroform procedures followed by alcohol precipitation	1.) RR (48.3%) & RX (36.7%)in soccer players significantly different from controls RR (28.5%) & RX (53.7%) and endurance athletes RR (26.5%) & RX (52%) (p=0.041); - % distribution of the R and X alleles in soccer players tended to be significantly different from the other two groups (p=0.061) - elite soccer players tend to have the sprint/power genotype	case-controll trial

		123 healthy sedentary Spanish males (n=123) age: 19-50			
Gomez-Gallego, F. et al.	2009	- elite male professional road cyclists (n=46) age: 26-28 - healthy sedentary men as controll group (n=46) age: 35-42 - spanish descent for >3 generations	- genotype analysis by EDTA ACE & ACTN3 as independent factor & age & body mass as covariates - Vo2max - PPO - VT - RCT - GE & DE	Cyclists: **1.) Body composition:** (RR+RX) (n=35) > XX (n=11) **2.) Effect on muscle:** - XX < PPO (0.035) < VT (0.029) < RCT (0.001) & sign. effect on covariate body mass (0.001) - sign. “combined genotype” (ACE+ACTN3) for PPO (p=0.004, power=0.916; VT (p=0.007, power=0.871) & RCT (p<0.001, power=1.000) - sign. covariate effects: PPO for age: p=0.01, power=0.959 PPO for body mass: p=0.016, power=0.697 VT for body mass: p=0.003, power=0.880 RCT for age: p=0.034, power=0.580 RCT for body mass: p<0.001, power=1.000 - Post hoc: strong/power genotype (DD+RR/RX) similar RCT endurance (II+XX) sign.> vs. intermediate (II+RR/RX; p=0.036) & (DD+XX; p=0.004) - no sign. differences in controls	cross-section study

Tabelle 3: ACTN3 Athletics without intervention

Author	Year	Probands	Parameters	Intervention	Results	Level of evidence
Kostek, M. C. et al.	2005	Caucasian men (n=32) & women (n=35) age: 52- 83	- genotype analysis by RT-PCR for IGF-I (192bp) & SNP - body composition - total FFM - 1- RM of knee-extensors before & after - MV - MQ	- 3 times/ week 5 sets (<75yrs) or 4 sets(>75yrs) of unilateral knee extension exercise of dominant leg (5 rep increased continously until 10 rep) for 10 weeks - shortening phase: ~2s lengthening phase: ~3s - rest periods: 30, 90, 150, 180s - untrained leg in relaxed position	**1.) Body composition:** *total:* 192/- 34(51) > 192/192 24(36) > -/- 9(13) *men:* 192/- 18 > 192/192 10 > -/- 4 *women:* 192/- 16 > 192/192 14 > -/- 5 192/192 men: n=10 women: n=14 192/- men: n=18 women: n=16 -/- men: n=4 women: n=5 **2.) Effects on muscle:** - IGF-I promoter groups: no significant differences in age, height, body mass, %body fat or FFM at baseline or training response 192 carriers sign. > 1-RM strength (67.3+/-6.3 N) than nonacarriers (39.8+/-7.6 N) covaried for sex & age ($P<0.05$) - no sign. diff. between 192 homozygotes & nonhomozygotes for change in 1-RM - MV & MQ increased in all groups after exercise ($P<0.01$) - no sign diff. in MV & MQ at baseline & after in IGF1 promoter genotype groups covaried for sex & age - 192 homozygote not sign. diff. from heterozygote & noncarriers	randomised controlled trial

Hand, B. D. et al.	2007	black (n=12) & white (n=46) men (n=58) & black (n=21) & white (n=49) women (n=70) age: 50- 85	- genotype analysis by EDTA - 1-RM before & after ST - body composition, -FFM - MV at baseline & after ST - MQ at baseline & after ST	- unilateral knee extension strength training of dominant leg 3 times/week for 10 weeks - untrained leg in relaxed position	**1.) Body composition:** *IGF1 CA Promoter Gene Polymorphism:* *total:* 192/- 63(49) > 192/192 39(30) > -/- 26(20) Allele frequencies: 192 141(55) - 115(45) *white:* 192/- 47(49) > 192/192 34(36) > -/- 14(15) Allele frequencies: 192 115(61) - 75(39) *black:* 192/- 16(48) > -/- 12(36) > 192/192 Allele frequencies: 192 26(39) - 40(61) - sign. diff. between races in allele frequencies ($P<0.05$) *IGFBP3 A-202C Promoter Gene Polymorphism:* *total:* A/C 62(48) > A/A 33(26) = C/C 33(26) Allele frequencies: A 128(50) C 128(50) *white:* A/C 46(48) > C/C 27(28) > A/A 22(23) Allele frequencies: A 90(47) C 100(53) *black:* A/C 16(48) > A/A 11(33) > C/C 6(18) Allele frequencies: A 38(58) C 28(42) *PPP3RI 5-bp I/D Promoter Gene Polymorphism:* *total:* I/I 100(78) > I/D 27(21) > D/D 1(1) Allele frequencies: I 227(89) D 29(11) *white:* I/I 82(86) > I/D 13(14) > D/D 0(0) Allele frequencies: I 177(93) D 13(7) *black:*	randomised controlled trial

					I/I 18(55) > I/D 14(42) > D/D 1(3) Allele frequencies: I 50(76) D 16(24) - sign. differences between races in allele frequencies (P<0.001) **2.) Effects on muscle:** - men: sign. > 1-RM (33+/-1.0) than women (22+/-1.0) & greater increase: men (41+/-1.2) & women (27+/-1.2) -. men: sign. > MV (1.770+/-34) than women (1,330+/-38) - men sign. > MQ (18.8+/-0.56) than women (16.2+/-0.63) - blacks: sign. > MV at baseline (1.589+/-39) than whites (1.380+/-31) - blacks: sign. > MQ increase (20.7+/-0.062) than whites (19.4+/-0.46) - change in strength influenced by combination of gene polymorphisms for IGF-I CA repeat main effects & IGF-I CA repeat X PPP3R1 I/D interaction effects - IGF1: combined effect: 3.46= 1.22 + ½ (4.48) (P<0.01) - IGFBP3: combined effect: 4.84= 2.83 + ½ (4.02) (P>0.05) - PPP3RI: combined effect: 2.27=0.03 + ½ (4.48) (P>0.05) - combined gene effect for IGF-I CA repeat influenced strength & MQ responses to ST IGF1: combined effect: 3.71= 0.95 + ½ (5.54) (P<0.05) PPP3RI: combined effect: 2.99 = 0.22 + ½ (5.54)	

					(P>0.05) - contribution to %variability attributable to IGF-I CA repeat X PPP3RI I/D interaction was ~4.5% & 5.5% - no combined effects for PPP3RI I/D - sign. difference between PPP3RI I/D genotype groups - no sign. influence of IGFBP-3 A202C gene polymorphism on muscle phenotypic responses to ST	

Tabelle 4: IGF-I Nonathletics with intervention

<table>
<tr><th>Author</th><th>Year</th><th>Probands</th><th>Parameters</th><th>Intervention</th><th>Results</th><th>Levels of evidence</th></tr>
<tr><td>Devaney, J. M. et al.</td><td>2007</td><td>men (n=73) & 78 women (n=78) age: 22-30</td><td>- genotype analysis 4,7 & 10 days postexercise
- MVC
- blood sample
- CK activity
- Mb concentration;</td><td>- 50 max isotonic eccentric contractions of elbow flexor of nondominant arm</td><td>
<table>
<tr><th>Gene</th><th>SNP</th><th>Homozygous Wild Type</th><th>Heterozygous</th><th>Homozygous rare allele</th><th>Allele Frequency Wild T.</th><th>Allele Frequency Rare</th></tr>
<tr><td>IGF-II</td><td>C16646T</td><td>135 (87.1%,CC)</td><td>19 (12.3%CT)</td><td>1 (0.6%TT)</td><td>0.932</td><td>0.068</td></tr>
<tr><td>IGF-II</td><td>G13790C</td><td>69 (44.2%GG)</td><td>58 (37.2%GC)</td><td>29 (18.6%CC)</td><td>0.628</td><td>0.372</td></tr>
<tr><td>IGF-II</td><td>T13705C</td><td>153 (99.3%TT)</td><td>1 (0.7%TC)</td><td>0 (CC)</td><td>0.997</td><td>0.003</td></tr>
<tr><td>IGF-II</td><td>G12655A</td><td>70 (45.4%GG)</td><td>60 (39.0%GA)</td><td>24 (15.6%AA)</td><td>0.649</td><td>0.351</td></tr>
<tr><td>IGF-II</td><td>G17200A</td><td>89 (54.6%GG)</td><td>56 (34.4%GA</td><td>18 (11.0%TT</td><td>0.718</td><td>0.282</td></tr>
<tr><td>IGFBP-3</td><td>A8618T</td><td>85 (56.7%AA)</td><td>50 (33.3%AT)</td><td>15 (10.0%TT)</td><td>0.733</td><td>0.267</td></tr>
<tr><td>IGFBP-3</td><td>-C1592A</td><td>111 (70.3%CC)</td><td>42 (28.0%CT)</td><td>5 (3.2%AA)</td><td>0.835</td><td>0.165</td></tr>
<tr><td>IGF-I</td><td>-C1245T</td><td>103 (65.6%CC)</td><td>44 (28.0%CT)</td><td>10 (6.4%TT)</td><td>0.796</td><td>0.204</td></tr>
<tr><td>IGF2AS</td><td>A1364C</td><td>55 (36.2%AA)</td><td>68 (44.7%AC)</td><td>29 (19.1%CC)</td><td>0.586</td><td>0.414</td></tr>
<tr><td>IGF2AS</td><td>G11711T</td><td>45 (27.8%GG)</td><td>75 (46.3%GT)</td><td>42 (25.9%TT)</td><td>0.509</td><td>0.491</td></tr>
<tr><td>INS</td><td>C1045G</td><td>106 /65.5%CC)</td><td>46 (28.4%CG)</td><td>10 (6.17%GG)</td><td>0.796</td><td>0.204</td></tr>
</table>
- no sig. Associations of phenotypes with IGF-I
- IGF-II SNP & IGFBP-3 SNP not associated with any variable - men: IGF-II, IGF-II antisense & IGFBP-3 SNP sign. associated with muscle damage
- homozygous rare IGF-II C13790G allele & rare allele ApaI (G17200A) SNP > strength loss immediately after exercise, >soreness & > postexercise serum CK activity
- homozygous wild type IGF2AS > strength loss & > muscle soreness
- homozygous wild type IGF2AS SNP> strength loss, > muscle soreness, > CK & myoglobin response to exercise
</td><td>cohort study</td></tr>
</table>

Tabelle 5: IGF-II Nonathletics with intervention

Author	Year	Probands	Parameters	Results	Level of evidence
Sayer, A. A. et al.	2002	men (n=397) & women (n=296) average age: 67.5	- genotype analysis - blood sample - grip strength - self-reported walking speed	**1.) Body composition:** *genotype array:* *men:* GG 202 > GA 162 > AA 33 *women:* GG 168 > GA 112 > AA 16 *mean(sd):* *men:* GA 39.1(6.9) > AA 38.4(5.6) > GG 37.5(7.3) *women:* GA 23(5.3) > GG 22.3(5.5) > AA 21.7(4) *mean grip strength according to bw & genotype:* *men < 112:* AA 38.4(4.9) > GA 38.1(5.9) > GG 34.9(8.1) *men =128:* GA 39.5(7) > GG 38.6(6.9) > AA 36.3(4.3) *men > 128:* AA 40.9(7.1) > GA (39.8(7.6) > GG 39.1(6.1) *women <112:* GG 22.3(5.8) > GA 22.2(5) > AA 20.2(3.2) *women =128:* AA 24.4(5.7) > GA 22.8(5.9) > GG 21.7(5.7) *women >128:* GA 25.1(4.3) > GG 23.2(5.8) > AA 22.7(2.1) **2.) Genotype interactions:** - grip strength sign. associated with gender, age, height, weight & self-reported speed (P<0.05) - strongest correlates of adult grip strength:age (men: r=-0.18;P=0.0003 & women: r=-0.19;P=0.0007)	cohort study

				- height > weight in men (r=0.29;P=0.0001) & women (r=0.20;P=0.0007) - birth weight sign. corr. with adult weight in women - IGF2 not associated with height, weight - birth weight > GG men & women (not sign.) - GG associated with lower IGF-II levels - IGF.II not associated with adult grip strength in men & women - univariate analyses: grip strength in men associated with IGF2 genotype (P=0.05) & birth weight (P=0.04) after ádjustment age & current height - IGF2 & birth weight simultaneously in men: sign. to grip strength allowing for age & adult height	
Schrager, A. et al.	2004	Baltimore longitudinal study: Cohort 1: men (n=94) age: 22-80 Cohort 2: men (n=246) & women (n=239) age: 20-94	- genotype analysis of IGF2 ApaI - Cohort1 (1960 -1985): isometric grip strength & SP - Cohort2 (1992 -2002): FFM & isokinetik peak tourque - 1-A arm power - 4-A arm power - BMI - LTPA	**1.) Body composition:** *genotype array:* *Cohort1: men:* GG 49 > GA 32 > AA 13 Allele frequencies: G 69.1% A 30.9% *Cohort2:* *total:* GG 238 > GA 190 > AA 57 Allele frequencies: G 68.7% A 31.3% *men:* GG 119 > GA 95 > AA 32 *women:* GG 119 > GA 95 > AA 25 *FFM, strength & power by IGF2 genotype & gender in cohorts 1 & 2 at age 35:* *men:* GA 55.1+/-1.6 > GG 54.6+/-1.3 > AA 54.1+/-2.4 **2.) Genotype interactions:**	cohort study

				- cohort 1: no sign. differences among genotype groups for levels of strength or SP at first visit - AA men sign. < isokinetic arm PTs than GG men (P<0.05) - AA women sign. < isokinetik Arm PTs & PTl than GG & GA women (P<0.05) - homozygous comparing: G/G women (age 35) > total FFM > isokinetic arm PTs & PTl & leg PTs (maintained at age 65) - no sign. association in change in grip strength, SP & aging with IGF2 ApaI genotype - men in cohort 1: grip strength: A/A < 3.7%, G/A < 2.6% & G/G < 1.7% SP: A/A < 7.5% G/A < 4.4% G/G < 3.3% per decade - cohort 2: G/G > loss in FFM than A/A	

Tabelle 6: IGF-II Nonathletics without intervention

Author	Year	Probands	Parameters	Intervention	Results	Level of evidence
Ferrell, R. E.	1999	- Caucasian (n=96) & African American (n=96) from general population - additional 72 subjects screened for exon 2 variant - men (n=127): African American (n=32) , Caucasian (n=91) & Asian (n=4) - women (n=26): African American (n=9), Caucasian (n=16) & Asian (n=1) (WC dybulider top 100 n=18, competititive bodybuilder top 100 n=25, elite power lifters n=7, university football players n=9, untrained subjects n=33, nonathletes n=61)	- genotype analysis by EDTA - general population: sequencing of myostatin gene regions & genotyping of common variants - subjects: categorized by increase in muscle mass from strength training - MV -FFM - questionnaire about ability to increase muscle mass (5=>400cm³, 0=no increase)	- 9 weeks of heavy resistance strength training of knee extensor	**1: Body Composition:** *Caucasians Exon 1 (A55T)* n=167: Ala/Ala (n=155) > Ala/Thr (n=12) > Thr/Thr (n=0) Allele frequencies: p(Ala)=0.964 q(Thr)=0.036 *Caucasians Exon2(K153R)* n=96: Lys/Lys (n=88) > Lys/Arg(n=7) > Arg/Arg (n=7) Allele frequencies: p(Lys)=0.963q(Arg)=0.037 *African Americans Exon 1 (A55T)* n=96: Ala/Ala (n=75) > Ala/Thr (n=19) > Thr/Thr (n=2) Allele frequencies: p(Ala)=0.880 q(Thr)=0.120 *African Americans Exon 2(K153R*) n=93: Lys/Lys (n=66) > Lys/Arg (n=24) > Arg/Arg (n=3) Allele frequencies: p(Lys)=0.839 q(Arg)=0.161 **2. Effect on strength training:** - muscle mass response to strength training is not signifficantly influenced by variation at the myostatin locus - no sign. impact in muscle mass response to strength training in either Caucasians or African Americans	case-controll trial

Ivey, F. M. et al.	2000	- 11 young men age: 20-30 - 11 young women age: 20-30 - 12 older men age: 65-75 - 11 older women age: 65-75	- genotype analysis - CSA - 1-RM - MV via MRI (before & after ST & detraining)	- 9-week unilateral ST program of knee extensor of dominant leg 3 times/week: 5 sets: set 1: 5 rep at 50% 1-RM, set 2: 5 rep at increased 5-RM value set 3: 10 rep (first 4 or 5 rep at 5-RM value) set 4: 5 rep at 5-RM & 10 more rep, set 5: 5 rep at 5-RM & 15 more rep; resting periods: 30, 90, 150 & 180 s - 31 weeks detraining period	**1.) Body composition:** n= 32: men n=18 & women n=14 **2.) Effect on muscle** - men > MV than women - no significant difference in MV response to ST between young & older - loss of absolute MV after 31 weeks of detraining: men > women, but no sign difference young & old - only women analyzed: less common myostatin allele > (68%) MV in response to ST	randomised controlled trial
Thomis M. et al.	2004	- Twins from Leuven Twin & Training Study (n=25 pairs) - age: 17-30	- Study 1: genotype-dependent similarity in training responses - Study 2: genotype x training interaction (pre & posttraining) - 1RM - muscle cross-sectional are	- 5 sets of biceps curls 3 times/week for 10 weeks set1: 14 rep 60% 1RM, set2: 12 rep 75% 1RM, set3: 10 rep 80% 1RM, set4: 8 rep 85% 1RM, set5: 5 rep 70% 1RM	- all measurements increased sign. - 1 subject carrier of K/R - no training response phenotypes	randomised controlled trial

Tabelle 7: Myostatin Nonathletics with intervention

Author	Year	Probands	Parameters	Results	Level of evidence
Seibert, J. E. et al.	2001	WHAS II study: - women (n=286) age: 70-79 88.1% Caucasian, 18.8% African American, 0.2% Asian or Hispanic	- overall strength by dynamometer defined as the sum of the strongest measures of hip, knee, and grip strength on the dominant side - BMI	**1. Body Composition:** African American: K/K (n=39) > K/R (n=13) > R/R (n=3) Allele frequencies: Caucasians (0.02) < African Americans (0.05) Nla III; (0.07) Hae III and (0.17) ApaI polymorphism Caucasian: K/K (n=225) > K/R (n=6) > R/R (n=0) Combined: K/K (n=264) > K/R (n=19) > R/R (n=3) **2. Effect on muscle strength:** suggested lower muscle strength in those African-American women: < muscle strength in R than K (K/K: 72.50+/-13.9 kg (n=39) vs K/R: 67.14+/-11.4 kg (n=13) vs R/R: 63.1+/-11.3 kg (n=3) adjustment for race in a linear regression model: R < strength levels (P=.04) (sign. decreased when BMI & race added (P=.09).	case-controll trial
Corsi, A. M. et al.	2002	InCHIANTI project: - men (n=189) and women (n=261) - of Italian population - mean age +/- standard deviation 69.5+/- 15.2, range 22-96;	genotype analysis by EDTA - isometric strength in eight muscle groups by handheld dynamometer -	- 6 heterozygous & 1 homozygous for K153R - 153R allele associated with lower muscle strength (155R +: 18.8 +/- 2.2 kg; 153R-: 26.5 +/- 1 kg; P=0.5 - not sagnificant after adjusting for age new missense single-nucleotide variation at codon 185, with a G to C substitution	randomised controlled trial

				implicating the change of an arginic residue with a threonine	
Huygens, W. et al.	2004	- male Caucasian sibs (n=329) from 146 families (sib-pairs n=115, trios n=25, quads n=6) age: 17-36 - nonactive	- genotype analysis by EDTA - muscle mass - maximal concentric knee strength - linkage patterns between knee extension & flexion peak tourque with markers - skinfold - cross- sectional muscle & bone area	- only two estimated muscle cross-sectional areas marginally linked	randomised controlled trial

Tabelle 8: Myostatin Nonathletics without intervention

6 Results

6.1 Types of included studies

All studies published before April 2009 and related to the role of genetic polymorphisms on anaerobic phenotype were identified. The initial search identified 122 matches of which 82 were discarded as not containing genome-wide linkage data. The literature selected was published between 1999 and 2009.

The search for ACTN3 gene yielded 5 studies for “nonathletics with intervention”. The levels of evidence subdevide this group in: 1 randomised controlled trial from Sweden (Norman, B. et al., 2009) and 4 cross-section studies evaluated in Belgium (Vincent, B. et al., 2007), and in the USA (Clarkson, P. M.et al., 2005; Clarkson, P. M.et al. 2005; Delmonico, M. J. et al., 2007).

The category of ACTN3 “nonathletics with intervention” consists of 5 studies: 2 randomised controlled trials from USA (Walsh, S. et al., 2008) and Spain (San Juan, A. F. et al., 2006), 2 cohort studies participated in USA (Delmonico et al., 2008) and UK (McCauley T. et al., 2008) and 1 cross- section study was held in Greece (Moran C. E. et al., 2007).

The highest output of 15 studies found refer to ACTN3 and “athletics without intervention”. This group consists of 12 case-controll trials. 3 of these studies were established in Spain (Santiago, C. et al., 2008; Lucia, A. et al., 2006; Muniesa, A. C. et al., 2008), 1 in Italy (Paparini, A. et al., 2007), 1 in Greece (Papadimitriou, I. D. et al., 2007) 1 in Taiwan (Li-Ling Chiu et al., 2005), 2 in Russia (Ahmetov, I. et al., 2008; Drzhevskaya, A. M. et al., 2008), 1 in South Africa (Saunders, C. J. et al., 2007), 1 in the USA (Roth, M. S. et al., 2008), 2 in Australia (MacArthur D. G. et al., 1999; Yang, N. et al., 2007). 3 cross-section studies were evaluated in Australia (Yang, N. et al., 2003), Spain (Gomez-Gallego, F. et al., 2009) and Finland (Niemi A.-K & Majamaa, K., 2005).

Fewer studies than expected were found for IGF-I “nonathletics without intervention” (2 randomised controlled trials). Both studies were developed in the USA (Kostek, M. C., 2005; Hand, B. D. 2007).

The IGF-II group consists of two cohort studies also investigating “nonathletics without intervention”. 1 of these studies was examined in the UK (Sayer, A. A. et al., 2002) and the other in the USA (Schrager, : A. et al., 2004). Only one study was found for IGF-II with association to trainings intervention in nonathletics (Devaney, J. M. et al., 2007)

The myostatin gene is determined by “nonathletics with intervention” (2 randomized controlled trials and 1 case-controll trial) and the “nonathletics without intervention” group (2 randomised controlled trials and 1 case- controll trial). Investigations on the “nonathletics with intervention” group took place in the USA (Ivey, F. M. et al., 2000; Ferrell, R. E., 1999) Italia (Corsi, A. M. et al., 2002) and Belgium (Thomis M. et al., 2004). Myostatin was observed for “nonathletics without intervention” in the USA (Seibert, J. E. et al., 2001) and Belgium (Huygens, W. et al., 2004).

The athletics mostly took part in individual kinds of sports like alpine – skiing (Drzhevskaya, A. M. et al., 2008), bodybuilding (Drzhevskaya, A. M. et al., 2008; Roth, S. M. et al., 2008), Cross-country skiing (Yang, N. et al., 2003), cycling (Gomez-Gallego, F. et al., 2009; Muniesa A. C. et al., 2008; Santiago, C. et al., 2008), endurancerunning (Lucia, A. et al., 2006; MacArthur D. G. et al., 1999; Niemi A.-K. et al., 2005; Santiago, C. et al., 2008; Yang, N. et al., 2003; Yang, N. et al., 2007; Zanoteli, E. et al., 2003), figureskating (Drzhevskaya, A. M. et al., 2008), ice-hockey (Drzhevskaya, A. M. et al., 2008), powerlifting (Drzhevskaya, A. M. et al., 2008; Yang, N. et al., 2007), ski jumping (Drzhevskaya, A. M. et al., 2008), speedskating (Drzhevskaya, A. M. et al., 2008), sprinting (Yang, N. et al., 2003), swimming (Yang, N. et al., 2003), track & field (Niemi A.-K., 2005; Papadimitriou et al., 2008; Yang, N. et al., 2003), triathlon (Saunders, C. J. et al., 2007), weighlifting (Drzhevskaya, A. M. et al., 2008) and wrestling (Drzhevskaya, A. M. et al., 2008) as well as teamsport: rowing (Ahmetov, I. et al., 2008; Paparini, A. et al., 2007; Yang, N. et al., 2003), soccer (Santiago, C. et al., 2008) and volleyball (Li-Ling Chiu et al., 2005). Interestingly, the ACTN3 gene is the only gene observed for Athletics and the subjects did not obtaine exercise intervention. The ACTN3 gene x exercise intervention has also been found in 5 studies with nonathletic cohorts.

Exercise interventions included concentric, eccentric and isometric strength training of knee extensor (6 studies) and arm elbow flexor muscle (4 studies). Interventions ranged from 9 to 12 weeks. Most studies required 10 weeks of knee extensor resistance training (Vincent, B. et al., 2007; Norman, B. et al., 2009, Delmonico, M. J. et al., 2007; Hand, B. D. et al., 2007; Kostek, M. C. et al., 2005). 2 studies had 9 weeks knee extensor resistance

training intervention (Ivey, F. M. et al., 2000; Ferrell, R. E., 1999). The study of Clarkson, P. M.et al. (2005) observed relative strength loss, blood creatin kinase and myoglobin concentration four, seven and ten days after eccentric exercise of the arm elbow flexor. The same research group investigated 12 weeks of elbow flexor and elbow extensor resistance training in association with genotype analysis. Training interventions of the arm elbow flexor were also available in a Twin study held by Thomis M. et al. (2004) and in the study of Devaney, J. M. et al. (2007).

6.2 Types of excluded studies

Limits were set on the search including: published in english, human studies and the exclusion of reviews. The search included different levels of evidence therefore the selected studies are of different quality.

Most of the interests relate to ACTN3 gene and the influence on athletic performance. Pubmed offered 31 potentially relevant trials in context to genotype and anaerobic muscle performance (Abb. 7). Two potentially appropriate syrves later turned out to be reviews so that in summary 3 reviews were excluded (MacArthur, D. G. & North, 2004; North, 2008; North et al., 1999). 1 animal study was also excluded (MacArthur, D. G. et al., 2008). 3 clinical trials examined genotype and McArdles desease interaction (Gonzalez- Freire, M. et al., 2009; Lucia, A. et al., 2007; Rubio, J. C. et al., 2007). North K. N. et al. (1996) described defficiency of α-actinin-3 in merosin-positive congenital muscular dystrophy. Vainzof, M. et al. (1997) observed the defficiency of ACTN3 in different forms of muscluar dystrophy such as limbe-girdle MD, sarcoglycanopathies and Duchenne MD. The survey of Yngvadottir, B. et al. (2009) on human nonsense SNPs and the survey of Luzia, A. et al. (2007) did not include genotype data. Finally one excluded study was published in Russian (Krakhmaleva, I. N. et al., 2005). By hand searching the reference lists, 6 additional trials were found (Himanshu, G. et al., 2007; MacArthur, D. G. et al., 1999; Moran, C. N. et al., 2007; Li-Ling Chiu et al., 2005; San Juan, A. F. et al., 2006; Yang, N. et al., 2007). These leads to a final result of 27 included studies. The study of Himanshu, G. et al (2007) was also found by hand search but later excluded because the study observed gene prevalence in North India without relation to muscle phenotype.

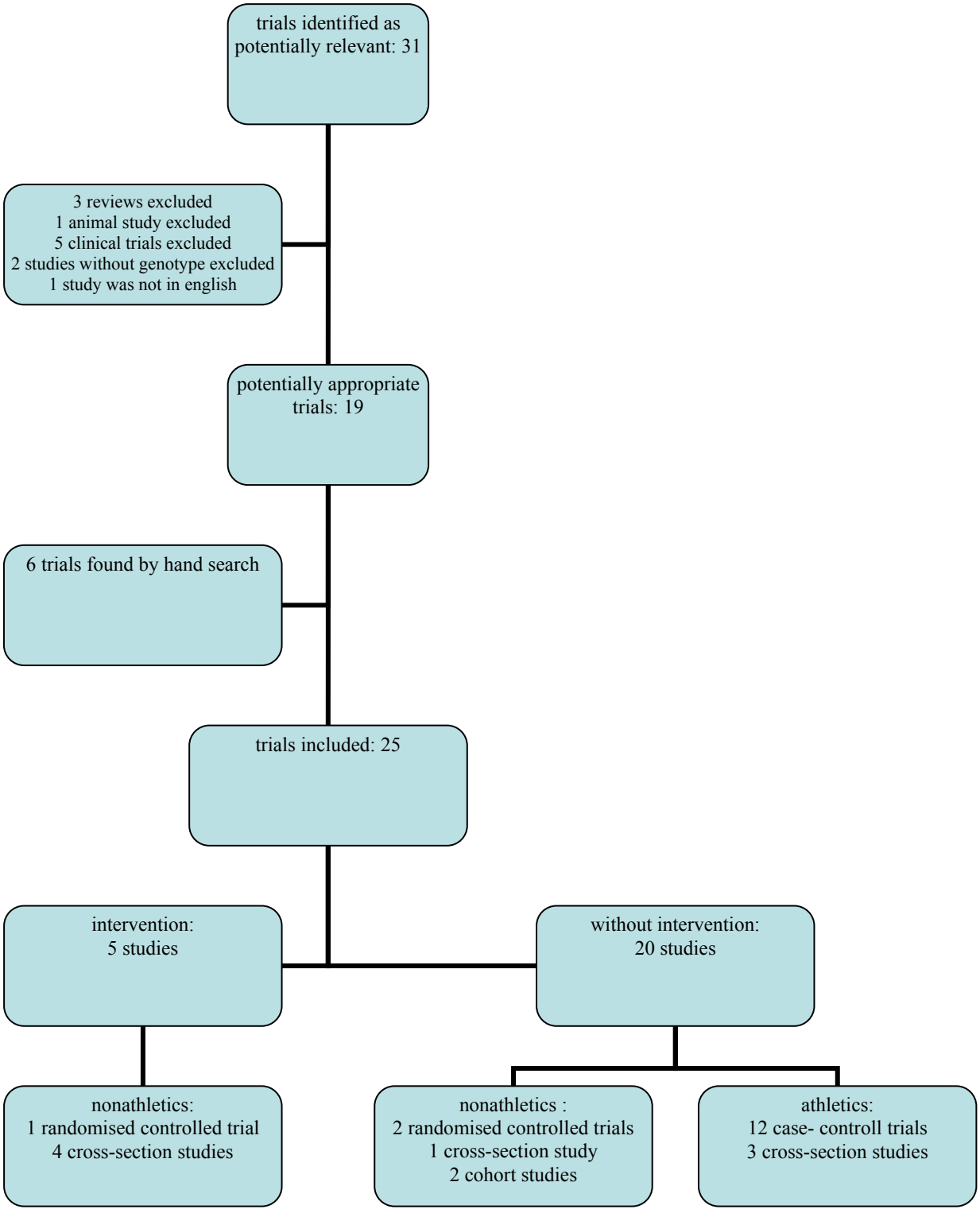

Abbildung 7: Systematic search strategy for “(ACTN3 OR R577X) AND genotype” in PubMed.

The IGF-I gene search delivered the most potentially relevant trials and the most clinical trials excluded (Abb. 8). The clinical trials observed acidosis (Janziszak, K. et al., 1998), acromegalie (Bianchi, A. et al., 2009; Bogazzi, F. et al., 2002; Mecardo, M. et al., 2008; Mendoza, V. et al., 2005; Mulatero, P. et al., 2006), Alzheimer (Kranzler, J. H. et al., 1998; Mustafa, A. et al., 1999; Rivera, E. J. et al., 2005), cancer (Al-Zahrani, A. et al., 2006; Bågeman, E. et al., 2007; Bianchi, A. et al., 2008; Birmann, B. M. et al., 2009; Brokaw, J. et al., 2007; Bustin, S. et al., 2001; Canzian, F. & Mckay, J. D., 2005; Canzian, F. et al., 2005; Caruso-Nicoletti, M. et al., 1992; Chen, C. et al., 2006; Chen, X. et al., 2008; Cheng I. & Stram D. O., 2006; Cheng, I. et al., 2006; Chia, F. M. et al., 2008; Chiang, D. Y. et al., 2008; Chokkalingam, A. P. et al., 2001; Chu, L. W. et al., 2008; Cleveland, R. J. et al., 2006; DeLellis, K. et al., 2003; Diorio, C. et al., 2008; Dossus, L. et al., 2008; Esteban, F. et al., 2008; Fall, K. et al., 2008; Fan, J. et al., 2006; Figer, A. et al., 2002; Friedrichsen, D. M. et al., 2005; Gonzalez-Zuloeta Giovannucci, E. et al., 2002; Ladd, A. M. et al., 2007; Hadsell, D. L. et al., 2001; Han, S. G. et al., 2008; Hong, C. C. et al., 2003; Hong, C. C. et al., 2004; Hudelist,G. et al., 2007; Jernström, H. et al., 2001; Jernström, H. et al., 2005; Jernström, H. et al., 2006; Johansson , M. & McKay, J. D. et al., 2007; Johansson, M. et al., 2007; Kelemen, L. E. et al., 2008; Khoury-Shakour S. et al., 2008; Lai, J. H. et al., 2004; Le Marchand, L. et al., 2005; Lembessis, P. et al., 2003; Li, H. et al., 2007; Li, L. et al., 2004; Li, Z. Q. et al., 2007; Luporini, S. M. et al., 2001; Maor, S. et al., 2007; Majeed, M. et al., 2005; McKay, J. D. et al., 2007; Missmer, S. A. et al., 2002; Moore, S. C. et al., 2009; Morimoto, L. M. et al., 2005; Mu, L. et al., 2008; Natrajan, R. et al., 2006; Patel, A. V. etal., 2008; Pechlivanis, S. et al., 2007; Reeves, S. G. et al., 2008; Rosmond, R. et al., 2000; Sarma, A. V. et al., 2008; Schernhammer, E. S. et al., 2003; Schildkraut, J. M. et al., 2005; Siahpush, S. H. et al., 2007; Silha, J. V. et al., 2006; Slattery, M. L. et al., 2004; Slattery, M. L. et al., 2005; Slattery, M. L. et al., 2007; Slattery, M. L. et al., 2008; Sonntag, W. E. et al., 2005; Streicher, K. L. et al., 2007; Suzuki, H. et al., 2008; Taboada, G. F. et al., 2007; Tamimi, R. M. et al., 2007; Theiss, A. L. et al., 2005; Tilli, M. T. et al., 2005; Tsuchia, N. et al., 2005; Voskuil, D. W. et al., 2004; Voskuil, D. W. et al., 2008; Wagner, K. et al., 2004; Wagner, K. & Hemminki, K., 2005; Wagner, K. et al., 2005; Wagner, K. et al., 2006; Wagner, K. et al., 2007; Weber, M. S. et al., 2000; Wen, W. et al., 2005; Wong, H. L. et al., 2005; Wong, H. L. et al., 2008; Zang, J. et al., 2008; Yang, X. F. et al., 1996; Yu, H. et al., 2001; Zhang, X. et al., 2007; Zhang, H. et al., 2009), cardiovascular desease (Bleumink, G. S. et al., 2004; Bleumink, G. S. et al., 2005; Boquist;

S. et al., 2008; Cheng, J. et al., 2008; Hietaniemi, M. et al., 2005; te Velde, S. J. et al., 2005; Jimeno, L. et al., 2005; Ukkola, V. et al., 2008; Ruigrok, Y. M. et al., 2005; van Houten, V. A. et al., 2008; van Duyvenvoorde, H. A. et al., 2008; Yazdanpanah, M. et al., 2006), dementia (Garcia, J. et al., 2006) diabetes (Almind, K. et al., 1999; Buongiorno, A. M. et al., 2007; Cama, A. et al., 1992; Dozio, N. et al., 1995; Eerligh, P. & Frayling, T. M. et al., 2002; Eerligh, P. et al., 2004; Heath, K. E. et al., 2008; Hittmeier, L. J. et al., 2006; Hovind, P. etal., 2007; Kido, Y. et al., 2002; Koeleman, B. P. et al., 2004; Landmann, E. et al., 2006; Longo, N. et al., 1992; Nielsen, E. M. et al., 2004; Peeters, R. P. et al., 2005; Rietveld, I. et al., 2006; Rosmond, R. et al., 2002; San Milan, J. L. et al., 2004; Shimokawa, I. et al., 2003; Stephens, R. H. et al., 2005; Uthra, S. et al., 2007; Vaessen, N. et al., 2001; Vella, A. et al., 2008; Vigoroux, C. et al., 1997; Wortley, K. E. et al., 2005; Yazdanpanah, M. et al., 2006), dysplasia (Kwinta, P. et al., 2008), growth hormone defficiency (Abuzzahab, M. J. et al., 2003; Adamis, D. et al., 2007; Bandmann, O. et al., 1997; Barbosa, E. J.et al. 2009; Barrenas, M. et al., 2000; Behmel, A. et al., 1988; Binder, G. et al., 1999; Binder, G. et al., 2003; Binder, G. et al., Bonafe, M. et al., 2003; Bozzola, M. et al., 1989; Carrascosa, A. et al., 2008; Chen, X. et al., 2003; Cheng, I. et al., 2007; Costalonga, E. F. et al., 2009; Cotterill, A. M. et al., 1998; Coutinho; D. C. et al., 2007; Desai, M. P. et al., 2005; Ealey; K. N. et al., 2008; Fang, P. et al., 2007; Ferreira, L. V. et al., 2005; Ferreira, L. V. et al., 2007; Fielder, P. J. et al., 1991; Fielder, P. J. et al., 1992; Grill, J. D. et al., 2005; Guevara-Aguirre, J. et al., 2007; Gleeson, H. et al., 2007; Gloria-Bottini, F. et al., 1994; Goddard, A. D. et al., 1997; Hale, D. E. etal., 2000; Hayashida, C. Y. et al., 2000; Henningson, M. et al., 2007; Hess, O. et al., 2007; Johnston, L. B. et al., 1999; Kaji, H. et al., 1997; Kay, D. C. et al., 2008; Höybye, C. et al., 2003; Höybye, C. et al., 2004; Höybye, C. et al., 2005; Ibáñez, L. et al., 2002; Joseph, M. et al., 1996; Jörge, A. A. et al., 2004; Kallio, J. et al., 2001; Kaspar, B. K. et al., 2005; Kawashima, Y. et al., 2005; Kennedy, M. J. et al., 2008; Kiess, W. et al., 2005; Kionshita, Y. et al., 2007; Ko, J. M. et al., 2009; Laron, Z. et al., 1989; Laszmezas, C. et al., 1993; Lettre, G. et al., 2007; Limal, J. M. et al., 2006; Maheshwari, H. G. et al., 1998; Marzullo, P. et al., 2002; Masala, A. et al., 2003; Meyer, S. et al., 2007; Meyer, S. et al., 2008; Morimoto, L. M. et al., 2005; Naves, L. A. et al., 2007; Okubo, Y. et al., 2004; Pantel, J. et al., 2003; Raile, K. et al., 2006; Ransome, M. I. et al., 2008; Roldan, M. B. et al., 2007; Sanchesz, J. E. et al., 1998; Schmid, C. et al., 2007; Sen, F. et al., 2008; Sjoberg, M. et al., 2001; Tauber, M. T. et al., 1998; Toyoshima, M. T. et al., 2007; van der Klaauw, A. A. et al., 2008; Vivenza, D. et al., 2004; Wasserstein, M. P. et al., 2003; Walenkamp, M. J. et al., 2006; Walenkamp, M. J. et

al., 2007; Walker, J. F. et al., 1998; Walton-Betancourth, S. et al., 2007; Wan, L. et al., 2007; Woods, K. A. et al., 1997; Zankl, A. et al., 2000; Zimmermann, A. et al., 2007) leprechaunism (Jospe, N. et al., 1996; Takahashi, Y. et al., 1997), osteoporosis (Baroncelli, G. I. et al., 1999; Bezzera, F. F. et al., 2008; Brenner, R. E. et al., 1993; Côté G. et al., 2007; Dresdner Pollack, R. et al., 2000; Garnero, P. et al., 2005; Kim, J. G. et al., 2002; Lakatos, P. L. & Bajnok, E. et al., 2004; Lakatos, P. L. et al., 2004; Lee, D. O. et al., 2008; Mersebach, H. et al., 2007; Meulenbelt, I. et al., 1998; Miyao, M. et al., 1998; Pereira, R. C. & Stadmeyer, 2006; Pereira, R. C. et al., 2006; Rivadeneira, F. et al., 2003; Rivadeneira, F. et al., 2004; Rosen, C. J. et al., 1998; Sheu, Y. T. et al., 2006; Takacs, I. et al., 1999; Wang, Y. et al., 2006; Wright, N. M. et al., 1996; Zhai, G. et al., 2004), pregnancy (Bajoria, R. et al., 2001; Choi, J. S., 2009; Day, I. N. et al., 2002; Fehringer, G. et al., 2008; Harrington, S. C. et al., 2007; Johnston, L. B. et al., 2003; Rivadeneira, F. et al., 2006; Setiawan, V. W. et al., 2006; Twickler, T. B. et al., 2002; Vaessen, N. et al., 2002; van der Vorm, E. R. et al., 1993), retinopathie (Balogh, A. et al., 2006; Dunai, G. et al., 2008; Ramocki; N. M. et al., 2008; Rietveld, I. et al., 2006), silver- russel syndrom (Binder, G. et al., 2006; Binder, G. et al., 2008), schizophrenia (Moises, H. W. et al., 2002; Perrin, M. A. et al., 2007) and thyroid dysfunction (Chen, A. C. et al., 2004; Kursunluoglu R. et al., 2009).

The following 169 animal studies were excluded: Adams, N. R. et al., 2000 ; Alb, M. et al., 2005; Alt, J. A. et al., 2003 ; Amador-Noguez, D. et al., 2005; Amills, M. et al., 2003 ; Andrade, P. C. et al., 2008; Anisimov, V. N. et al., 2004 ; Anzo, M. et al., 2008 ; Beamer, W. G. et al., 2000 ; Beccavin, C. et al., 1999 ; Beccavin, C. et al., 2001 ; Behl, R. et al., 2006 ; Behringer, R. R. et al., 1990 ; Bennett, A. K. et al., 2006 ; Bessone, S. et al., 1999 ; Bian, L. H. et al., 2008; Bikle, D. D. et al., 2002 ; Boge, A. et al., 1995 ; Camarero, G. et al., 2001 ; Cao, Y. et al., 1995 ; Casas-Carrillo, E. et al., 1997 ; Chagnon, M. J. et al., 2006 ; Chakravarty, G. et al., 2003 ; Chandrashekar, V. et al., 2007 ; Chase, C. C. et al., 1998 ; Chase, K. et al., 2005 ; Corva, P. M. et al., 2000 ; Coschigano, K. T. et al., 2000 ; Coschigano, K. T. et al., 2003 ; Curi, R. A. et al., 2005; Da Silva, A- et al., 2009 ; Danilovich, N. et al., 1999 ; Daugaard, J. R. et al., 1998 ; Daugaard, J. R. et al., 1999 ; Davis, M. E. et al., 2000 ; Day, J. K. et al., 2001 ; de Lima, A. R. et al., 2007 ; D`Ercole, A. J. et al., 1994 ; Desbois-Mouthon, C. et al., 2006 ; Dewil, E. et al., 1999 ; De Cola, G. et al., 1997 ; Dierkes, B. et al., 2000 ; Doublier, S. et al., 2000 ; Doublier, S. et al., 2001 ; Dozmorov, I. et al., 2001 ; Ealey, K. N. et al., 2008 ; Eckstein, F. et al., 2002 ; Elchebly,

M. et al., 1999 ; Elzaouk, L. et al., 2003 ; Estany, J. et al., 2007 ; Femiano, P. et al., 2005 ; Fiorotto, M. L. et al., 2003 ; Flyvbjerg, A. et al., 1992 ; Fournier, M. & Lewis, M. I. et al., 2000 ; García-Tornadú, I. et al., 2006 ; Gardan, D, et al., 2008 ; Garigan, D. et al., 2002 ; Gao, W. Q. et al., 1999 ; Gao, X. et al., 2006 ; Ge, W. et al., 2001 ; Ge, W. et al., 2002 ; Goddard, C. et al., 1996 ; Gonzalez, E. et al., 2003 ; Gore, M. T. et al., 1994 ; Grégoire, F. M. et al., 1995 ; Grochowska, R. et al., 2001 ; Guernec, A. et al., 2003 ; Hansen, P. J. et al., 2007 ; Harada, N. & Okjima, K., 2007 ; Harada, N. et al., 2007 ; Harper, J. M. et al., 2003 ; Hausman, G. J. et al., 1991 ; Hausman, G. J. et al., 1992 ; Herman, A. C. et al., 2004 ; Harper, C. E. et al., 2007 ; Hirose, Y. et al., 2004 ; Hoeflich, A. et al., 1999 ; Holland, M. D. et al., 1997 ; Høj, S. et al., 1993 ; Huybrechts, L. M. et al., 1987 ; Jenet, A. et al., 2006 ; Johnson, K. R. et al., 2007 ; Khan, A. S. et al., 2003 ; Kadowaki, T. et al., 1996 ; Katoh, K. et al., 2008 ; Kim, M. H. et al., 2004 ; Klindt, J. et al., 1992 ; Klindt, J. et al., 1995 ; Lee, Y. H. et al., 1997 ; Lei, M. et al, 2007 ; Lei, M. et al., 2008; Leininger, M. T. et al., 2000 ; Li, C. et al., 2004 ; Li, M. H. et al., 2006 ; Li, J. Q. et al., 2003 ; Liu, J. L. et al., 1998 ; Liu, J. P. et al., 1993 ; Liu, Z. et al., 2008; Longobordi, S. et al., 2000 ; Ma. et al., 2008; Macrae, V. E. et al., 2009; Mai, V. et al., 2003 ; Masternak, M. M. et al., 2005 ; McCampbell, A. S. et al., 2008; Medrano, J. F. et al., 1991 ; Meyer, C. W. et al., 2004 ; Michaylira, C. Z. et al., 2006 ; Mitchell, R. D. et al., 1995 ; Miller, R. A. et al., 2002 ; Moerth, C. et al., 2007 ; Moody, D. E. et al., 1996 ; Moore, T. et al., 2008; Morel, P. C. et al., 1994 ; Mostyn, A. et al., 2006 ; Movérare, S. et al., 2003 ; Naar, E. M. et al., 1991 ; Nagaraja, S. C. et al., 2000 ; Pausová, Z. et al., 2003 ; Peng, X. D. et al., 2003 ; Phatsara, C. et al., 2008; Pugliese, G. et al., 1997 ; Ramsey, M. M. et al., 2002 ; Rieusset, J. et al., 2004 ; Rogler, C. E. et al., 1994 ; Rosenberg, L. A. et al., 2006 ; Rowland, J. E. et al., 2005 ; Salih, D. A. et al., 2004 ; Sawczenko, A. et al., 2005; Schuenke, M. D. et al., 2008; Shefi-Friedman, L. et al., 2001 ; Shimokawa, I. et al., 2002 ; Shuldiner, A. R. et al., 1990 ; Simmen, F. A. et al., 1990 ; Spence, S. L. et al., 2006 ; Sperandeo, M. P. et al., 2007 ; Spicer, L. J. et al., 1993 ; Spicer, L. J. et al., 2002 ; Stefaneanu, L. et al., 1999 ; Sun, L. Y. et al., 2005; Sun, J. et al., 2006 ; Sutter, N. B. et al., 2007; Symons, A. L. et al., 2003 ; Tagami, M. et al., 1999 ; Tamemoto, H. et al., 1994 ; Tesseraud, S. et al., 2003 ; Tixier-Boichard, M. et al., 1990 ; Tixier-Boichard, M. et al., 1991 ; Tomas, F. M. et al., 1991 ; van de Loo, F, A. et al., 1998 ; van de Ven, M. et al., 2006 ; Vasilatos-Younken, R. et al., 1997 ; Vicario-Abejón, C. et al., 2004; Vidal, O. et al., 2000 ; Wang, B. et al., 2009 ; Whisnant, C. S. et al., 1998 ; Woitge, H. W. et al., 2000 ; Wu, G. Q. et al., 2007 ; Yamashita, K. et al., 2001 ; Yilmaz, A. et al., 2004; Zaczek, D. et al., 2002 ; Zhang, M. et

al., 2002 ; Zhang, Y. et al., 2008; Zhao, X. F. et al., 2007; Zigman, J. M. et al., 2005; Zhong, J. et al., 2002 ; Zhou, H. et al., 2005; Zhou, J. et al., 2000 ; Zinovieva, N. et al., 1998.

35 reviewes were also excluded: Bonjour, J. P. et al., 2007; Brauer, V. F. et al., 2004; Camacho- Hübner, C. et al., 2001; Dagogo- Jack, S. et al., 2001; DePrimo, S. E. et al., 2001; Druckmann, R. et al., 2002; Dunger, D. et al., 2002; Dumitrescu, R. G. & Cotarla, I., 2005; Edouard, T. et al., 2008; Eisman, J. A. et al., 1999; Franceschi, C. et al., 2005; Gennari, L. et al., 2001; Hansen, P. J., 2007; Hansen, P. J., 2007; Heald, A. et al., 2006; Higaki, Y., 2000; Holmström, G. et al., 2007; Holly, J. M. et al., 1999; Ichinose, K. et al., 2007; Jiang, M. et al., 2004; Kang, D. et al., 2003; Kelemen, L. E., et al., 2008; Lea, R. G. et al., 1991; Lewinski, A. & Wojciechowska, K., 2007; Miedlich, S. et al., 2001; O`Dell, S. D. et al., 1998; Patalano, A. et al., 2009; Patel, A. C. et al., 2004; Rosenbloom, A. L. et al., 2000; Sandhu, M. S. et al., 2005; Spector, T. D. et al., 2004; Wagner, K. et al., 2007; Walenkamp, M. J. et al., 2008; Woods, K. A. et al., 1999; Yamada, H. et al., 2005).

In some studies genotype data was missing (Backström, M. C. et al., 2001; Blümel, P. & Mullis, P. E., 2001; Buckway, C. K. et al., 2001; Buckway, C. K. et al., 2002; Cadoret, A. et al., 2005; Dahlen, G. H. et al., 1994; dÀlesio, A. et al., 2005; David, A. et al., 2007; Däpp, C. et al., 2006; Espinos, C. et al., 2008; Fenton, J. I. et al., 2008; Finkeltov, I. et al., 2002; Frayling, T. M. et al., 2002; Guo, H. et al., 2008; He, J. et al., 2007; Hernandez, M. I. et al., 2008; Holzenberger, M., 2004; Jernström, H. et al., 2006; Kelley, K. W. et al., 2004; Kofoed, E. M. et al., 2003; Kojima, T. et al., 2004; Li, Q. et al., 2008; McColl, G. et al., 2005; Meyer, S. et al., 2009; Oliver, W. T. et al., 2005; Pantsulea, I. et al., 2005; Palles, C. et al., 2008; Platz, E. A. et al., 1999; Rietveld, I. et al., 2003; Rietveld, I. et al., 2004; Rowland, J. E. et al., 2005; Slattery, M. L. et al., 2005; Suh, Y. et al., 2008; Takada, D. et al., 2003; Tran, N. et al., 2004; Voorhoeve, P. G. et al., 2006; Walenkamp, M. J. et al., 2005; Willcox, B. J. et al., 2008; Yilmaz, A. et al., 2005; Zafon, C. et al., 2003; Zaoh, J. et al., 2007).

Studies excluded because of no IGF-I genotype content were: Abrahamsen, B. et al., 2006; Blum, W. F. et al., 2006; Carrascosa, A. et al., 2006; Devaney, J. M. et al., 2007; Hansen, J. A. et al., 1997; Inanlou, M. R. et al., 2005; Lichtenauer, U. D. et al., 2007; Lida, K. et al., 1998; Oliveira, H. A. et al., 2003; Olney, R. C. et al., 2006; Patterson, J. L. et al., 2002; Pereira, R. M. et al., 2007; Ravio, T. et al., 1996; Rosenbloom, A. L. et al., 1998; Rouard, M. et al., 1997; Schreiner, F. et al., 2007; Syed, F. A. et al., 2005;

Finally, one study was published in french (Savage, M. O. et al., 1998) and two studies did not relate to an effect on muscle phenotype (DÀloisio, A. A. et al., 2009; Kato, I. et al., 2003).

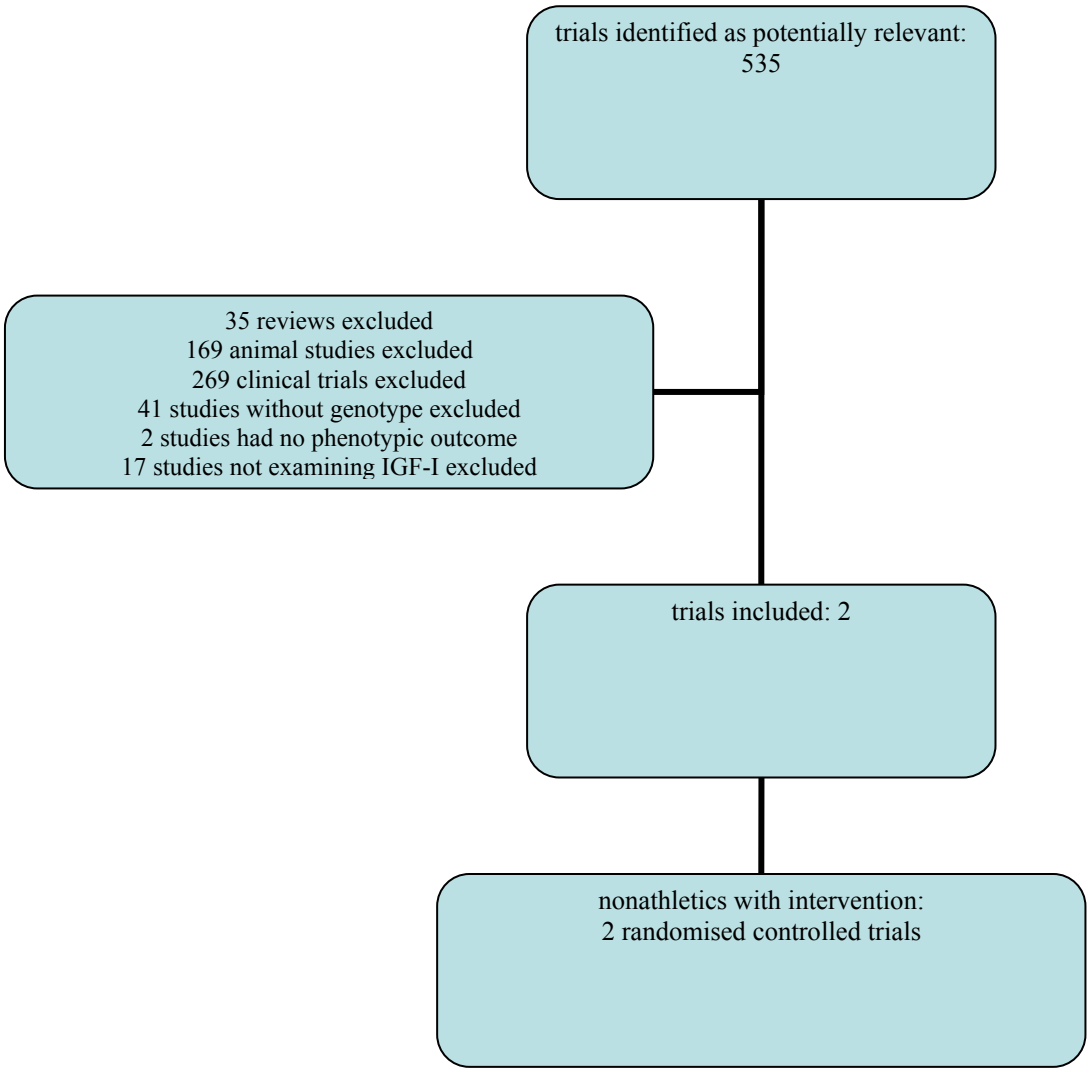

Abbildung 8: Systematic search strategy for "(IGF-I OR IGF-1) AND genotype" in PubMed

The IGF-II search delivered 267 appropriate publications (Abb. 9). But only a few accomplished the inclusion criterias. 67animal studies were excluded (Ainscough, J. F. et al., 1997; Amills, M. et al., 2003; Andrade, P. C. et al., 2008; Anisimov, V. N. et al., 2004;

Beccavin, C. et al., 1999; Beccavin, C. et al., 2001; Bennett, S. T. et al., 1996; Braunschweig, M. H. et al., 2004; Burns, J. L. et al., 2007; Cadoret, A. et al., 2005;; Casola, S. et al., 1996; Charalambous, M. et al., 2003; Constância, M. et al., 2005; Corcoran, R. B. et al., 2008; Crossey, P. A. et al., 2002; DeChiars, T. M. et al., 1990; Denhardt, D. T. et al., 1991; DÈrcole, A. J. et al., 1994; Dewil, E. et al., 1999; Dikkes, P. et al., 2007; Dindot, S. V. et al., 2004; Duselis, A. R. et al., 2007; Dittmer, F. et al., 1998; Estelle, J. et al., 2005; Flisikowski, K. et al., 2007; Frank, D. et al., 2002; Gardan, D. et al.,2008; Gardner, R. L. et al., 1999; Goodall, J. J. et al., 2007; Gore, M. T. et al., 1994; Haddad, R. et al., 1997; Han, R. H. et al., 2008; Harper, J. et al., 2006; Hausman, G. J. et al., 1991; Hoeflich, A. et al., 1999; Holland, M. D. et al., 1997; Høj, S. et al., 1993; Kadlecova, M. et al., 2008; Kadowaki, T. et al., 1996; Kido, Y. et al., 2002; Kim, M. H. et al., 2004; Klindt, J. et al., 1992; Klindt, J. et al., 1995; Kolaríková, O. et al., 2003; Leighton, P. A. & Ingram, R. S., 1995; Leighton, P. A. et al., 1995; Li, E. et al., 1993; Liu, G. L. et al., 2003; Liu, J. P. et al., 1993; Ludwig, T. et al., 1994; McCampbell, A. S. et al., 2008; Macrae, V. E. et al., 2009; Moerth, C. et al., 2007; Nezer, C. et al., 2003; Nolan, C. M. et al., 1999; Ojeda, A. et al., 2008; Pravtcheva, D. D. et al., 1998; Ripoche, M. A. et al., 1997; Rohbe, L. et al. 2004; Rogler, C. E. et al., 1994; Schmidt, J. V. et al., 1999; Schori, H. et al., 2007; Smith, J. et al., 2000; Sperandeo, M. P. et al., 2007; Szabo, P. E. et al., 1996; Tamemoto, H. et al., 1994; Tesseraud, S. et al., 2003; Todoka, N. et al., 2000; Van den Magdenberg, K. et al. 2004; Van den Magdenbergg, K. et al., 2007; Wanderling, S. et al., 2007; Wang, G. et al., 2005; 2008; Wise, T. L. et al., 1997; Zaina, S. et al., 2003; Zaina, S. et al., 1998; Zechner, U. et al., 2002).

Most of the excluded studies were clinical trials: Algar, E. et al., 2000; Awata, T. et al., 1997; Bachner-Melman, R. et al., 2005; Bachner-Melman, R. et al., 2007; Bajoria, R. et al., 2001; Barlaskar, F. M. et al., 2007; Binder, G. et al., 2006; Binder, G. et al., 2008; Bermingham, J. et al., 2000; Boquist, S. et al., 2008; Cano-Gauci, D. F. et al., 1999; Casola, S. et al., 1997; Cerrato, F. et al., 2008; Chen, C. L. et al., 2000; Chia, V. M. et al., 2008; Choi, Y. S. et al., 2009; Chokkalingam, A. P. et al., 2001; Christofori, G. et al., 1995; Cui, H. et al., 1997; Cui, H. et al., 2003; Dahlén, G. H. et al., 1994; dÀlesio, A. et al., 2005; Day, I. N. et al., 2006; de Fraipont, F. et al., 2000; De Souza, 1995; Doria, A. et al., 1996; Doublier, S. et al., 2001; Duarte, A. et al., 1998; Dunai, G. et al., 2008; el-Naggar, A. K. et al., 1999; Engel, J. R. et al., 2000; Enomoto, A. et al., 2001; Fielder, P. J. et al., 1991; Fielder, P. J. et al., 1992; Fournet, J. C. et al., 2001; Giannoukakis, N. et al.,

1993; Gicquel, C. et al., 1994; Gicquel, C. et al., 1997; Hashimoto, K. et al., 1996; Hattori, H. et al., 2000; He, W. Z. et al., 2004; Heath, K. E. et al., 2008; Heude, B. et al., 2007; Hernandez, L. et al., 2003; Herault, J. & Petit, E., 1994; Herault, J. et al., 1994; Hess, O. et al., 2007; Ho, G. Y. et al., 2003; Iida, K. et al., 1998; Inaba, T. et al., 1989; Ingrosso, D. et al., 2003; Jandziszak, K. et al., 1998; Jimeno, L. et al., 2005; Julier, C. et al., 1991; Kaku, K. et al., 2007; Kaur, R. et al., 2005; Kim, H. S., 2001; Kim, S. J. et al., 2002; Kim, Y. J. et al., 2006; Kondo, Y. et al., 1999; Kong, F. M. et al., 2000; Kotsinas, A. et al., 2008; Lai, M. T. et al., 2005; Lakatos, P. L. & Bajnok, E., 2004; Lakatos, P. L. et al., 2004; Li, E. et al., 1993; Li, H. & Zhang, N., 2004; Li, S. R. et al., 2004; Li, Z. Q. et al., 2007; Li, X. et al., 1997; Majores, M. et al., 2002; Mariani, S. et al., 2003; McCann, J. A. et al., 2004; Micha, A. E. et al., 1999; Mitchell, S. M. et al., 2004; Mosse, Y. P. et al., 2007; Moulton, T. et al., 1994; Moulton, T. et al., 1996; Möller, B. et al., 2007; Mu, L. et al., 2008; Murrell, A. et al., 2004; Nagai, M. et al., 1999;Nakagawa, H. et al., 2001; Nyström, A. et al., 1992; Ober, C. et al., 1989; Ogawa, O. et al., 1993; Ohshima, K. et al., 2000; Oliveira, H. A. et al., 2003; Ong, K. K. et al., 2004; Ostojić, S. et al., 2008; Patel, R. et al., 2000; Perrotti, D. et al., 1990; Petry, C. J. & Ong, K. K., 2005; Petry, C. J. et al., 2005; Polychronakos, C. et al., 1995; Ramocki, N. M. et al., 2008; Ransohoff, D. F., 2003; Rivera, E. J. et al., 2005; Rodriguez, S. et al., 2004; Rodriquez, S. & Gaunt, R., 2006; Rodriquez, S. et al., 2006; Sandovici, I. et al., 2003; San Schofield, P. N. et al., 1995; Millán, J. L. et al., 2004; Schneid, H. et al., 1991; Schwienbacher, C. et al., 2000; Spencer, H. G. et al., 1995; Sperandeo, M. P. et al., 2000; Shih, D. Q. et al., 2000; Sten-Linder, M. et al., 1993; Stessman, J. et al., 2005; Stier, S. et al., 2006; Sutherland, G. et al., 2008; Tait, K. F. et al., 2004; Takada, D. et al., 2003; Tauber, M. T. et al., 1998; Tessema, M. et al., 2005; Theiss, A. L. et al., 2005; Thorvaldsen, J. L. et al., 1998; Tomlinson, G. E. et al., 1992; Tsai, F. J. et al., 2003; Ulaner, G. A. et al., 2003; Vafiadis, P. et al., 1996; Vafiadis, P. & Grabs, R., 1998; Vafiadis, P. et al., 1998; Villuendas, G. et al., 2006; Voskuil, D. W. et al., 2004; Vuononvirta, R. et al., 2008; Wagner, K. et al., 2004; Wasserman, L. et al., 2004; Weksberg, R. et al., 1993; Wilkin, F. et al., 2000; Woods, K. A. et al., 1997; Wu, H. K. & Weksberg, R., 1997; Wu, H. K. et al., 1997; Xu, Y., et al., 1993; Xu, W. et al., 2006; Yamada, T. et al., 1997; Yang, X. F. et al., 1996; Yun, K. et al., 1998; Yun, K. et al., 1999; Zankl, A. et al., 2000; Zatkova, A. et al., 2004; Zavras, A. I. et al., 2003; Zhai, G. et al., 2004.

5 studies could not be approached because of missing genotype data: Adkins, R. M. et al., 2007; DeLuca, M. et al., 2001; Lee, H. J. et al., 2005; Paquette, J. et al., 1998; Tost, J. et al., 2006.

The same amount of studies showed genotype measurements but the effect on muscle phenotype was missing: Cox, N. J. et al., 1988; Gaunt, T. R. et al., 2001; Giannoukakis, N. et al., 1996; Gomes, M. V. et al., 2005; Gu, D. et al., 2002; O`Dell, 1997; O`Dell, 1999; Roth, S. M. et al., 2003.

Some studies were excluded because they did not relate to IGF-II:

Abu- Amero, S. et al., 1997; Chen, J. et al., 2008; Frankish, H., et al., 2001; Goddard, A. D. et al., 1997; Harvey, J. J. et al., 2008; Killian, J. K. et al., 2001; McGinnis, R. E. et al., 1994; Pritlove, D. C. et al., 2004; Rosenblum, A. L. et al., 1994; Sun, A. et al., 2005; Suzuki, M. et al., 2008.

Finally all reviews were excluded (Barlaskar, F. M. et al., 2007; Chen, C. P. et al., 2007; Geenen, V. et al., 2005; Haig, D. & Graham, C., 1991; Han, V. K., 1993; Moore, T. et al., 2001; O`Dell, S. D. & Day, I. N., 1998; Ong, K. K. et al., 2004; Patalano, A. et al., 2009; Spector, T. D. et al., 2004; Squire, J. & Weksberg, R., 1996; Ukkola, o. et al., 2004; Utsunomya, J., 2005; Wilkin, F. et al., 2000; Witte, D. P. & Bove, K. E., 1994; Zaina, S. & Nilsson, J., 2003).

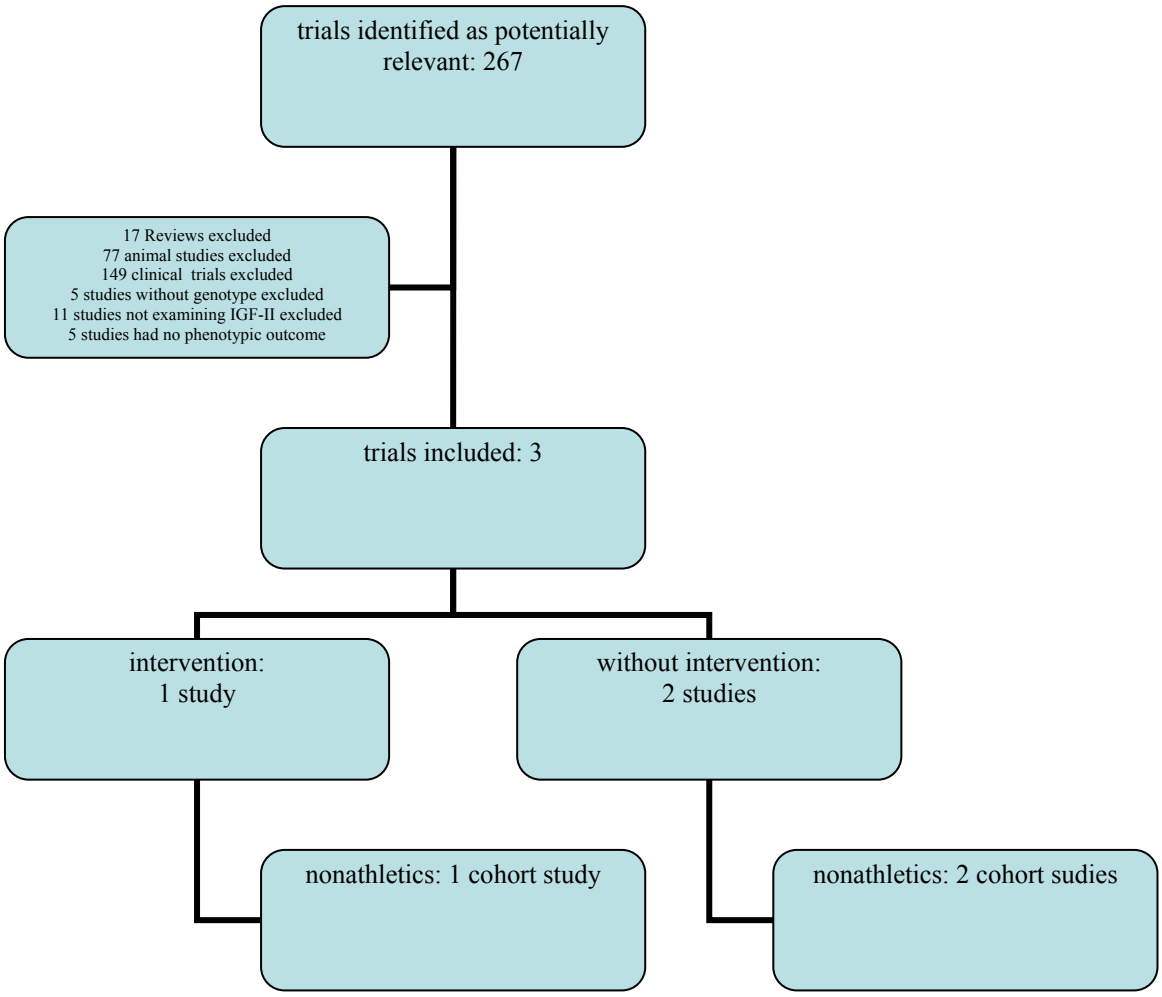

Abbildung 9: Systematic search strategy for "(IGF-II OR IGF-2) AND genotype" in PubMed

The search for myostatin also delivered a small output of included studies (Abb. 10). Out of the 66 potentially relevant surveys 55 animal studies were excluded (Antoniou, E. & Grosz, M., 1999; Bouley, J. et al., 2005; Bünger, L. et al., 2004; Casas, E. et al., 1999; Cornelison, D. D. et al., 2000; De la Rosa, X. F. & Rodrguez Perez, M. A., 2006; De la Rosa-Reyna, X. F. et al., 2006; Deveaux, V. et al., 2001; Di Stasio, L. & Rolando, A., 2005; Dunner, S. et al., 2003; Esmailizadeh, A. K. et al., 2008; Fahrenkrug, S. C. et al., 1999; Grobet, L. et al., 1997; Grobet, L. et al., 1998; Gu, Z. L. et al., 2002; Guernec, A. et al., 2003; Hadjipavlou, G. et al., 2008; Hamelin, M. et al., 2006; Hamrick, M. W. & Pennington, C., 2006; Hamrick, M. W. et al., 2006; Johsnon, P. L. & McEwan, J. C., 2005; Scheuermann, G. N. et al., 2004; Jiang, Y. L. et al., 2001; Jiang, Y. L. et al., 2002; Johnson, P. L. et al., 2005; Keele, J. W. et al., 2001; Kellum, E. et al., 2009; Kijas, J. W. et al., 2007; Klauzinska, M. et al., 2001; Lehnert, S. A. et al., 2007; Li, X. L. et al., 2006; Li,

Z. F. et al., 2005; Lin, J. et al., 2003; Martyn, J. K. et al., 2004; McPerron, A. C. et al., 1997; Mosher, D. S. et al., 2007; Oldham, J. M. et al., 2009; Parsons, S. A. et al., 2006; Phoca, F., 2009; Sadkowski, T. et al., 2008; Sellick, G. S. et al., 2007; Short, R. E. et al., 2002; Smith, J. A. et al., 2000; Szabo, G. et al., 1998; Varga, L. et al., 2003; Varga, L. et al., 2005; Walling, G. A. et al., 2004; Wheeler, T. L. et al., 2001; Wiener, P. et al., 2002; Ye, X. et al., 2007; Yu, L. et al., 2007; Zhiliang, G. et al., 2004; Zuh, Z. et al., 2007).

2 clinical trials were excluded (González-Freire, M. et al., 2009; Zhang, Z. L. et al., 2008) and 2 studies without genotype were excluded (Munies, C. A. et al., 2008; Williams, M. S., 2004). Another 2 studies turned out not to examine myostatin (McPherron, A. C. et al., 1999; Walsh, S. et al., 2007) and in 1 study the effect on muscle phenotype was absent (Saunders, M. A. et al., 2006). At least 2 reviews were excluded (Rodgers, B. D. et al., 2008; Vainzof, M. et al., 2008).

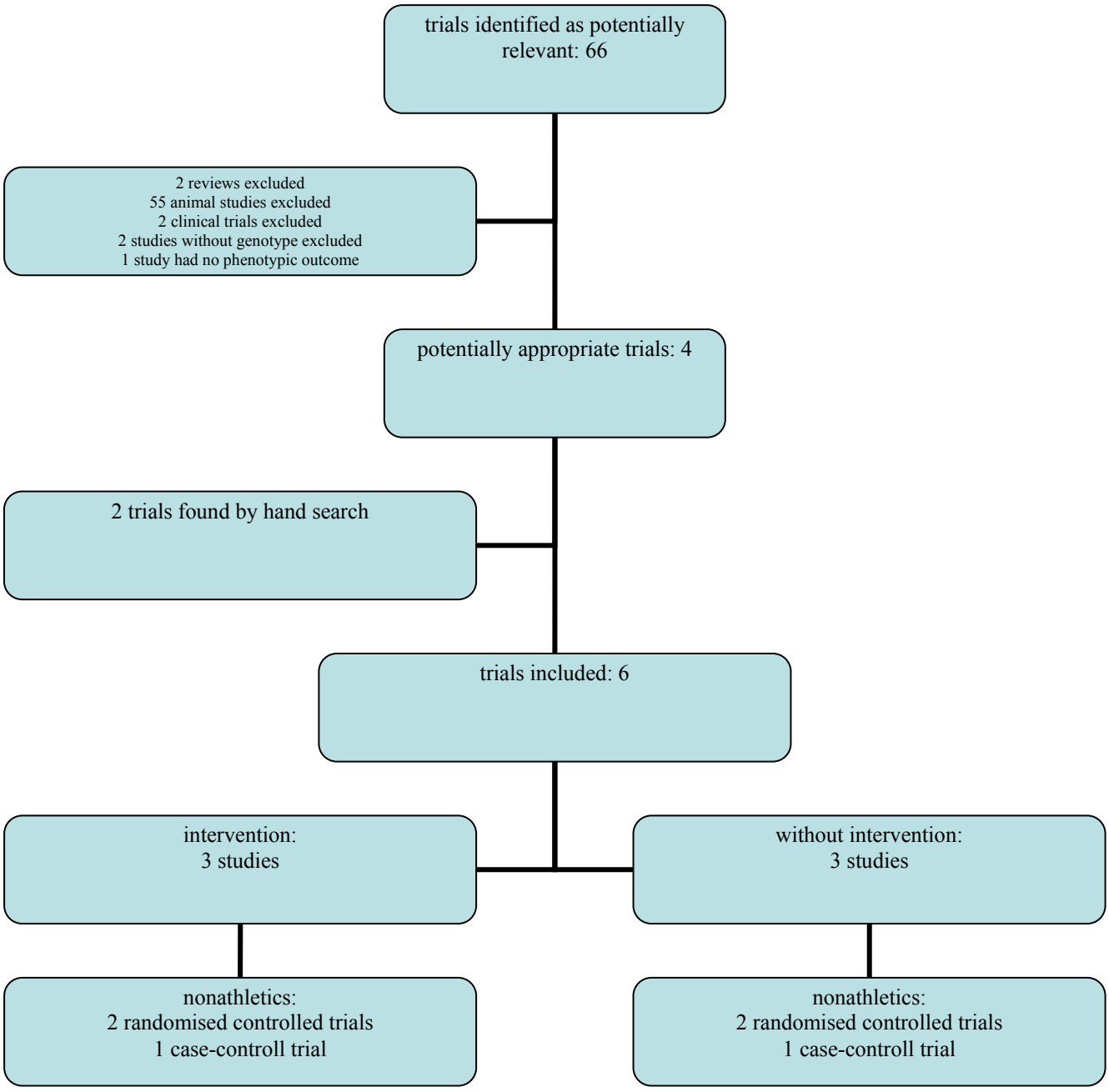

Abbildung 10: Systematic search strategy for „(myostatin OR GDF8) AND genotype“ in PubMed

7 Discussion

The outcome of twentyfive relevant studies for ACTN3 gene yielded nineteen studies with effect on muscle phenotype (eleven athletic and eight nonathletic cohorts) and six studies detected no significant relation (four athletic and two nonathletic investigations). The ACTN3 athletics group without intervention had the highest output in relevant studies. Internal relationships with genotype effects in this group will be discussed later. Five studies reporting associations with training response all showed positive effects of ACTN3 on muscle phenotype. The physical performance phenotypes for which genetic data were available include cardiorespiratory endurance, elite endurance athlete status, muscle strength and other muscle performance traits. The speciall point of view for this gene is, that regardless the heterogeneity and distribution of different types of fiber in skeletal muscle, the structural organization of the contractile apparatus is dependent on protein complexes which bind the sarcomeres among each other and sustain them in the muscle fiber. Within this context α-actinin constitutes the predominant protein. Interestingly, α-actinin-3 deficiency does not derive in a pathological phenotype as muscular dystrophy or myopathies, suggesting that the ACTN2 isoform with 80% homology in amino acid sequence could compensate for the absence of α-actinin-3 and hence counteract the phenotypic consequencies of the deficiency. As all muscle fiber types express α-actinin-2, Norman (2009) demonstrated that the expression of ACTN-2 is affected by the content of α-actinin-3 in moderately well trained men. The author also suggested that α-actinins do not play a significant role in determining muscle fiber type composition. In contrary, Vincent (2007) showed a possible role of the ACTN3 gene in the determination of fiber type distribution in young men. α-actinin-3 was present in all type IIa fibers of RR carriers and systematic higher levels of α-actinin-3 in IIx fibers. In XX- homozygotes. No extra compensation seemed to occur concerning the lack of α-actinin-3. Both studies measured static and dynamic tourques of the knee-extensor muscles at baseline and after exercise intervention. In older women (64 years), knee extensor concentric peak power with strength training was found to be higher in X allele homozygotes compared with RR genotype individuals (Delmonico et al., 2007). Clarkson and colleagues (2005) reported no association between ACTN3 R577X genotype and muscle phenotype in men when investigating isometric elbow flexor strength (1-RM gains in response to a 12-wk strength

training), although these authors reported that women homozygous for the XX allele had lower baseline isometric strength compared with RX. Clarkson also (2005) examined genotypes in the ACTN3 and myosin light chain kinase (MLCK) gene in another study. In 157 predominantly Caucasian men and women genotype associations with exertional muscle damage after isometric and eccentric elbow flexor exercise where determined. Creatin kinase (CK), myoglobin and isometric strength were tested before and after the exercise bout. Although subjects homozygous for the 577X allele had the lowest muscle strength and the lowest resting CK activity (which may indicate that these individuals are less active and/or have lower type II fiber composition), no associations were observed for other phenotypes before or after exercise. Polymorphisms in the MLCK gene were associated with baseline muscle strength, CK and myoglobin responses and strength loss after the eccentric exercise bout.

Taken together, the variation of fiber type in skeletal muscle is a phenotype well characterised in athletes and nonathletes and this is explained to approximately 45% by genetic factors (Simoneau, J. & Bouchard, C., 1995, S.1091-1095) While cross-sectional studies have constantly shown that the XX genotype is under-represented in sprint-related athletes or associated with inferior performance, longitudinal studies have produced more mixed results as further review will clarify. It is hypothesized that ACTN3 might be a genetic factor important to normal phenotype variation in muscle function. The X allele seems to be functional and the XX genotype completely disables the ACTN3 protein. Especially located in Type II muscle fibers ACTN3 arises the key question, if the lack of ACTN3 protein in Type II muscle fibers in X-homozygotes effects muscular performance? A group surrounding MacArthur D. (1999) sought to answer this question by performing a case-controll study. Significant associations between the presence of α-actinin-3 and sprint performance at an elite level were considerable, suggesting a role for α-actinin-3 in the generation of force at high velocity. The frequency of the XX genotype was threefold lower in sprint athletes compared to controls, and more than four-fold lower in sprinters compared to endurance athletes (Tab. 3). If α-actinin plays an important role in type II muscle fibers, it would be reasonable to predict differences in skeletal muscle funtion among individuals with different genotypes (R577X). This activated several research groups to clarify frequency of XX genotype in endurance athletes. In a follow-up study Yang and colleagues (2003) hypothesized that the deficiency of ACTN3 would reduce performance in strength-related sports and would therefore be less frequent in elite sprint

athletes. In other words the XX genotype would be a disadvantage in sprint or power-related sports, in which Type II fibers are recruited. The strength of the study was the size of the sample and the quality of the subjects tested. The genotype was examined in 429 Australian elite athletes from 14 different sports grouped in sprint/power (n=107), endurance sports (n=194) and 436 control subjects. There were significant allele frequency differences between sprint athletes and controls for both males and females. An interesting point was that strength/power and endurance athletes showed allele frequencies in opposite directions. Sprint athletes had a lower frequency of XX genotype (6%) than controls (18%) and endurance athletes (24%). The sprint athlete group also had a higher frequency of the RR genotype (50%) than controls (30%) and endurance (31%). None of the female elite sprint athletes were XX and in fact the XX genotype was completely absent in both female sprint and power athletes and male and female olympic sprint and power athletes. The authors concluded that the R allele of the ACTN3 R577X polymorphism provides an advantage for sprint or power related activities compared to the X allele and that the effect of ACTN3 genotype on performance differs between males and females. These findings have been supported by the independent replications in cross-sectional studies of Nijemi & Majamaa (2005), including three pairs of twins and five pairs of siblings. The frequency of ACTN3 XX genotype was lower (frequency of XX genotype: 0 vs. 9.2%) in sprint athletes compared to endurance athletes. Confirming Yang and colleagues, non of the top Finnish sprinters carried the XX genotype. It seemed that the athletic gene has been found and all people can be genetically screened to determine if they are a “good” athlete or a “bad” athlete, marking the 577R as “good” and the 577X as “bad” allele. Popular press articles speculated that athletic ability could be based solely on the ACNT3 gene. But controversely to the findings of Yang and his colleagues, Lucia et al., (2006) reported no significant differences in indices of endurance performance. Comparing cohorts of professional spanish cyclers with olympic male endurance runners and a control group, the genotype distribution of the ACTN3 gene and the frequency of the R and X alleles were similar in the three groups. Interestingly, all the three genotypes were present in the seven top cyclers. The researchers came to the conclusion that deficiency of α-actinin-3 in working muscle does not necessarily confer a performance benefit in ultra-endurance events in males. A fact that reconciders the point of view on the ACTN3 gene, although the small sample size decreases the statistical power. Another potential limitation in this study comes from the fact that female athletes did not participate in the study. The study of Yang reported significantly higher frequency distribution of the XX genotype in female

endurance athletes than in controls. In this regard, Clarkson et al. (2005) hypothesized, that ACTN3 could have a potentially smaller effect in men than in women. The research group evaluated associations between ACTN3 genotype and muscle size (cross-section area of the biceps brachii and elbow flexor MVC and 1-RM). The large group of nonathletic men and women enrolled in 24 supervised elbow flexor/extensor resistance training sessions of the nondominant arm. Significant associations of ACTN3 with muscle phenotypes in women were found with ACTN3 explaining ~2% of all variations within the associated phenotypes. Absence of ACTN3 protein indicated greater response to training compared with presence. Despite greater absolute gains in men, the profound data showed that women gain significantly more isometric strength than men (22 vs. 16%) and significantly more relative dynamic strength than men (64 vs. 40%) with resistance training. Three years later Walsh S. and his group examined this appearent benefit in strength in women across age 22 to 90 years. ACTN3 genotype associations with muscle phenotypes and knee extensor shortening and lengthening peak tourque as well as FFM were determined. Although no genotype-related differences were observed in men, the absence of α-actinin-3 in women displaced lower knee extensor shortening and lengthening peak torque values compared with women grouped for the R allele. These differences in muscle strength appeared to be driven by lower levels of body and lower limb FFM. Sex-related associations have also been found in the athletic group by Li-Ling Chiu (2005) in Taiwanese women. The frequency of ACTN3 577X was significantly lower in individual sports compared to teamsports and the control group. Individuals carrying both RR and RX genotype showed the highest genotype frequencies. A possible outcome may hypothesize that success in more complex sports is less influenced by the RR genotype. It is not obvious which kinds of sport the individual sports group is refering to, but it is considered that individual sports can be equated with endurance performance and teamsports with sprinting ability. A closer look on sex differences suggests that this may be partially due to sex-specific hormonal differences between men and women. According to MacArthur and North the lower average levels of testosterone in female athletes compared to men could increase the influence that variations in some biological parameters have on athletic performance.

For some authors the gender differences are not that appreciated. In a study with power athlete status in Russians Drzhevskaya and her colleagues evaluated an under-represented XX genotype in both sexes compared to controls (males: 6.4 vs. 16.4%; females: 6.5 vs.

12.5%). The ACTN3 X allele frequencies in men (34.3 vs. 39.8%) and women (30.5 vs. 37.8%) were significantly different compared to controls. In a small nonathletic population Norman (2009) and researchers also did not find sex specific effects of ACTN3 genotype and differences in fiber- type composition.

San Juan et al. (2006) reported similar findings in a small population of women X-homozygotes mean age ~70 years. In this population group complete defficiency of α-actinin-3 did not affect ventilatory threshold and peak oxygen uptake performance during functional tests or maximal muscle strength. The subjects in this study were elderly women. In particularly aging leads to an increase in mtDNA mutations. As humans age, there is an accumulation of mtDNA mutations and a decrease in mitochondrial enzyme activity and it is hypothesized that this leads to a decrease in the oxidative capacity of muscle tissue (Cortopassi, Shibata, Soong & Arnheim (1992), S.7370-7374). From this point of view aging is a slow form of mitochondrial desease and exercise can improve performance both in aging individuals and in those with myopathies, altough it does not reverse the mitochondrial defects present. According to Lindle, Metter, Lynch (1997, S. 1581-1587) skeletal muscle gradually declines starting at about 45 years. As women lose muscle mass with age, ACTN3 genotype may further reduce muscle mass and strength in XX women. Women who are defficient in α-actinin-3 appear to be at disadvantage for muscular strength and this may help to contribute the lower extremity limitations that occur with aging shown in the longitudinal study of Delmonico. In the five- year follow-up study, Delmonico and his colleagues demonstrated that 70- to 79 years old X-homozygote women had an ~35% greater risk of incident persistent lower extremity limitation combared to R-homozygotes. Altough no strength differences were observed among ACTN3 genotype groups in that investigation, men of the same age homozygous X exhibited significantly greater increases in 400m walk time compared with R-homozygotes and heterozygotes. A previous report by Delmonico et al., (2007) found unexpectedly higher muscle strength in X-homozygotes compared with R-homozygote older women. According to the study, increases in knee extensor peak power with strength training were influenced by ACTN3 R577X genotype in both men and women, such that older adults who are R-allele homozygotes had a greater PP response to strength training than X-homozygotes had. There was a big sample size of 50 to 85 years old sedentary adults, whose muscle function values may not correspond to those highly trained young athletes of Yang and colleagues. Nevertheless, this data show greater improvements in RR men and

women in response to strength training, consistent with the findings of Yang and colleagues, suggesting a gene - environment interaction with training necessary to elicit performance differences among ACTN3 genotype groups. There is a big amount of studies supporting the interaction of environment, genetics and training and it seems that muscle phenotype is likely influenced by numerous genes and polymorphisms, as well as other environmental factors that may be interacting with these genes in unknown ways. Cote, J., Macdonald, D. J., Baker, J. & Abernethy, B. (2006) compiled the birthplaces of professional athletes in the USA and Canada and came to the conclusion that cities over 500.000 in population are consistently under-represented in terms of proceeding athletes. According to that study environment plays a role in determining the outcome of an athlete and small cities seem to provide early opportunities for athletic progressions that are not matched by large cities. Emmanuel Van Praagh estimates the components to the total phenotypic variation in human maximal anaerobic performance phenotypes with 50% genetic variance, 30% environmental variance, 15% genotype-training interaction and 5% technical variance (Van Praagh, 1998, S. 18). The X allele has been observed in all human populations so far. The lowest X allele frequencies occur in Kenian, Nigerian and South African populations (8-11%), resulting in approximately 1% XX genotype frequency. A circumstance that has been brought in connection with the success of the East African elite endurance runners relative to their source populations. This hypothesis has not been supported by the study of Yang, N. (2007) investigating the ACTN3 R577X polymorphism in East and West African athletes. The XX genotype was absent in Nigerians, extremely low in Kenyans and higher in Ethiopians. There was no evidence found for an association between the R577X polymorphism and endurance performance in East African athletes. One reason may be that many East Africans are subject to environmental influences, such as living and training at altitude and high levels of incidental running during childhood. Another possibility could be that Ethiopians expirienced considerable genetic interaction with neighboring Arabian populations in recent time, so gene flow from non-African populations may explain the higher frequency of the X allele in Ethiopians relative to Kenyans. The distribution of SNPs around the R577X polymorphism suggests that the polymorphism has existed for a considerable amount of evolutionary time and that balancing selection may have been involved in its maintenance. The fact that the X allele is evolutionary conserved, forms a basis for the hypothesis that the X allele confers an advantage in endurance performance, although the mechanism by which this occurs is not clear and may involve uncharacterised genetic interactions. Moran (2007) showed a

complexity of phenotype associated with the R577X polymorphism. In a population of 992 adolescent greeks significant associations between the R577X polymorphism and 40m sprint time occurred. The polymorphism was not associated with power phenotypes related to 40m sprint, nor with an endurance phenotype. Furthermore, the polymorphism was not associated with obesity-related phenotypes, which would have indicated a possible thrifty effect of the polymorphism on metabolism. Papadimitriou (2007) provided ACTN3 genotype analysies in elite Greek Track and Field athletes. Concluding this study, ACTN3 is the first skeletal muscle gene which demonstrated a completely absence of XX in three different population groups (Australia, Finnish, Greece) in sprinters competing at the Olympic, world and European level. As the RR genotype was highly present in endurance runners (57%) the study also supports the hypothesis of Lucia et al., that top-level endurance runners require not only slow-twitch myofibres, but also the ability to recruit type II fast-twitch myofibres during phases in which they must effectively sprint for short distances in competition. The beneficial effect of α-actinin-3 deficiency on endurance performance seems to be less important than its presence on spriniting- power performance, as sprinters had an α-actinin-3 deficient XX genotype, but many of the endurance athletes had an RR genotype. The high speeds and near-maximal intensities during races support the notion that both strength and power are important traits in rowing. Except the fact that rowing times become approximately 0.7 sec faster per year, this circumstance is confirmed by studies of Ahmetov (2008) in Russian and Muniesa (2008) in Spanish rowing athletes. The frequencies of the ACTN3 577XX genotype and 577X allele were significantly lower in endurance oriented athletes and none of the highly elite athletes had the 577XX genotype. Rowers with ACTN3 577RR genotype showed better results in long-distance rowing than carriers of 577RX or 577XX genotypes. Next to the studies mentioned before on Finnish (n=40), Spanish (n=102), Ethiopian (n=76) and Kenyan (n=284) athletic populations, the hypothesis that α-actinin-3 deficiency may confer some advantage in endurance performance events has also not been supported by the independent studies of Italian (n=42) endurance athletes (Paparini et al., 2007) and (Saunders et al., 2007) Caucasian triathletes (n=457). On the other hand three recently published studies support the hypothesis that the performance constraint, in which athletes are called upon to perform at high levels in both sprint and endurance races, may have a genetic basis. Santiago et al. (2008) found significant associations between elite soccer players and sprint/power genotype. Gomez-Gallego et al. (2008) reported that professional

road cyclists with the ACTN3 RR/RX genotypes had significantly higher peak power output and ventilatory threshold values than their XX counterparts. Stephen M. Roth evaluated low XX genotype frequencies in black and white elite-level strength athletes. The XX genotype was significantly lower in white athletes (9.7%) vs controls (19.9%) and no black athlete carried the XX genotype. This is consistent with the findings of X-allele frequencies in African-descent populations.

This controversal discussion on ACTN3 XX and RR genotype may be due to different reasons. First of all rowers, cyclists, runners or other athletes who participate in overall endurance sports cannot be grouped together in genetic association studies. Further performance in competition is unlikely to be reducable to a single phenotypic trait. Least, according to training principle of individuality, each athlete responds differently to the same quantitative and qualitative training stimuli (Rushall & Pyke, 1990, S. 57-64), leading to a range of responses among athletes who have experienced otherwise identical training programmes. It is unknown whether the ACTN3 R577X polymorphism defines the athlete`s initial levels of power ability or it actually affects the response to training.

The IGF-I search delievered a small output of two studies, both obtaining nonathletics with intervention. There is a high level of evidence for both studies characterised as randomised controlled trials. There were similar presuppositions for both studies and in fact the studies were undertaken from the same laboratory. Both studies relate to older men and women age 50 to 83 years. The exercise interventions were unilateral knee extensions of the dominant leg three times per week for ten weeks. The IGF-I promoter polymorphism and single-nucleotide polymorphisms were genotyped. Muscle volume, muscle quality and 1-RM strength were assessed at baseline and after 10 weeks of training. While the study of Kostek (2005) investigated sixtyseven Caucasian men and women, the follow-up study of Hand (2007) included onehundred-twentyeight subjects of Caucasian and African American ethnicity. Different ethnic groups show different prevalence of the polymorphism with ethnicity. Kostek found that the development of muscular strength in response to a resistance training programm was associated with the cytosin adenine (CA) dinucleotide repeat polymorphism in the promoter region of the IGF-I gene such that carriers for 192 gained significantly more strength than noncarriers. Although no nonsense, missense or functional polymorphisms have been identified for the IGF-I gene, it is plausible that other polymorphisms within the IGF-I pathway could be involved in muscular hypertrophy and strength response to strength training. On this background,

Hand was evaluating additionally genes within the IGF pathway such as insulin-like growth factor binding protein 3 (IGFBP3) and calcineurin B (PPP3R1). The 1-RM strength of the trained leg did not differ significantly at baseline muscle phenotypes among IGF-I CA repeat genotype groups which is also valid for IGFBP3 A-202C and PPP3R1 I/D. Men showed greater mean values than women for baseline 1-RM strength and African American subjects had greater MV results than Caucasians at baseline. Although all groups increased significantly with training, the IGF-I promoter allele carriers increased their 1-RM strength significantly more than noncarriers when covaried for sex and age. In both studies no significant differences between the absolute or relative changes in MV or MQ with strength training have been found. In addition there were no significant differences between Caucasian and African American individuals for absolute or relative changes in MV with strength training, but there was a significant difference in the absolute change in MQ in African Americans compared with Caucasian individuals. Hand also observed significant race x sex interactions for change in muscle strength but not for gene x race interactions for the changes in 1-RM strength, MV or MQ. Combined Caucasian and African American genotype analysis showed significant effects including both IGF-I CA repeat main effect and IGF-I CA repeat x PPP3R1 I/D gene x gene interaction effect on change in strength with strength training. Interestingly, no significant combined effects for PPP3R1 I/D on changes in strength and MQ were observed, suggesting that the influence of calcineurin on muscle phenotypic response to strength training may be less than that of IGF-I because of the presence of other IGF-I linked signaling pathways influencing muscle phenotypic responses to strength training. The role of calcineurin in the muscle phenotypic response is discussed controversely in literature and the effect that Hand observed no significant combined gene effects for PPP3R1 I/D on changes in strength and MQ suggests that the influence of calcineurin on the muscle phenotypic response to strength training may be less than that of IGF-I because of the presence of other IGF-I linked signaling pathways influencing muscle phenotype during exercise. In light of the trend for a significant IGFBP3 A-202C x race interaction it is possible, that race effects may play a greater role than genotype effects on muscle phenotypic responses to strength training. Although a causal relationship between acute or chronic muscle contraction and IGF-I expression has not been documented in humans, IGF-I remains one of the strongest candidate genes for strength training- induced increases in muscle mass and strength and there is a need to investigate other IGF-I-dependent mechanical signaling pathways that influence muscle phenotypic responses to strength training.

Two studies with nonathletic cohorts reported significant associations of IGF-II ApaI polymorphism and muscle phenotypes. Sayer (2002) found the ApaI polymorphism of the IGF-II gene was associated with grip strength for men but not women in a large sample of 397 men and 296 women in the UK. In a longitudinal study Schrager (2004) genotyped subjects for the IGF-II ApaI polymorphism from cohorts of prior studies and tested for associations with arm and leg strength and body composition. For men, arm strength was greater for the homozygous wildtype than the homozygous rare alle group, while for women the homozygous rare allele group showed lower arm and leg strength and lower FFM compared with homozygous wildtype. In contrast to Sayer, who found significantly higher grip strength in GG men compared with AA men, Schrager found no significant genotype association with grip strength. Summarizing, IGF-II does not explain associations between eayrly growth and grip strength, but it may influence muscle mass and function in later life.

Reports on association studies of myostatin polymorphisms with baseline muscle strength or responses to strength training in humans are scarce. The interventional studies mostly observed muscle volume, meanwhile observational studies determined the relation of genotype with strength. Out of the six studies included in this review, four studies showed genotype associations with muscle phenotypes (Ivey, F. M. et al., 2000; Seibert, J. M. et al., 2001; Corsi, A. M. et al., 2002; Huygens, W. et al., 2004) and in two studies no significant relations were obvious (Ferrel, R. E. et al., 1999; Thomis, M. et al., 2004).

Ferrell (1999) first determined the nucleotide sequence for human myostatin gene in fourty individuals and discovered that two missense subtitutions, specifically an A to G change on codon 55 in the exon 1 (A55T) and an A to G substitiution in exon 2 (K153R), were appreciably represented in Caucasian and African American populations. In contrary to the bovine gene mutation acting as a missense polymorphism. Allele frequencies for the less frequent 153R allele were 0.037 in the Caucasian sample of the general population and 0.16 in African Americans. Similar differences in allele frequencies were found for the 55T allele with 0.036 and 0.12 in both ethnic groups respectively. In a substudy comparing elite athletes with previously untrained subjects and nonathletes (extreme responder- , responder- and nonresponder groups) none of the high responder athletes were carriers of the R153R genotype. Neither of these common polymorphisms had significant effect on the magnitude of increment of muscle mass in response to heavy resistance training of the quadriceps muscle, although K153R was overrepresented in the nonresponders cohort.

Homozygote myostatin R153R carriers were rare and only observed in the African American non- responders. Researchers from the same group tested whether the K153R genotype could explain hyperthrophy in MV of quadriceps muscle group after a 9-week heavy-resistance knee extension training program (Ivey et al., 2000). Women with the less common myostatin allele exhibited a 68% larger increase in MV in response to strength training. This trend maintained when baseline MV was covaried. Although the K153R polymorphism has a rare allele frequency, the effect it has on the phenotype seems to be meaningful. The trend observed in quadriceps MV increases in response to strength training in female carriers (n=5) of the myostatin K153R genotype indicates relevant effects on individual variability in training responses. Tomis (2004) found only one carrier of the K153R genotype in twentyfive pairs in the Leuven Twin and Training study. Male monozygotic twins age 17-30 participated in a program of ten weeks elbow flexor training.

Genotype dependent similarity in pre- and posttraining responses and genotype x training interaction were not significant in this small sample size. Genetic association studies without training intervention also showed a rare K153R allele frequency in other cohorts of young and older subjects. In the WHAS II study of Seibert (2001) variant genotypes for A55T and K153R were also very uncommon in Caucasian population with gene frequencies of less than 0.02. A higher allele frequency for three variant alleles was noted in the African-American participants (0.05). Association studies between K153R and strength measuerements suggested lower muscle strength in women with the R genotype. As African Americans tended to have a greater overall strength, genotype was a significant predictor of overall strength. The race x genotype interaction was not significant. Hip, knee and grip strength in addition to the overall strength measurement identified a significant difference in hip flexion strength by K153R myostatin genotype. This may be due to the fact that the iliapsoas muscle is primarily composed of type 1 muscle fibers. As myostatin is expressed at higher levels in type 1 muscle fibers (Sakuma, Watanabe & sano, 2000, S. 77-88) the gene may therefore have a more significant functional impact in this muscle group. The WHAS II study is also supported by Corsi (2002), who reported lower muscle strength in older men and women (mean age 70) carrying the R-allele, though the sample size was small. Since the allele frequencies of the polymorphism in human myostatin are very low, association studies with this missense polymorphism are difficult. Huygens underwent this problem by using markers in a linkage analysis of myostatin pathway genes with knee strength in humans. In this Leuven Genes for Muscular Strength Study (LGfMS)

the role of the myostatin pathway explaining interindividual variation in estimated muscle cross-sectional area and strength were explored in 329 male Caucasian sibs (including sib-pairs, trios and quads). Linkage was mainly found with strength phenotypes, but only marginal evidence was present for its effects on estimated muscle cross-sectional area. Since the myostatin polymorphism described in animals mainly affects muscle mass and muscle mass is more correlated with isometric strength, it is not surprising that the research group found more suggestive linkage signals with slower velocities.

Myostatin is physiologically more related to muscle mass through possible effects of hyperplasia and hypertrophy than it is to strength. Although most studies evaluated the relationship between myostatin and muscle mass rather than muscle strength. Muscle mass does not always correlate directly with muscle strength and muscle strength loss cannot uniformly be explained by changes in muscle size.

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9 Appendix

PUBMED search strategy:

1.: ACTN3 genotype phenotype (13 matches)

2.: α-actinin-3 genotype phenotype (12 matches)

3.: R577X genotype phenotype (11 matches)

4.: ACTN3 genotype exercise (11 matches)

5.: α-actinin-3 genotype exercise (11 matches)

6.: R577X genotype exercise (9 matches)

7.: ACTN3 genotype phenotype exercise (6 matches)

8.: α-actinin-3 genotype phenotype exercise (6 matches)

9.: R577X genotype phenotype exercise (5 matches)

10.: ACTN3 genotype training (5 matches)

11.: α-actinin-3 genotype training (4 matches)

12.: R577X genotype training (4 matches)

13.: ACTN3 genotype phenotype training (2 matches)

14.: α-actinin-3 genotype phenotype training (0 matches)

15.: R577X genotype phenotype training (1 matches)

16.: ACTN3 genotype strength (11 matches)

17.: α-actinin-3 genotype strength (11 matches)

18.: R577X genotype strength (10 matches)

19.: ACTN3 genotype phenotype strength (4 matches)

20.: α-actinin-3 genotype phenotype strength (4 matches)

21.: R577X genotype phenotype strength (3 matches)

22.: ACTN3 genotype muscle (22 matches)

23.: α-actinin-3 genotype muscle (21 matches)

24.: R577X genotype muscle (17 matches)

25.: ACTN3 genotype muscle strength (10 matches)

26.: α-actinin-3 genotype muscle strength (10 matches)

27.: R577X genotype muscle strength (10 matches)

28.: ACTN3 polymorphism phenotype (10 matches)

29.: α-actinin-3 polymorphism phenotype (10 matches)

30.: R577X polymorphism phenotype (9 matches)

31.: ACTN3 polymorphism exercise (9 matches)

32.: α-actinin-3 polymorphism exercise (9 matches)

33.: R577X polymorphism exercise (9 matches)

34.: ACTN3 polymorphism phenotype exercise (4 matches)

35.: α-actinin-3 polymorphism phenotype exercise (4 matches)

36.: R577X polymorphism phenotype exercise (4 matches)

37.: ACTN3 polymorphism training (5 matches)

38.: α-actinin-3 polymorphism training (5 matches)

39.: R577X polymorphism training (5 matches)

40.: ACTN3 polymorphism phenotype training (2 matches)

41.: α-actinin-3 polymorphism phenotype training (2 matches)

42.: R577X polymorphism phenotype training (2 matches)

43.: ACTN3 polymorphism strength (9 matches)

44.: α-actinin-3 polymorphism strength (9 matches)

45.: R577X polymorphism strength (9 matches)

46.: ACTN3 polymorphism phenotype strength (2 matches)

47.: α-actinin-3 polymorphism phenotype strength (2 matches)

48.: R577X polymorphism phenotype strength (2 matches)

49.: ACTN3 polymorphism muscle strength (9 matches)

50.: α-actinin-3 polymorphism muscle strength (9 matches)

52.: R577X polymorphism muscle strength (9 matches)

53.: ACTN3 genotype anaerobic phenotype (0 matches)

54.: α-actinin-3 genotype anaerobic phenotype (0 matches)

55.: R577X genotype anaerobic phenotype (0 matches)

56.: ACTN3 polymorphism anaerobic phenotype (0 matches)

57.: α-actinin-3 polymorphism anaerobic phenotype (0 matches)

58.: R577X polymorphism anaerobic phenotype (0 matches)

59.: IGF-I genotype phenotype (115 matches)

60.: Insulinlike growth factor genotype phenotype (134 matches)

61.: IGF-I genotype exercise (11 matches)

62.: Insulinlike growth factor genotype exercise (8 matches)

63.: IGF-I genotype phenotype exercise (2 matches)

64.: Insulinlike growth factor genotype phenotype exercise (2 matches)

65.: IGF-I genotype training (4 matches)

66.: Insulinlike growth factor genotype training (4 matches)

67.: IGF-I genotype phenotype training (1 match)

68.: Insulinlike growth factor genotype phenotype training (1 match)

69.: IGF-I genotype strength (16 matches)

70.: Insulinlike growth factor genotype strength (14 matches)

71.: IGF-I genotype phenotype strength (5 matches)

72.: Insulinlike growth factor genotype phenotype strength (3 matches)

73.: IGF-I genotype muscle (48 matches)

74.: Insulinlike growth factor genotype muscle (78 matches)

75.: IGF-I genotype muscle strength (6 matches)

76.: Insulinlike growth factor genotype muscle strength (8 matches)

77.: IGF-I polymorphism phenotype (49 matches)

78.: Insulinlike growth factor polymorphism phenotype (56 matches)

79.: IGF-I polymorphism exercise (11 matches)

80.: Insulinlike growth factor polymorphism exercise (9 matches)

81.: IGF-I polymorphism phenotype exercise (2 matches)

82.: Insulinlike growth factor polymorphism phenotype exercise (2 matches)

83.: IGF-I polymorphism training (5 matches)

84.: Insulinlike growth factor polymorphism training (6 matches)

85.: IGF-I polymorphism phenotype training (1 match)

86.: Insulinlike growth factor polymorphism phenotype training (1 match)

87.: IGF-I polymorphism strength (11 matches)

88.: Insulinlike growth factor polymorphism strength (11 matches)

89.: IGF-I polymorphism phenotype strength (3 matches)

90.: Insulinlike growth factor polymorphism phenotype strength (3 matches)

91.: IGF-I polymorphism muscle strength (3 matches)

92.: Insulinlike growth factor polymorphism muscle strength (7 matches)

93.: IGF-I genotype anaerobic phenotype (0 matches)

94.: Insulinlike growth factor genotype anaerobic phenotype (0 matches)

95.: IGF-I polymorphism anaerobic phenotype (0 matches)

96.: Insulinlike growth factor polymorphism anaerobic phenotype (0 matches)

97.: IGF-II genotype phenotype (58 matches)

98.: IGF-II genotype exercise (0 matches)

99.: IGF-II genotype phenotype exercise (1 match)

100.: IGF-II genotype training (0 matches)

101.: IGF-II genotype phenotype training (0 match)

102.: IGF-II genotype strength (4 matches)

103.: IGF-II genotype phenotype strength (1 match)

104.: IGF-II genotype muscle (43 matches)

105.: IGF-II genotype muscle strength (3 matches)

106.: IGF-II polymorphism phenotype (29 matches)

107.: IGF-II polymorphism exercise (2 matches)

108.: IGF-II polymorphism phenotype exercise (1 match)

109.: IGF-II polymorphism training (0 matches)

110.: IGF-II polymorphism phenotype training (0 match)

111.: IGF-II polymorphism strength (5 matches)

112.: IGF-II polymorphism phenotype strength (1 match)

113.: IGF-II polymorphism muscle strength (4 matches)

114.: IGF-II genotype anaerobic phenotype (0 matches)

115.: IGF-II polymorphism anaerobic phenotype (0 matches)

116.: Myostatin genotype phenotype (28 matches)

117.: GDF-8 genotype phenotype (28 matches)

118.: Growth differentiation factor-8 genotype phenotype (28 matches)

119.: Myostatin genotype exercise (6 matches)

120.: GDF-8 genotype exercise (6 matches)

121.: Growth differentiation factor-8 genotype exercise (6 matches)

122.: Myostatin genotype phenotype exercise (2 matches)

123.: GDF-8 genotype phenotype exercise (2 matches)

124.: Growth differentiation factor-8 genotype phenotype exercise (2 matches)

125.: Myostatin genotype training (4 matches)

126.: GDF-8 genotype training (4 matches)

127.: Growth differentiation factor-8 genotype training (4 matches)

128.: Myostatin genotype phenotype training (2 matches)

129.: GDF-8 genotype phenotype training (2 matches)

130.: Growth differentiation factor-8 genotype phenotype training (2 matches)

131.: Myostatin genotype strength (8 matches)

132.: GDF-8 genotype strength (8 matches)

133.: Growth differentiation factor-8 genotype strength (8 matches)

134.: Myostatin genotype phenotype strength (3 matches)

135.: GDF-8 genotype phenotype strength (3 matches)

136.: Growth differentiation factor-8 genotype phenotype strength (3 matches)

137.: Myostatin genotype muscle (54 matches)

138.: GDF-8 genotype muscle (54 matches)

139.: Growth differentiation factor-8 genotype muscle (54 matches)

140.: Myostatin genotype muscle strength (8 matches)

141.: GDF-8 genotype muscle strength (8 matches)

142.: Growth differentiation factor-8 genotype muscle strength (8 matches)

143.: Myostatin polymorphism phenotype (15 matches)

144.: GDF-8 polymorphism phenotype (15 matches)

145.: Growth differentiation factor-8 polymorphism phenotype (15 matches)

146.: Myostatin polymorphism exercise (2 matches)

147.: GDF-8 polymorphism exercise (2 matches)

148.: Growth differentiation factor-8 polymorphism exercise (2 matches)

149.: Myostatin polymorphism phenotype exercise (3 matches)

150.: GFD-8 polymorphism phenotype exercise (0 matches)

151.: Growth differentiation factor-8 polymorphism phenotype exercise (0 matches)

152.: Myostatin polymorphism training (2 matches)

153.: GDF-8 polymorphism training (2 matches)

154.: Growth differentiation factor-8 polymorphism training (2 matches)

155.: Myostatin polymorphism phenotype training (3 matches)

156.: GDF-8 polymorphism phenotype training (0 matches)

157.: Growth differentiation factor-8 polymorphism phenotype training (0 matches)

158.: Myostatin polymorphism strength (3 matches)

159.: GDF-8 polymorphism strength (3 matches)

160.: Growth differentiation factor-8 polymorphism strength (3 matches)

161.: Myostatin polymorphism phenotype strength (1 match)

162.: GDF-8 polymorphism phenotype strength (1 match)

163.: Growth differentiation factor-8 polymorphism phenotype strength (1 match)

164.: Myostatin polymorphism muscle strength (3 matches)

165.: GDF-8 polymorphism muscle strength (3 matches)

166.: Growth differentiation factor-8 polymorphism muscle strength (3 matches)

167.: Myostatin genotype anaerobic phenotype (0 matches)

168.: GDF-8 genotype anaerobic phenotype (0 matches)

169.: Growth differentiation factor-8 genotype anaerobic phenotype (0 matches)

170.: Myostatin polymorphism anaerobic phenotype (0 matches)

171.: GDF-8 polymorphism anaerobic phenotype (0 matches)

172.: Growth differentiation factor-8 polymorphism anaerobic phenotype (0 matches)

LEBENSLAUF

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ANGABEN ZUR PERSON

Staatsangehörigkeit	Österreich
Geburtsdatum	5.12.1975

ARBEITSERFAHRUNG

• Seit 2008	EA- Generali
• Beruf oder Funktion	Trainer
• Tätigkeiten und Zuständigkeiten	Planung und Organisation von Aerobicstunden (High-Low, Kräftigung, Freestyle), Spezialgymnastikstunden (Yoga, Tai chi, Pilates, Smart Bells) und Massagestunden

• Seit 2007	U4- Fitnesscenter
• Beruf oder Funktion	Trainer, Kraftkammerleiter
• Tätigkeiten und Zuständigkeiten	Planung und Organisation von Kraftkammereinheiten und Personal Trainerstunden Muskelfunktionstests nach Janda, Körperfettmessung mit Kaliper, Dynamometrie mit Dr. Wolff back check test, Belastungsergometrie, gezielte Trainingsplanerstellung anhand der erhobenen Parameter zum Ausgleich muskulärer Dysbalancen und je nach Zieldefinition Verbesserung der Ausdauerleistungsfähigkeit, Betreuung von Kunden mit besonderen Bedürfnissen wie zum Beispiel Downsyndrom, Multiple sklerose, Osteoporose, Skoliose,

	Rückenschmerzen sowie muskuläre Stabilisation nach Schulter- Hüft- bzw. Knieoperationen, Betreuung der Kunden im Kraft- und Ausdauertrainingsbereich, Individuelle Betreuung „on-the-floor“, Leitung von Gymnastikstunden verschiedenster Zielgruppen (Rückentraining, Seniorengymnastik, Aerobic, Zirkeltraining, Spinning),
• Seit 2005	Schwimmschule Waterfly
• Beruf oder Funktion	Leitung von Schwimmeinheiten verschiedenster Zielgruppen (Kinderschwimmen, Seniorengymnastik, Mastersschwimmen), Schwimmtrainer
• Tätigkeiten und Zuständigkeiten	individuelle Betreuung mit Technikverbesserung Schwimmen ganzjährige Betreuung von Hobbytriathleten
• 2005 bis 2007	American International School Schwimmtraining
• Beruf oder Funktion	Schwimmlehrer
• Tätigkeiten und Zuständigkeiten	Leitung von Beginner, Intermediate und Expert Schwimmeinheiten für Kinder des Alters von 3- 14 Jahren
• 2001 bis 2007	Baxter- Immuno Wellness Center des Pharmakonzerns Baxter
• Beruf oder Funktion	Kraftkammerleiter, Personal Trainer, Betreuung der Mitarbeiter
• Tätigkeiten und Zuständigkeiten	Koordination und Planung von Kursen, Teamorganisation Belastungsergometrie (Conconi- , Cooper- Tests), Muskelfunktionstests, ganzheitliche Trainingsplanerstellung (Kraft, Ausdauer, Koordination), Leitung von Ausdauertrainingskursen, Krafttrainingskursen, Therabandkursen, Progressive Muskelrelaxation, Dehnübungen, Core-Stability, MFT
•2001 bis 2002	Fitnessstudio Simmafit Dr. Blanka
• Beruf oder Funktion	Personal Trainer
• Tätigkeiten und Zuständigkeiten	Trainingsplanerstellung im Bereich Krafttraining, Kontrolle und Motivation der Mitglieder

• seit 17.10.2007 Magisterstudium Sportwissenschaft, Universität Wien

Die vorliegende Diplomarbeit bildet den Abschluss meines Magisterstudiums im Fachbereich der Sport- und Leistungsphysiologie. Das Magisterstudium der Sportwissenschaft befähigt mich, ausgewählte Forschungsmethoden der Sportwissenschaften kompetent und wissenschaftlich reflektiert für die Lösung von Praxisfragen einzusetzen. Ich verfüge über fachwissenschaftliche und forschungsmethodische Qualifizierung im Bereich der angewandten und der grundlagenbezogenen Forschung über sportwissenschaftliche Kompetenzen in der Anwendung von Forschungsmethoden, in fundierter Planung und Steuerung von Trainingsprozessen, in der Organisation fachwissenschaftlich fundierter Planung und Steuerung von Maßnahmen der Vorbeugung und Rehabilitation durch Bewegung und Sport, in der fundierten Anwendung leistungsphysiologischer und trainingswissenschaftlicher Kenntnisse in der sport- und bewegungsbezogenen Praxis, in der Erarbeitung wissenschaftlicher Konzepte für die Primär-, Sekundär-, und Tertiärprävention sowie in der Auswahl und Anwendung von sportinformatorischen und biomechanischen Methoden und Werkzeugen. Ich besitze höchste fachliche Qualifikation in der zielgerichteten und langfristig orientierten Förderung und Betreuung von Kindern, Jugendlichen und Erwachsenen aller Leistungsstufen in ausgewählten Sportarten und Sportbereichen sowie im Coaching in Wettkampf- und Belastungssituationen unter Einbeziehung eines umfassenden Grundlagenwissens aus der Sportmedizin, den verschiedenen Fachbereichen der Bewegungswissenschaft, der Sportpädagogik und Sportpsychologie sowie weiterer relevanter Erkenntnisse der Natur- und Sozialwissenschaften.
Im Projekt- und Qualitätsmanagement erwarb ich Kompetenzen in der Organisations- und Projektgestaltung mit dem Schwerpunkt des Prozessmanagements und der Sicherung und Entwicklung umfassender Qualität im Sportbereich. Dies basiert auf einer beschreibenden und darstellenden Ebene einerseits sowie einer steuernden und verändernden Ebene andererseits. Kompetenzen wurden in den Bereichen Auftragsgestaltung, Konzeption, (Finanz)Controlling, wissenschaftliche Formen der Evaluation, Marketing, MitarbeiterInnen- Führung und -entwicklung, Schnittstellenorganisation, Prozesssteuerung und Medienarbeit vertieft aufgebaut. Weiters ist Wissen über Konzeption, Durchführung und Evaluation von Beratungen im Projekt- und Programmbereich sowie in Sportorganisationen vermittelt worden.

• 01.10.2003 - 16.10.2007 Bakkalaureatsstudium Gesundheitssport, Universität Wien mit Abschluss als
Bakk.rer.nat. Gesundheitssport

Während des Bakkalaureatsstudiums Sportwissenschaft an der Universität Wien erwarb ich mir
zentrale sportwissenschaftliche, sportdidaktische, sportorganisatorische und trainingsspezifische Kompetenzen, die dazu qualifizieren,

Tätigkeiten in vielfältigen bewegungs- und sportbezogenen Berufsfeldern erfolgreich aufzunehmen. Die Studienausbildung ermöglichte es mir, sowohl eigenständig als auch in einem Team unter Berücksichtigung von Erkenntnissen aus unterschiedlichen sportwissenschaftlichen Disziplinen Lösungen für praxisbezogene Problemstellungen im Feld Bewegung und Sport erarbeiten und konkret umsetzen zu können. Als Absolvent des Bakkalaureatsstudiums Sportwissenschaft an der Universität Wien bin ich befähigt im Zusammenhang mit Bewegung und Sport stehende Themen und Fragestellungen auf der Basis sportwissenschaftlicher Erkenntnisse zu bearbeiten und in zielgruppenadäquate
Konzepte sowie sportpraktische Angebote umzusetzen. Dabei lernte ich, mich an die Erfordernisse neuer Praxisfelder und Zielgruppen anzupassen und die eigene Geschlechterrolle zu reflektieren. Im Laufe des Studiums erhielt ich fachwissenschaftliche und sportpraxisbezogene Kenntnisse, sodaß ich über grundlegende Kompetenzen zur Anleitung unterschiedlicher Gruppen im Sport verfüge.
Schlüsselqualifikationen im Umgang mit modernen Medien wurden durch eine kontinuierliche flexible Form des Studierens im Sinne des Blended Learning Konzepts (Kombination von Präsenz- und Online-Phasen) in unterschiedlichsten Phasen des Bakkalaureatsstudiums erworben. Dies wurde durch ein peer-to-peer Mentoringprogramm unterstützt bzw. kompensiert. Zusätzlich wurden die Lernprozesse gefördert durch Verwendung von multimedialen Materialien, angeleitetem Selbststudium, Selbstevaluationstools und problem- und teambasierten Lernszenarien.

• 1.3.2001- 7.11.2003	Studium der Leibeserziehung und Italienisch, Universität Wien
• 1999- 2001	Studium der Zahnmedizin, Karl- Franzens- Universität Graz
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• 1996- 97	Ableistung des Präsenzdienstes als Sanitäter in Aigen/ Ennstal
• 1993	Certificat de Langue Francaise- Centre International d`Antibes
•1991-96	Borg Monsbergergasse Graz mit AHS- Matura- Abschluss
•1986-91	BRG Körösistrasse, Graz
•1983-86	Volksschule Muchargasse, Graz
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