Genes whose gain or loss-of-function changes type 1, 2A, 2X or 2B muscle fibre proportions in mice: A systematic literature review

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Abstract

Background: Adult muscle fibres are classified as type 1, 2A, 2X, and 2B muscle fibres based on the expression of the dominant myosin heavy chain isoform. Muscle fibre-specific gene expression and muscle fibre types change during development and in response to changes in contractile activity such as exercise, chronic electrical stimulation versus inactivity or denervation.

Methods: To identify genes whose gain or loss-of-function changes type 1, 2A, 2X or 2B muscle fibre proportions in mice, we conducted a systematic review following the 2020 PRISMA guidelines and the PICO framework.

Results: We identified 25 "muscle fibre genes" (*Akirin1, Bdkrb2, Bdnf, Camk4, Ccnd3, Cpt1a, Epas1, Esrrg, Foxj3, Foxo1, Il15, Mapk12, Mstn, Myod1, Ncor1, Nfatc1, Nol3, Ppargc1a, Ppargc1b, Sirt1, Sirt3, Thra, Thrb, Trib3, Vgll2*) whose gain or loss-of-function changes type 1, 2A, 2X or 2B muscle fibre proportions in mice. The fact that 15 of the 25 muscle fibre genes are transcriptional regulators suggests that muscle fibre-specific gene expression is primarily regulated transcriptionally. Muscle fibre genes such as *Ppaargc1a* and *Vgll2* increase or *Mstn* decrease their expression after exercise, respectively, suggesting that this contributes to muscle adaptation to exercise. Finally, there are many known DNA sequence variants of muscle fibre genes suggesting that this contributes to the large variation of muscle fibre percentages in humans.

Conclusion: Muscle fibre genes are a set of genes that often regulate gene expression and where DNA variants are likely to change human muscle fibre distribution.

Background

Muscle fibres are cells that produce force and heat and can be up to 20 cm long [1]. Human muscle fibres are multinucleated cells, also termed syncitia, that develop as a result of myoblast fusion. Per millimetre of length, human muscle fibres have ≈50–250 myonuclei [2] and so we would expect 10,000–50,000 nuclei in a single, 20 cm-long human muscle fibre. Each muscle contains hundreds, up to thousands of muscle fibres depending on its size. For example, the human vastus lateralis of ≈20 year-aged males contains 393,000 to 903,000 muscle fibres [3].

The identification of different adult skeletal muscle fibres evolved over time. From 1960–1967 researchers distinguished fast white and slow red muscle fibres, from ≈1967–1975 type 1, 2A and 2B fibres and from ≈1986–1991 type 1, 2A, 2X, and 2B muscle fibres [4]. Different muscle fibres were first distinguished using enzyme assays [5, 6] as well as histochemical and microscopic visualisation of ATPase activity after pre-incubation with an acidic or alkaline pH [7]. Myosin heavy chain isoforms (MyHC), which determine the contraction velocity, were then identified by immunocytochemistry utilising myosin heavy chain type 1, 2A, 2X and 2B-specific antibodies [8] or with electrophoretic separation of myosin heavy chain isoforms [9]. Today, the concentrations of thousands of proteins in a single muscle fibre can be measured by first isolating single muscle fibres followed by an unbiased, proteomic analysis

by mass spectrometry [10, 11]. Currently, muscle fibres are mainly classified by the myosin heavy chain isoform(s) that they express. The major myosin heavy chain isoforms in humans are slow type 1 (gene *MYH7*), intermediate type 2A (gene *MYH2*) and fast 2X (gene *MYH1*) myosin [8]. Additionally, some rodent muscles but not human muscles contain very fast type 2B myosin heavy chain protein (gene *Myh4*) [12]. In addition to fibres that only exclusively (i.e. >90%) express one myosin heavy chain, there are hybrid fibres that express two myosin heavy chain isoforms [13]. Moreover, embryonal (*MYH3*) and perinatal myosin (*MYH8*) heavy chains are expressed in embryonic, foetal and regenerating muscle fibres [14].

In mammals, the distribution of muscle fibres varies greatly intra- and inter-individually. For example, the red soleus is a predominantly type 1 slow twitch muscle whereas the more pale rectus femoris is a more type 2 fast twitch muscle [15]. In addition to this inter-muscle variability, muscle fibre percentages vary greatly in-between individuals. For example, an analysis of 126 women and 144 men that were sedentary and of 77 women and 71 men that were physically active revealed 15–79% type 1 fibres, 13–77% type 2A fibres and 0–44% type 2X fibres in the vastus lateralis and similarly large variations of metabolic enzymes [16]. Extreme muscle fibre compositions occur in athletes, with endurance athletes having typically many type 1 and sprint and power athletes having many type 2 fibres percentages in key locomotory muscles such as the vastus lateralis or gastrocnemius [17–20]. Extreme fibre type percentages are likely prerequisites for elite performance in both power/speed and endurance sports.

The distribution of skeletal muscle fibres depends both on an individual's genetics (i.e. variations of the DNA sequence, or heritability) and environmental factors such as exercise training or diet as well as experimental variability e.g. genetic manipulation on mice. In humans, Bouchard and colleagues estimate that the variation of the proportion of type 1 fibres depends 45% on genetics, 40% on environmental factors and 15% on experimental variability [21]. In addition to genetics, more innervation and contraction e.g. due to endurance training or fewer contractions e.g. due to denervation or reinnervation, or immobilisation alter fibre type-related gene expression and muscle fibre proportions. Specifically, exercise training promotes gene expression changes and minor fibre type shifts in a type 2-to-1 direction. In their classic study, Gollnick, Saltin and co-workers found that 5 months with four 1 h training sessions per week increased the percentage of slow twitch (i.e. type 1) fibres in the vastus lateralis non-significantly by 4% from 32–36% [22]. In the Heritage study, twenty weeks of endurance training increased the percentage of type 1 fibres by 3.5% and decreased the percentage of type 2X fibres by 5.4% [23]. Analysing the whole body of evidence suggests that exercise training over months can induce especially conversions of hybrid fibres (e.g. type 2X/2A) to pure (e.g. 2A) fibres and promote some (i.e. <10%) pure fibre conversions e.g. from pure 2X to pure 2A fibres [24].

Whilst exercise training interventions of less than a year result only in limited fibre transitions it is unclear whether years of exercise training can cause major fibre type transitions where e.g. >10% of fibres shift their type in a given muscle. In contrast to exercise training, near complete fibre type transformations are caused by either denervation where fibres change in a slow-to-fast direction [25], innervation by a

different motor neuron [26], or by chronic electrical low-frequency stimulation where many or almost all fibres change in a fast-to-slow direction [27, 28].

Given that approximately half of the variation of human muscle fibre proportions is inherited, the question arises as to what genes and DNA sequence variants influence the proportions of muscle fibre types within a given muscle. Transgenic mouse models with germline mutations or injection of genetic constructs have helped to identify genes whose gain or loss-of-function can significantly alter the proportions of type 1, 2A, 2X or 2B muscle fibres. An important early study used gene expression, reporter assays and pharmacological inhibition to identify the calcineurin-Nfat (nuclear factor of activated T-cells) pathway as a regulator of muscle fibre proportions [29, 30]. Other transgenic mouse studies around the millennium showed that the overexpression of constitutively active Ras promotes a fast-to-slow fibre type change [31] and that the gain-of-function of the transcriptional co-activator Pgc-1α in muscle not only promotes mitochondrial biogenesis but also increases the number of type 1 fibres [32].

To date the International Mouse Phenotyping Consortium (IMPC) has created and phenotyped over 5000 transgenic mouse strains [33]. However, the IMPC does not determine the muscle fibre composition of their mice, leaving a knowledge gap over what genes influence fibre type proportions in what muscles by how much.

To address this key questions in skeletal muscle physiology, we systematically searched the literature to identify genes whose gain or loss-of-function significantly alters the proportion of type 1, 2A, 2X or 2B muscle fibres in mice. For simplicity, we refer to these genes and to the proteins that they encode from here on as “muscle fibre genes”. In a second step, we used online databases and re-analysed published datasets to answer questions such as “In what tissues are muscle fibre genes expressed?” and “Does exercise alter the expression of muscle fibre genes or the phosphorylation of the proteins that they encode?”

Methods

Literature Search

We conducted a systematic review to identify genes whose gain or loss-of-function results in a statistically significant change of the percentage of at least one muscle fibre type or a significant change of myosin heavy chain isoform protein abundance in a mouse muscle *in vivo*. For the systematic literature review, we followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline (PRISMA (Page et al., 2020)). The PICO framework (Schardt et al., 2007) was used to choose the key search word list as follows: Population/Problem; Intervention; Comparison; Outcome. Based on this, we used the following MeSH (Medical Subjects Headings) terms list: ((mice OR "mouse" OR "mouse transgenic" OR "mice transgenic" OR "mouse knockout" OR "mice knockout" OR "mouse model" OR "mice model" OR "mice overexpressed" OR "mouse overexpressed")) AND ("gene expression" OR "gene knockout" OR "gene overexpression" OR "gene knock in" OR "gene transfer techniques" OR "gene deletion")) AND ("muscle fiber distribution" OR "muscle fiber fast twitch" OR "muscle fiber slow twitch" OR

"muscle fiber type I" OR "muscle fiber type II" OR "oxidative muscle" OR "oxidative fiber" OR "glycolytic muscle" OR " glycolytic fiber"). We used this search strategy to search the PubMed-Medline database for studies published up until November 2020.

After the search, we screened all titles and abstracts to remove studies that did not report the effects of transgenesis on muscle fibre proportions in mice. After that, we selected studies from peer-reviewed journals, written in English, that reported muscle fibre type distribution and/or myosin heavy chain expression in gene-manipulated mouse models. We included studies that reported a measure of skeletal muscle fibre type numbers, percentages or quantify myosin heavy chain isoform expression. We excluded studies as follows: 1) rat or *in vitro* study, 2) no transgenesis or double mutation, 3) miRNA manipulation, 4) mice with disease or pathological changes, 5) no statistically significant effect on muscle fibre distribution or myosin heavy chain isoform expression, 6) no comparison to wildtype or other valid control, 7) the gene manipulation resulted in a disease.

From all included studies, the following information was independently extracted by two researchers: author, gene name, protein name, method of gene manipulation, animal acclimation, output measure, section of paper where the data were extracted (figure or table), muscle(s) studied, number of fibre type or MyHC expression in transgenic and control mice, difference between transgenic mice and control mice in percentage (this analysis was performed in Rstudio version 3.6.3, then exported to an excel sheet for further analysis), age of mice, mouse strain, additional measurements, and remarks. Additional columns for Pubmed identificatory (PMID) paper, official gene name by Universal Protein Resources (UniProt, NCBI) and aliases in mice and humans. When the output measured appears only in bar graph or in stained muscle section, we estimated the relative difference between transgenic and control group using ImageJ Software (Rasband, 1997–2018), and indicated this with (*) on worksheet S2 in the supplementary table 1.

Bioinformatical Analyses

After identifying muscle fibre genes, we conducted five bioinformatical analyses to e.g. add more information on the tissue of expression, common functions and properties and their regulation by exercise:

1. To find out whether muscle fibre proteins encoded by them interact we performed a String analysis (Szklarczyk et al., 2015; https://string-db.org/; RRID:SCR_005223).
2. To identify common functions and properties of muscle fibre genes, we performed a ToppGene enrichment analysis (https://toppgene.cchmc.org/ [34]).
3. To determine whether the skeletal muscle distribution and MyHC expression genes are expressed specifically in skeletal muscle or elsewhere, we retrieved expression figures from the Genotype-Tissue Expression (GTEx; RRID:SCR_001618; GTEx Consortium, 2015) database and pasted the results into worksheet S5 in Supplementary Table 1.

4. To identify associations between muscle fibre genes and human phenotypes we searched the Genome Wide Association Studies (GWAS) catalogue (MacArthur et al., 2017; https://www.ebi.ac.uk/gwas/; RRID:SCR_012745).
5. To find out whether muscle fibre genes change their expression after acute endurance exercise, resistance exercise, or in response to activity, we used the Meta-analysis of Skeletal Muscle Response to Exercise (MetaMex) gene expression database to determine expression changes in muscle biopsies after acute endurance exercise, acute resistance exercise, and activity in health subjects (Pillon et al., 2020; https://www.metamex.eu/). We also investigated whether muscle fibre proteins become phosphorylated or dephosphorylated after exercise. For this, we retrieved supplementary data from two phospho-proteome studies. Study 1 investigated protein phosphorylation changes after a single bout of high intensity training in human muscles (Hoffman et al., 2015). Study 2 investigated protein phosphorylation in mouse skeletal muscle after electrically evoked maximal-intensity contractions (Potts et al., 2017).

Results

The initial Pubmed-Medline search yielded 371 studies published before November 2020. We identified another three studies through other sources. After reading titles and abstracts, we excluded 254 manuscripts and 113 articles remained. We then read the full text of these articles and excluded more articles based on our inclusion and exclusion criteria. In the end, 24 publications were analysed quantitatively and compiled in a table. The PRISMA flowchart in worksheet S1 in Supplementary Table 1 summarises the search and selection of publications.

Genes whose gain or loss-of-function significantly changes muscle fibre distribution in mice

Overall we identified 25 genes whose gain or loss-of-function significantly changed the percentages of type 1, 2A, 2X or 2B muscle fibres or myosin heavy chain abundance in at least one muscle in mice. Genes whose gain or loss-of-function significantly changed the percentage of type 1, 2A or 2X fibres are presented in Fig. 1 and genes that affect myosin heavy chain isoform expression in Fig. 2.

Specifically, we identified 13 genes whose loss-of-function (*Bdkrb2, Bdnf, Camk4, Ccnd3, Cpt1a*, *Foxj3, Mapk12, Mstn, Myod1, Nfatc1, Nol3, Thra, Thrb*) and 2 genes whose gain-of-function (*Foxo1, Ppargc1a*) significantly changed the proportions of at least one muscle fibre type. Additionally, we identified one gene whose knock out (*Ncor1)* and 5 genes whose overexpression (*Esrrg, Il15, Ppargc1b, Sirt3, Trib3*) significantly altered the expression of at least one myosin heavy chain isoform in mice. Moreover, loss-of-function of two genes (*Epas1* and *Vgll2*) and the gain-of-function of two other genes (*Akirin-1* and *Sirt1*) significantly altered both the proportions of at least one muscle fibre type and significantly changed the expression of at least one myosin heavy chain isoform. The effect sizes of the aforementioned gene manipulations range from a reduction of a fibre type by 37% (*Ppargc1a*, Plantaris type 2B) to a gain of 28% of a single fibre type (*Epas1*, soleus type 2B). Genes whose knockout affected more than one fibre type in soleus are *Bdkrb2*, *Camk4*, *Mpak12*, *Nol3*, *Thra* and *Thrb*. The muscle fibre genes *Bdnf*, *Ccnd3*, and

Mstn affected muscle fibre distribution in thetibialis anterior, *Bdnf* in the extensor digitorum longus and *Nol3* in the plantaris. Related to genes whose overexpression changes muscle fibre types, *Foxo1* affected more than one fibre type in the soleus, and *Ppargc1a* in the plantaris. Associated with myosin heavy chain expression we have *Ncor1* knockout affecting the myosin heavy chain expression in the gastrocnemius and quadriceps. On the other hand, overexpression of *Esrrg*, *Il15*, *Ppargc1b* and *Sirt3* changed muscle fibre proportions in the gastrocnemius, *Il15* and *Trib3* in the soleus, *Il15* and *Ppargc1b* in the extensor digitorum longus, and *Ppargc1b* and *Trib3* in the tibialis anterior.

Next, we used the list of 25 muscle fibre genes to answer direct research questions through further bioinformatical analyses.

1) Do muscle fibre proteins interact and do muscle fibre genes share common functional features?

To answer this question we completed a String protein interaction analysis [35] and a Toppgene enrichment analysis [34]. The string analysis suggests interactions in-between muscle fibre genes. Clusters of muscle fibre genes included a cluster of genes that encoded thyroid (the expression of all MYH genes responds to thyroid hormone [36]) and oestrogen hormone receptors (*Thra, Thrb, Essrg*), a cluster with the transcriptional co-factors and transcription factors *Ppargc1a, Ppargc1b*, *Vgll2, Foxo1, Myod1, Nfatc1*, the sirtuins *Sirt1* and *Sirt3*, and a cluster of the circulating factors *Mstn* and *Bdnf* as well as the kinases *Mapk12* and *Camk4*.

We also used a ToppGene functional enrichment analysis to identify common features and functions among the muscle fibre genes identified. Specifically, we found 15 muscle fibre genes that regulate gene transcription (*Foxo1, Ppargc1a, Ncor1, Ppargc1b, Thra, Thrb, Akirin1, Trib3, Nfatc1, Foxj3, Vgll2, Myod1, Epas1, Sirt1, Esrrg)*, 5 genes that regulate muscle adaptation to contractile activity (see also below), loading conditions, substrate supply, and environmental factors. Of the 25 muscle fibre genes, 13 genes regulate cellular responses to hormones (*Ccnd3, Foxo1, Ppargc1a, Ncor1, Ppargc1b, Thra, Thrb, Mstn, Myod1, Bdnf, Sirt1, Esrrg*) and six genes are linked to energy metabolism e.g. in the form of mitochondrial biogenesis (*Foxo1, Ppargc1a, Ppargc1b, Camk4, Sirt3, Sirt1*) (worksheet S4 in Supplementary Table 1).

2) In what human tissues are muscle fibre genes expressed?

To find out whether muscle fibre genes are primarily expressed in skeletal muscle or elsewhere, we retrieved human gene expression data from the Genotype-Tissue Expression (GTEx) Project website (https://gtexportal.org/home [37]). This analysis reveals that two of the muscle fibre genes, *Vgll2* and *MyoD1*, are exclusively expressed in skeletal muscle. Moreover, *Mapk12, Foxo1*, and *Nol3* are most expressed in human skeletal muscle but also elsewhere.

3) Are muscle fibre genes regulated in response to exercise or inactivity?

To systematically investigate whether muscle fibre genes are regulated by exercise, we retrieved from the MetaMEx website (https://www.metamex.eu/) meta-analysed human muscle fibre gene expression data comparing pre and post exercise or inactivity (Fig. 5. Worksheet S7 in Supplementary Table 1 [38]). To

find out whether muscle fibre proteins are phosphorylated and become phosphorylated or dephosphorylated after a bout of human exercise in muscle, we also retrieved published phosphoproteomics data [39]. The gene expression analysis identifies *PPARGC1A* (which encodes Pgc-1α) and *VGLL2* as genes that roughly double their expression after acute bouts of endurance or resistance exercise in human vastus lateralis muscle and that decrease their expression in inactive muscles. *EPAS1*, which encodes a hypoxia-induced transcription factor also increases its expression after a bout of endurance and resistance exercise, but decreases in response to inactivity. Conversely, *MSTN* expression decreases after a bout of endurance and resistance exercise but increases in response to inactivity. The expression changes of all muscle fibre genes in response to acute endurance exercise, acute resistance exercise and inactivity are shown in Fig. 5.
This reveals that muscle fibre genes such as *PPARGC1A* and *VGLL2* increase their expression whereas *MSTN* decreases its expression especially after a bout of endurance exercise. The opposite is true for inactivity.

When analysing muscle protein phosphorylation, we found that *Vgll2* Ser261 phosphorylation increased by 30% after maximal muscle contractions in mice ($p = 0.07$) [40]. In addition, FOXO1, MAPK12, NOL3, NCOR1 and SIRT1 were detected as phosphorylated proteins in human muscle after a single high-intensity exercise bout. However, of these muscle fibre proteins, only MAPK12 Ser362 phosphorylation increased by more than 1.5-fold ($p < 0.05$) [39]. Collectively this suggests that several muscle fibre genes are regulated in response to acute endurance or resistance exercise or inactivity.

5) What is known about sequence variability of the muscle fibre genes in human exome?

Human fibre type distribution in muscles vary in the human population and this is ≈45% explained by genetics [21]. To determine the frequency of human DNA sequence variants of muscle fibre genes, we retrieved exome sequence data for 60,706 humans [41]. The analysis of this data revealed that each muscle fibre gene had on average 160 missense, 3 loss-of-function and 87 synonymous DNA variants. For *BDKRB2, CCND3, NOL3, THRA, NCOR1* and *EPAS2* homozygous loss-of-function DNA variants are reported [41]. Together this suggests that exome sequence variability of human muscle fibre genes could at least partially explain the currently poorly explained variability of muscle fibre genes.

Discussion

By conducting a systematic review, we have identified 25 genes whose gain or loss-of-function significantly changes muscle fibre percentages or the abundance of myosin heavy chain isoforms in mouse muscle. This confirms that muscle fibre type proportions are a polygenic trait. The effect sizes of the mutated, individual genes range from a 37% reduction of plantaris type 2B fibres (*Ppargc1a*) to a 28% increase of type 2B fibres in the soleus muscle (*Epas1*). There is no muscle fibre gene whose manipulation results in a transformation of all muscle fibres to one muscle fibre type. There are known DNA sequence variants for all muscle fibre genes and this could be useful to identify DNA sequence variants that have a measurable effect sizes on human muscle fibre distribution.

The fact that 15 of the 25 muscle fibre genes (*Foxo1, Ppargc1a, Ncor1, Ppargc1b, Thra, Thrb, Akirin1, Trib3, Nfatc1, Foxj3, Vgll2, Myod1, Epas1, Sirt1, Esrrg),*) are transcriptional regulators (i.e. transcription factors and transcriptional co-regulators) suggests that muscle fibre-specific gene expression is primarily regulated transcriptionally. How these transcription factors and co-factors combine to regulate the coordinated expression of hundreds of muscle fibre-specific genes in either a binary (i.e. an on/off regulation as for *Myh* genes in pure fibres) or graded fashion (i.e. a higher/lower expression e.g. of energy metabolism and mitochondrial genes) is incompletely understood. Generally, the identity of cells such as muscle fibre identity is often regulated by super-enhancers. Such super-enhancers are groups of enhancers bound by master transcription factors such as Brd4 and Med1 that compartmentalise DNA and genes, allowing a coordinated regulation of the expression of the target gene(s) [42, 43]. Consistent with this, the muscle-specific knock out of the super-enhancer-associated factor *Med1* (note that *Med1* is not only involved in super-enhancer function) resulted in increased expression of *Myh7* (type 1 myosin heavy chain) and *Myh2* (type 2A), myoglobin and metabolic gene mRNA, suggesting a coordinated regulation of muscle fibre identity-related genes [44]. This is consistent but does not proof that Med1 targets a fibre identity-regulating super enhancer. Super-enhancers are often associated with long intergenic non-coding RNA (lincRNAs) [45]. In relation to this, Sakakibara et al have identified *linc-MYH* as a lincRNA in “fast fibre” nuclei that inhibits slow-type enhancers and promotes fast/glycolytic muscle fibre gene expression [46]. The regulation of multiple fibre identify-associated genes is consistent with a fast/glycolytic fibre super enhancer. Finally, Gunderson and co-workers have investigated the epigenetics of purified myonuclei from more fast twitch extensor digitorum longus and more slow twitch soleus mouse muscles [47]. They found an over representation of binding sites for *Mef2C, Nfatc2* and *Ppara* in the soleus and of *MyoD1* and *Sox1* in the EDL [47]. The knowledge of multiple, muscle fibre type identify regulating transcription factors, the likely existence of a fibre type-regulating super enhancers [46] and methods allowing to analyse transcriptional regulation of nuclei with a fast/glycolytic or slow/oxidative identity [47] should enable future researchers to find out why more than ten transcription factors can regulate sets of genes associated with a fast/glycolytic or slow/oxidative muscle fibre identity.

Motor neuron activity and contractions are the main stimuli for muscle fibre-specific gene expression and for muscle fibre transitions. Consistent with this, our analysis reveals several muscle fibre genes that are regulated by contractile activity in the form of exercise or immobilisation. A key mode of regulation of adaptation to muscle contractions and exercise is transcriptional regulation. For example, acute human endurance or resistance exercise increases the expression of muscle fibre genes such as *PPARGC1A* and *VGLL2* but decreases the expression of *MSTN* [38]. In contrast, inactivity decreases the expression of muscle fibre genes such as *VGLL2* but increases the expression of *MSTN* [38]. A second mode of regulation is post-translational modification of muscle fibre proteins especially by phosphorylation. One example for this is the 1.5-fold increased phosphorylation of MAPK12 at Ser362 [39]. Finally, muscle fibre proteins can also be regulated by translocation. Prime examples of this are Nfat transcription factors. For example, Nfatc1 is more nuclear in slower type 1 than faster type 2 fibres and translocates to the nucleus in response electrical stimulation [48]. Whether and how this drives gene expression that is related to muscle fibre identity is poorly understood.

Finally, all muscle fibre genes are affected by DNA sequence variation. This ranges from rare, homozygous knockouts of the whole gene in the case of *MSTN* [49] to single nucleotide polymorphisms in all muscle fibre genes [41]. Given that the distribution of muscle fibres is ≈50% inherited [21] and given that we know few muscle fibre-proportion varying DNA sequence variants, the list of muscle fibre genes could be used to find out whether DNA sequence variants of muscle fibre genes occur at a higher or lower frequency in e.g. elite sprinters or endurance athletes with often extreme fibre type proportions when compared to the sedentary population. Such a targeted, genetic analysis might help to uncover the genetic causes of the variability of muscle fibre proportions in the human population.

The first limitation of this study are that the choice of the targeted genes is subjective, that not all genes in the genome have been manipulated and that e.g. the IMPC phenotyping pipeline does not include muscle fibre typing. A second limitation is that it is impossible to determine whether a gene manipulation affects development e.g. by blocking the slow-to-fast switch that occurs after birth in fast muscles or is related to adult muscle fibre plasticity by e.g. promoting a fast-to-slow twitch [4]. A third limitation is strict inclusion and exclusion criteria including the use of “statistical significance” as an inclusion criterion. For example, the manipulation of genes such as *Actn3* results in nearly significant fibre type changes (e.g. p = 0.051 in the spinalis) [50] and this is an issue because of the limitations p-values [51]. However, a systematic review requires clear cut inclusion and exclusion criteria and we have chosen statistical significance as an inclusion criterion. Fourth and finally, some publications suggest fibre type shifts based on mRNA expression alone and these were not included. Examples are transgenic mice with transgenes of *p43* [52] and *Med1* [44].

Conclusion

In summary, we detected 25 genes whose gain or loss-of-function determines muscle fibre proportions in mice. Given that the 25 genes causally affect fibre proportions, functionally relevant DNA sequence variants related of these genes should affect human muscle fibre type proportions provided that the function of these genes is conserved between mice and men. Together with a list of muscle hypertrophy genes [53], endurance genes [54] and glucose uptake genes [55] this additional list of causative genes should help to identify causative DNA variants that influence human sport and exercise-related traits [56].

List Of Abbreviations

Actn3 Actinin alpha 3

Akirin-1 Akirin 1

Bdkrb2 Bradykinin receptor 2

Bdnf Brain derived neurotrophic factor

Brd4 Bromodomain containing 4

Camk4 Calcium/calmodulim dependent protein kinase IV

Ccnd3 Cyclin D3

Cpt1a Carnitine palmitoyltransferase 1A

EDL Extensor digitorum longus

Epas1 Endothelial PAS domain protein 1

Esrrg Estrogen related receptor gamma

Foxj3 Forkhead box J3

Foxo1 Forkhead box O1

GTEx Genotype-Tissue Expression

GWAS Genome Wide Association Studies

Il15 Interleukin 15

IMPC International Mouse Phenotyping Consortium

lincRNAs long intergenic non-coding

Mapk12 Mitogen-activated protein kinase 12

Med1 Mediator complex subunit 1

Mef2C Myocyte enhancer factor 2C

MeSH Medical Subjects Heading

MetaMex Meta-analysis of Skeletal Muscle Response to Exercise

MyHC Myosin Heavy Chain

Mstn Myostatin

MYH1 Myosin heavy chain 1

MYH2 Myosin heavy chain 2

MYH3 Myosin heavy chain 3

MYH4 Myosin heavy chain 4

MYH7 Myosin heavy chain 7

MYH8 Myosin heavy chain 8

Myod1 Myogenic differentiation 1

NCBI National Center for Biotechnology Information

Ncor1 Nuclear receptor corepressor 1

Nfatc1 Nuclear factor of activated T cells 1

Nfatc2 Nuclear factor of activated T cells 2

Nol3 Nuclear protein 3

PICO Population/Problem, Intervention, Comparision, Outcome

PMID Pubmed indentificatory

Ppargc1a Peroxisome proliferative activated receptor, gamma, coactivator 1 alpha

Ppargc1b Peroxisome proliferative activated receptor, gamma, coactivator 1beta

Ppara Peroxisome proliferator activated receptor alpha

PRISMA Prefered Reporting Itens for Systematic Review and Meta-Analysis Guideline

Sirt1 Sirtuin 1

Sirt3 Sirtuin 3

Sox1 SRY (sex determining region Y)-box 1

Thra Thyroid hormone receptor alpha

Thrb Thyroid hormone receptor beta

TPM Transcript per million

Trib3 Tribbles peseudokinase 3

Uniprot Universal Protein Resources

Vgll2 Vestigial like family member 2

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials. The data are Supplementary data table in excel file
Competing interest. Gabyela Kuhnen, Tiago Guedes Russomanno, Marta Murgia, Nicolas J, Pillion, Martin Schönfelder & Hennign Wackerhage declare that they have no conflict of interest to the content of this review

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Figures

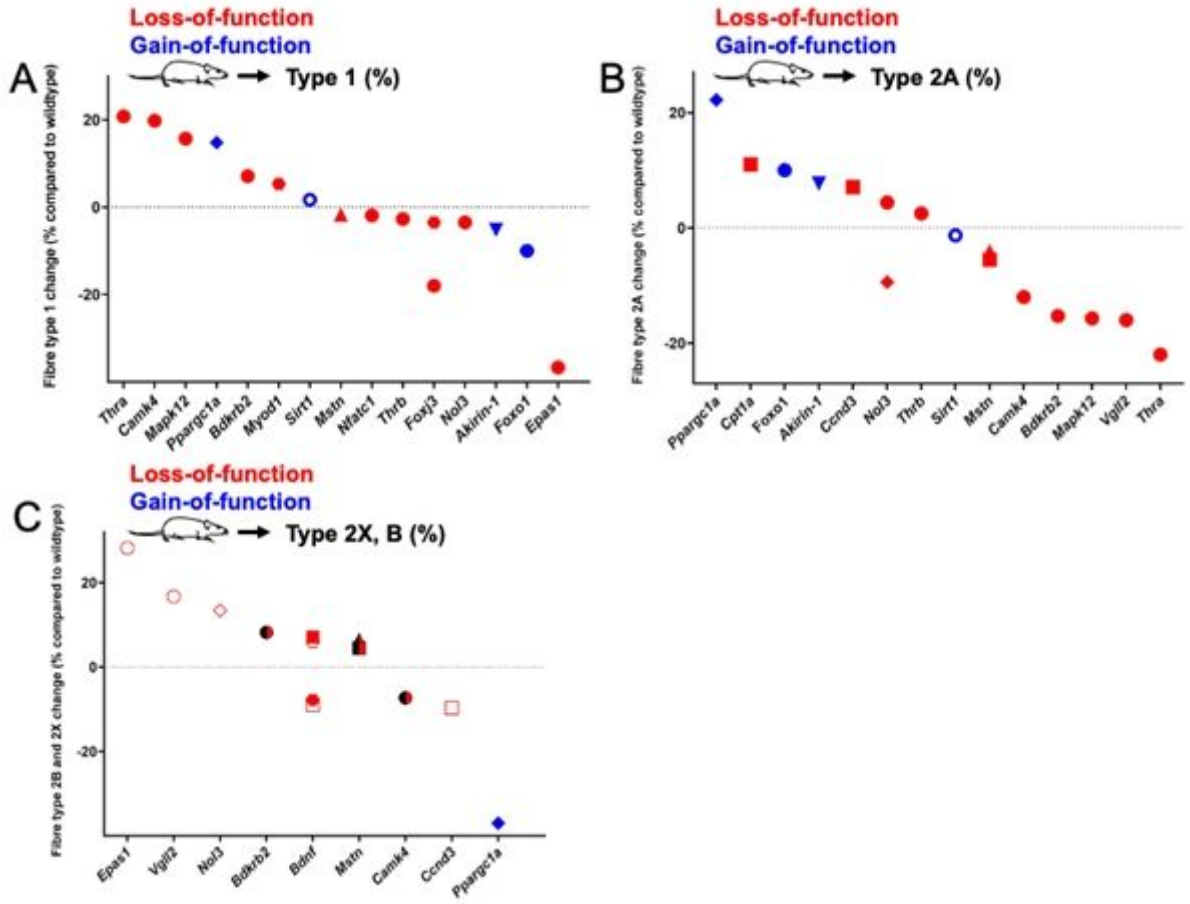

Figure 1

Genes whose gain or loss-of-function significantly changes the percentages of type 1 (A), type 2A (B) or type 2X/B (C) fibres when compared to wildtype or control mice. ●Soleus; ▯Extensor digitorum longus (EDL); ▯Plantaris; ▯Tibial anterior; ▲Biceps femoris; ▼Quadriceps; OGastrocnemius. Note that the "O"-marked data in A and B were reported as statistically significant even though there are close to "0" (=no change).

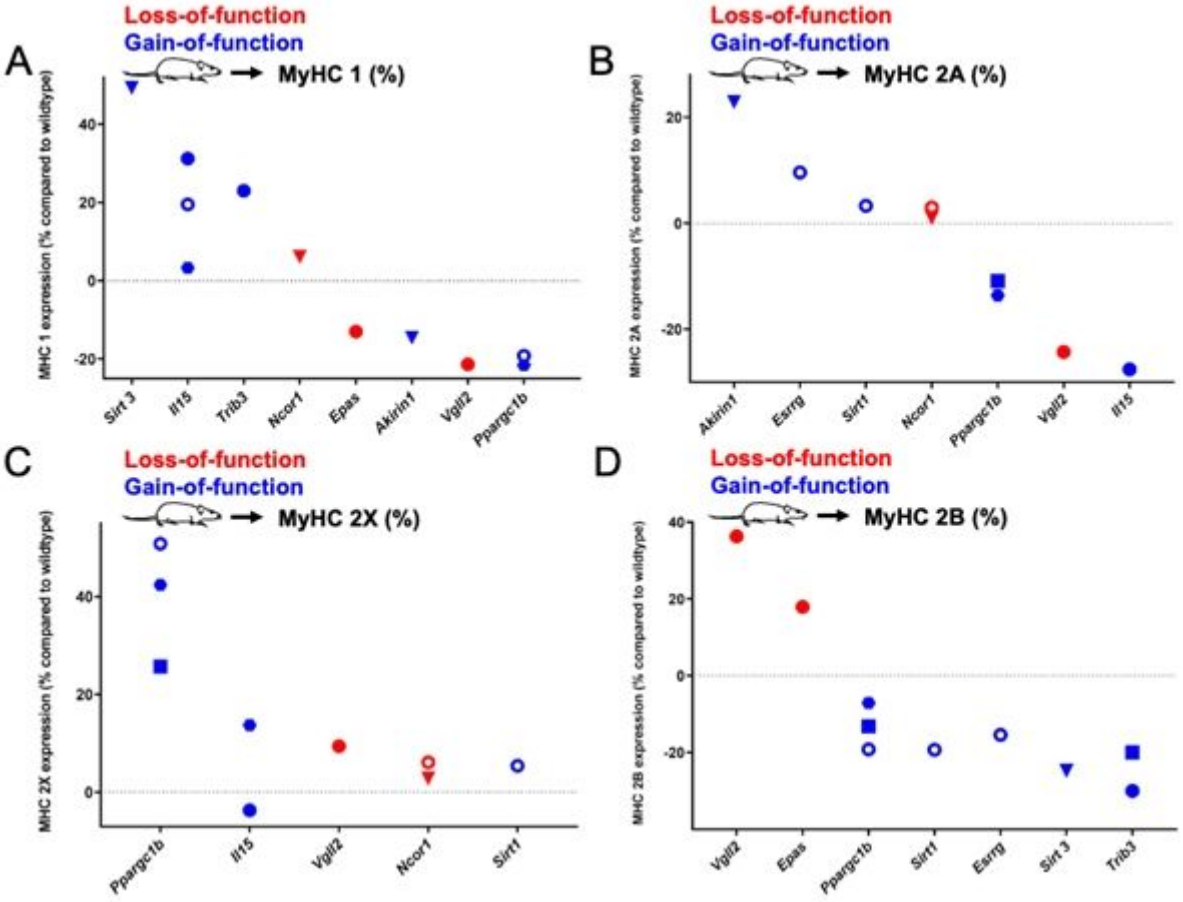

Figure 2

Genes whose gain or loss-of-function significantly changes the relative expression of type 1 (A), type 2A (B), type 2X (C) or type 2B myosin heavy chain (MyHC) isoforms when compared to wildtype or control mice. ●Soleus; ▯Extensor digitorum longus (EDL); ▯Plantaris; ▯Tibial anterior; ▲Biceps femoris; ▼Quadriceps; **O**Gastrocnemius.

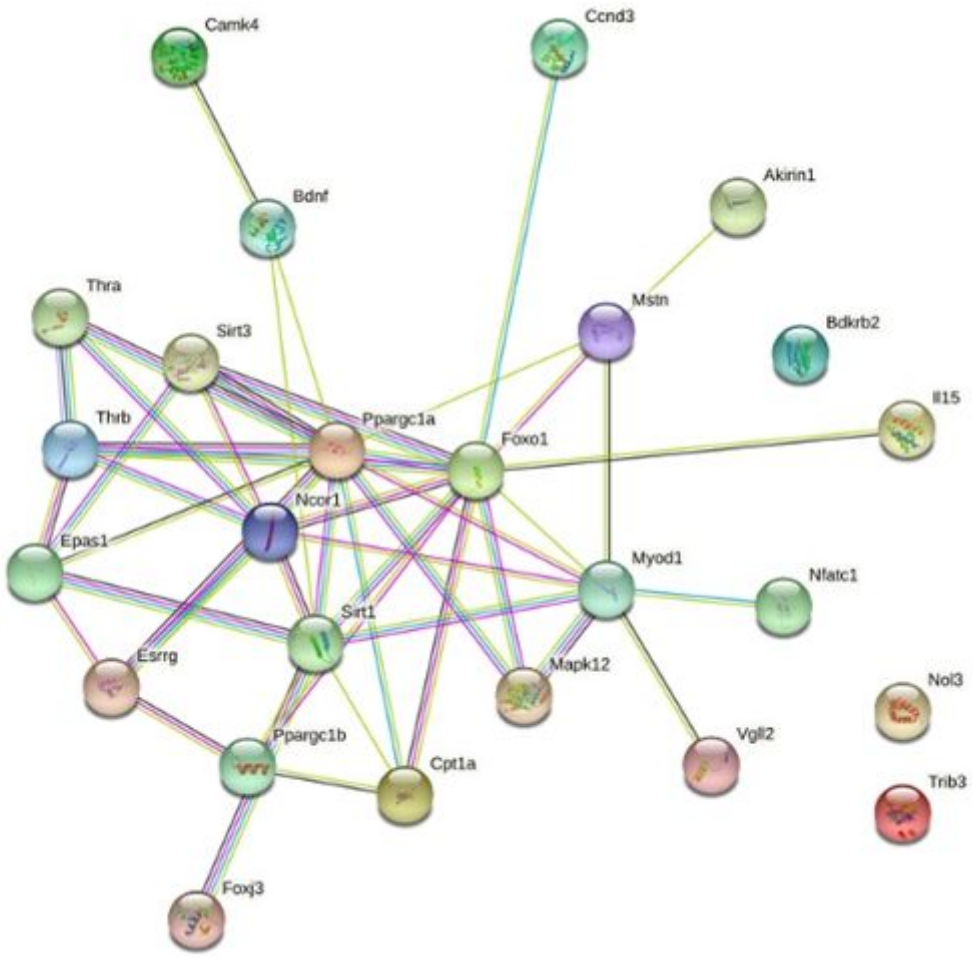

Figure 3

String analysis for interactions between muscle fibre proteins. Lines between proteins indicate evidence for interaction.

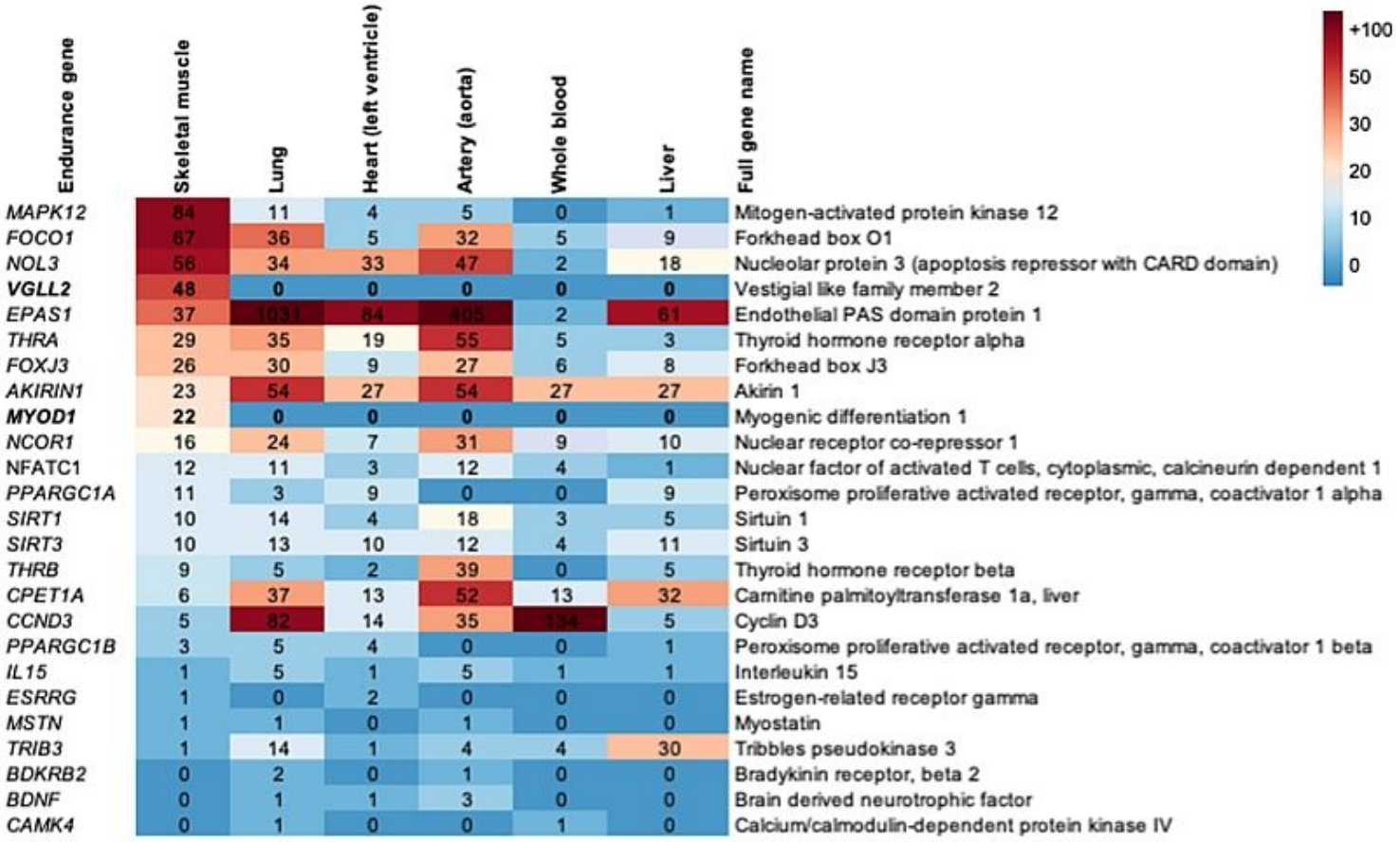

Figure 4

Heatmap illustrating the expression of muscle fibre genes in different human tissues in transcript per milion (TPM) and in the order of highest expression in skeletal muscle.

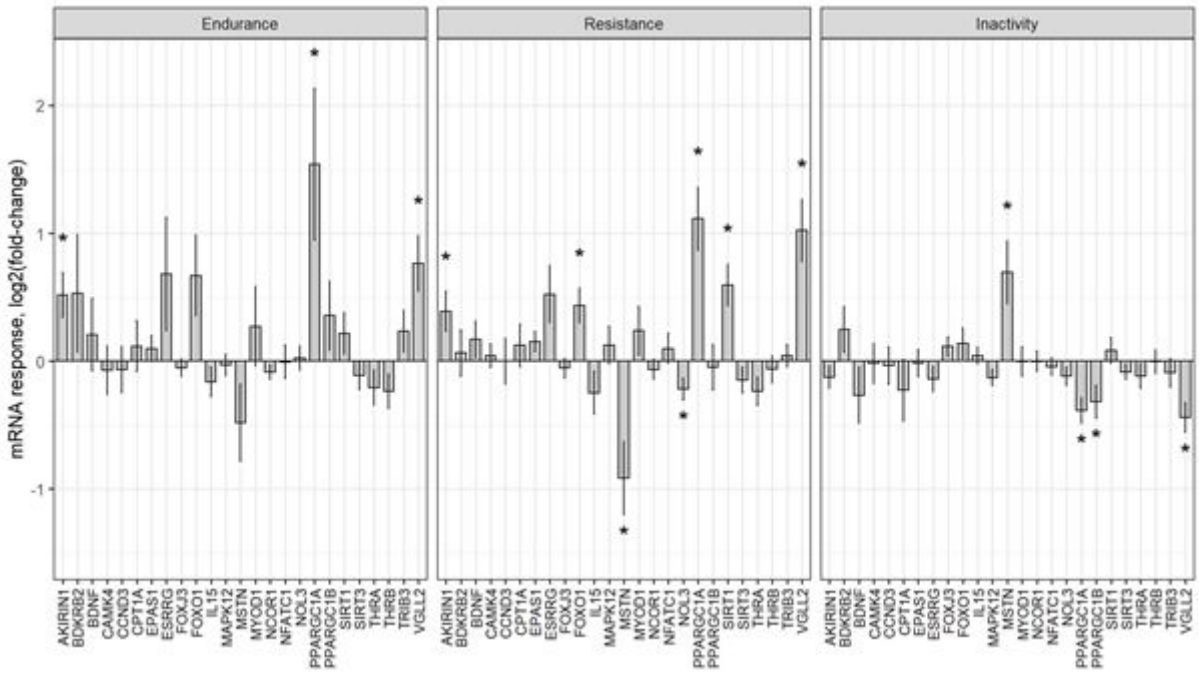

Figure 5

Meta-analysed expression change data of muscle fibre genes after acute bouts of endurance exercise, resistance exercise and inactivity (red: FDR<0.05).

Supplementary Files

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