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REVIEW

Genetic and epigenetic sex-specific adaptations to endurance exercise

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ABSTRACT

In recent years, the interest in personalised interventions such as medicine, nutrition, and exercise is rapidly rising to maximize health outcomes and ensure the most appropriate treatments. Exercising regularly is recommended for both healthy and diseased populations to improve health. However, there are sex-specific adaptations to exercise that often are not taken into consideration. While endurance exercise training alters the human skeletal muscle epigenome and subsequent gene expression, it is still unknown whether it does so differently in men and women, potentially leading to sex-specific physiological adaptations. Elucidating sex differences in genetics, epigenetics, gene regulation and expression in response to exercise will have great health implications, as it may enable gene targets in future clinical interventions and may better individualised interventions. This review will cover this topic and highlight the recent findings of sex-specific genetic, epigenetic, and gene expression studies, address the gaps in the field, and offer recommendations for future research.

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Introduction

As hunter-gatherers, males and females had different contributions to subsistence in society. While there are divergent views of their respective roles among different societies, anthropologists agree that there has always been a division of labour between males and females. For example, while the indigenous males and females of Paraguay both engaged in a high level of activity by traveling great distances and carrying heavy items, males were often hunting while women were moving the household and involved in childcare [1,2]. The roles of males and females in society throughout history are correlated with their physiological strengths and weaknesses. Generally, males are taller, heavier, leaner and stronger, while women have better relative endurance [3–6]. Decades ago, studies identified that, as a result, males and females adapt differently to endurance exercise [5,7–10]. Nonetheless, relative to body size, males and females are able to achieve comparable gains in strength and fitness after exercise training [5,7,10]. However, the mechanisms driving sex-specific adaptation to exercise are largely unknown. The purpose of this narrative review is to compile the sex differences in gene expression, genetics, and epigenetics of endurance exercise to bring new insight into the underlying mechanisms for the sex differential response to exercise.

Males and females adapt differently to endurance exercise

Endurance exercise training leads to a host of adaptations that contribute to improved health and skeletal muscle function. Among the most significant of these is an increase in maximal oxygen uptake (VO_2max), and many other exercise-related phenotypes [11]. Examples of sex-specific adaptations to endurance exercise are numerous. After a nine-month endurance exercise program of 45 minute sessions five time a week, older males and females (ages 60–69) both increased their VO_2max by comparable relative amounts, but males did so primarily by increasing stroke volume (volume of blood pumped to body from heart per beat) while females mostly increased

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arteriovenous oxygen supply [10]. It is also well-known that males and females differ in substrate utilisation during endurance exercise. A plethora of studies have shown that, when compared to males, females rely less on carbohydrate and protein sources and more on fat sources to support substrate oxidation during endurance exercise [12–15]. These sex differences may partly be explained by estrogen concentration and activity, since estrogen (specifically 17-β-estradiol) administration increases intra-muscular triglycerides in male rats [7]. Additionally, there are sex differences in fibre type distribution and cross-sectional area in many muscle groups [3,16,17]. Females tend to have a higher percentage of slower type I and IIA fibres compared with males. This reflects the lower contractile velocity and the enhanced fatigue-resistance of females, as oxidative fibres allow for enhanced endurance and recovery [3]. Reviews have already discussed sex differences in skeletal muscle fatigability [18] and metabolism [12,19] during exercise, thus our review will focus on the sex differences in genetics and gene regulation of endurance exercise to expand on the underlying molecular mechanisms involved.

Recently, individualised medicine, nutrition, and exercise have gained much attention due to the observation that every individual is different and responds differently to treatment [20–22]. While there is much inter-individual variation in response to exercise [23–25] and some of the mechanisms involved remain to be understood, the between-sex variation in response to exercise at the molecular level has not been well-explored. Most studies investigating the molecular modulators of response to endurance exercise have either solely studied males [26–28], or combined males and females and adjusted for sex as a confounder in statistical modelling [23,29–32]. The few studies that have directly compared the response to exercise between males and females will be discussed. More endurance exercise studies on both males and females are required to compare underlying molecular adaptations between the sexes.

Sex differences in skeletal muscle gene expression following endurance exercise

Skeletal muscle is among the tissues with the most sex-differentially expressed genes in humans [33,34]. Studies have found between 66 to 3000 sex-differentially expressed genes in skeletal muscle at rest [33,35–39]. Using high-throughput microarray analysis, Maher *et al.* identified 49 sex-differentially expressed genes (after Y-linked genes were removed) at rest that have known functions in metabolism, mitochondrial function, transport, protein biosynthesis, cell proliferation, signal transduction pathways, transcription and translation. For example, females had higher mRNA levels of acyl-coenzyme A acetyltransferase (*ACAA2*), trifunctional protein β (*HADHB*), catalase, lipoprotein lipase (*LPL*), and uncoupling protein-2 (*UCP2*) compared with males. However, protein content of *HADHB, ACAA2*, and catalase did not show any sex-based differences, and UCP2 and LPL protein content was not measured [37]. RNA deep sequencing of human skeletal muscle at rest identified ~3000 genes that were differentially expressed in males and females [39]. Mitochondrial genes involved in acid and ketone metabolism, oxidation and reduction, cellular respiration, and fatty acid metabolism (i.e., peroxisome proliferator-activated receptor PGC-1α and citrate synthase) were enriched in females, while protein turnover genes (i.e., translation initiation factors) were enriched in males. However, there were no sex differences in citrate synthase enzymatic activity and PGC-1α protein levels were not evaluated [39].

Since exercise upregulates multiple genes in human skeletal muscle [40,41] and many of those genes display sex-specific differences at rest, studies have attempted to elucidate skeletal muscle mRNA differences between males and females following exercise. Males and females display distinct skeletal muscle mRNA and protein response of exercise-related genes following both endurance and resistance training [35,38,42–46]. One study has investigated sex differences in global gene expression following 3 months of endurance training and reported no sex differences [47]. However, a comprehensive study of acute resistance exercise did report differences between male and female skeletal muscle transcriptomes in response to exercise. The authors detected sex differences in the timing of regulation of many biological processes, including but not limited to oxidative phosphorylation, muscle protein proteolysis, and tissue remodelling. Specifically, the changes in gene expression were prolonged in males yet rapidly restored in females. [35] While the one study that compared genome-wide gene expression following

endurance exercise between males and females did not find any sex differences, more studies are required to confirm and explain these findings.

Sex-based genomics in endurance exercise responses

The heritability of VO_2max, a strong indicator of endurance performance, is estimated to be between ~ 22–57%, meaning that ~22–57% of the variability in VO_2max observed in a population can be attributed to genetic variation [48]. Completion of the sequencing of the human genome in 2001 [49] paved the way for DNA sequencing for identification of specific genetic variants correlated with a particular phenotype (e.g., exercise responses/performance outcomes). Since then, various genetic variants that may provide an advantage in exercise performance have been identified; for a detailed review see references [24,50]. Identifying such genetic variants and their downstream modes of action provide new insight to exercise adaptations. However, it is important to note that athletic ability is a complex trait that is influenced by many aspects and genetic variants, thus making it challenging to identify variants with large effect sizes. Furthermore, common variants typically have small influences on a given trait. A thorough review [51] and a recent commentary [24] on sports genetics highlight the need for larger sample sizes, and both ethnicity-specific and sex-specific analyses to confirm effect sizes of common variants.

To date, two gene variants associated with exercise phenotypes have been substantially replicated in multiple cohorts: alpha-actin-3 (*ACTN3 R577X*) and angiotensin converting enzyme (*ACE I/D*). Both variants were discovered using the candidate gene approach, which is used to find correlations between pre-specified single nucleotide polymorphisms (SNPs) and phenotypes. Most studies found associations between exercise response/performance and the *ACTN3* and *ACE I/D* variants, however, some studies have not. It has been hypothesized that some of the heterogeneity in results is due to sex differences as cohorts are often mixed-sex [52].

ACTN3 encodes the alpha-actin-3 protein that is expressed in the sarcomere of fast glycolytic type II fibres and is important for the generation of explosive power contractions. The substitution of an arginine (R) with a stop codon (X) at the 577 amino acid results in deficiency of the ACTN3 protein (*ACTN3* XX genotype). Most of the studies regarding the association between the *ACTN3* variant and performance report that the RR genotype or the R allele is associated with strength and muscle power [53–55]. Some studies reported sex differences in the genotype-phenotype association of the *R577X* variant [54,56,57], for example, Shang *et al.* studied the frequency of RR among endurance athletes and found lower frequency of the RR genotype in female endurance athletes compared with controls, but not in males (18.6% RR in female endurance athletes (n = 250) *vs* 33.6% RR in control females (n = 450)) [57]. These findings suggest that the X allele may have an advantageous effect on endurance performance in females but not in males. This sex difference could be explained by androgen hormones. Specifically, higher testosterone levels in males could contribute to performance improvements and reduce the relative influence of the *ACTN3* on muscle power, but this hypothesis has not been verified experimentally [54,56,58]. However, a study of 486 power athletes and 1,197 controls reported no sex differences in the association of *ACTN3* with performance [53]. Therefore, the *R577X* polymorphism may be contributing to exercise performance differently in males and females, but is not certain at this point.

ACE encodes the central component of the renin–angiotensin system (RAS), angiotensin converting enzyme, which is expressed in skeletal muscle, cardiac muscle, endothelial and kidney epithelial cells [59,60]. ACE indirectly increases blood pressure by causing blood vessels to constrict. The deletion (termed 'D allele') or insertion (termed 'I allele') of a 287 base pair fragment at location 17q23.3 is a common variant of the gene. The I allele is generally associated with decreased ACE activity and better endurance performance, while the D allele is associated with increased ACE activity and improved muscle strength [60–68]. One study on Japanese endurance track athletes found associations between the I allele and race distance in men but not in women (12.1% II in short distance male runners *vs* 49.3% II in long distance male runners, n = 277 athletes) [61]. Also, one study found that the *D* allele is associated with hypertension in young males but not in young females (n = 5014, randomly selected from population); specifically, in DD men the odds

of having hypertension increased by a factor of 1.75 compared with II men. Interestingly, this difference was not observed between men and women aged 61–79 [69]. Therefore, the *ACE* I/D genotype-phenotype association may be sex-dependent, however as previously mentioned, many studies either have mixed-sex cohorts [64], only male cohorts [66], or do not have large enough sample sizes to detect potential sex-differences [64,68].

Genome-wide association studies (GWAS) have emerged as a more effective way to determine the contribution of SNPs to a specific trait or phenotype. As opposed to the candidate-gene approach that is hypothesis-driven, GWAS are unbiased, hypothesis-free, and allow for discovery of novel SNPs and their associated phenotypes. Many exercise GWASs adjust their statistical model for sex [23,70,71]; however, some recent GWASs found sex differences in the contribution of particular SNPs to exercise phenotypes [72,73]. Since females may have increased parasympathetic and decreased sympathetic control of heart rate in comparison to males, Ramirez *et al.* studied the association of genotype with the capacity of heart rate response during acute exercise. They identified two SNPs that showed sex-specific associations with the heart rate response to exercise in ~40,000 individuals. Specifically, one locus (*HLA-DRB5/HLA-DRB1*, rs9270779) was only significant in females (after exercise, every additional C allele at rs9270779 was associated with an additional HR change of 0.538 beats/min) while the other locus (*TAF2*, rs60717250) was only significant in males (after exercise, every additional C allele at rs607-17250 was associated with an additional HR change of 0.486 beats/min) [73]. However, it is important to note that statistical analyses between the sexes was not performed, in other words, although significance at a given locus was reached in one sex and not the other, it does not mean that there was statistical significance between the sexes. Another large-scale GWAS (n = 195,180) determined the association of 16 SNPs with grip-strength and found no sex differences in individual SNP association with the trait; however, this study found a stronger association between the 16 SNP genetic score and grip strength in males than females (in males every unit increase in genetic score was associated with a 0.2 kg increase in grip strength while in women the increase was only 0.13 kg) [72]. Therefore, it is particularly important to determine SNP contributions to exercise phenotype in a sex-specific manner.

A recent and comprehensive review on the role of sex in genomics of human complex traits brings up important aspects to be taken into consideration in sex-specific genomics. The review proposes three models/mechanisms that contribute to the observed phenotypic sex differences (in human complex traits, specifically epidemiological studies). The first model states that differences in heritability (which SNPs and their effect sizes) contribute to the observed sex differences, however, heritability studies estimate that *only* <5% of the genetic basis of complex traits differ between males and females. The second model states that sex differences in the sex chromosomes have some associations with disease, but alone are unlikely to explain a large proportion of the phenotypic sex differences. Finally, the third model states that sex differences in gene-by-environment interactions are indeed common and are more likely to contribute to the observed sex differences in complex traits [74]. As previously stated, exercise-related phenotypes are complex traits, therefore focusing on the gene-by-environment, or epigenetic, contribution to sex differences will be important for understanding the underlying mechanisms of exercise-related sex differences.

Skeletal muscle epigenetic differences between males and females in response to endurance exercise

Epigenetic modifications can be defined as the structural adaptation of chromosomal regions that bring about altered activity states [75,76]. The main types of epigenetic modifications include DNA methylation, histone modifications, and non-coding RNA including microRNA (miRNA) and long noncoding RNA expression [77]. Epigenetic events up- or down-regulate gene expression and corresponding protein translation, resulting in phenotypical and physiological changes [78]. The mammalian male and female autosomal epigenomes (DNA methylation, histone modifications, and miRNA) display considerable differences in tissues such as human blood, saliva and skeletal muscle as well as mouse liver and brain [79–87]. Recently, it was suggested that epigenetic modifications influence exercise adaptation [88], and comprehensive reviews have described the potential regulatory effects of epigenetic modifications in the

response to exercise training [31,76,88–92]. Epigenetic differences may therefore explain some of the sex differences observed in exercise adaptations. Our current understanding of exercise adaptations is based on studies that have mostly investigated only males or grouped males and females together, and have not taken into consideration the potential sex differences in exercise adaptations. Furthermore, there may be sex differences in the epigenetic response to exercise. Since epigenetic changes are associated with health and disease (i.e., cancer and metabolic disorders) [93,94], and exercise influences epigenetics, epigenetics may be one of the underpinning mechanisms behind the lower disease rate in physically active individuals [95]. Therefore, it is important to elucidate the sex differences in exercise epigenetics.

DNA methylation

DNA methylation is the addition by DNA methyltransferase (DNMT) enzymes of a methyl group to the 5☒ position of a cytosine base. DNA methylation alters protein-protein and protein-DNA interactions, affecting chromatin structure and ultimately increasing or decreasing transcription [96]. DNA methylation is stable through cell divisions, yet dynamic throughout one's lifetime as it is influenced by environmental stimuli (such as exercise training and nutrition) [30,78]. Previous studies have shown that exercise triggers small (< 10%) and widespread DNA methylation changes in skeletal muscle [29,97]. To date, two studies have suggested that there may be sex-specific changes in skeletal muscle DNA methylation following exercise, given that sex was a major determinant of variability [29] and that larger effect sizes were observed in females [31], however these potential sex differences were not further investigated (discussed below). Exercise epigenetics is a new and exciting research field, and we currently have limited knowledge on if and how epigenetic signals, such as DNA methylation, mediate exercise responses.

A seminal study in 2012 reported lower DNA methylation in specific genes 20 minutes after a bout of high-intensity endurance exercise [30], demonstrating the rapid dynamics of DNA methylation. Potential sex-specific responses were not reported in this study. However, the rapid demethylation of exercise-responsive genes shows that acute control of DNMT activity during exercise is important for this response. *In vitro* studies suggest that DNMT3B is an important regulator of this gene program [98]. Interestingly, DNMT3B expression in human liver is significantly higher in females than males [99], although it is unclear whether this is also the case in skeletal muscle. While DNMTs are involved in DNA methylation, ten-eleven translocation (TET) enzymes are involved in DNA demethylation. TET enzymes are expressed in human skeletal muscle [100], and given how recently they were discovered, sex differences in skeletal muscle TETs have yet to be investigated. However, one study did not find sex differences in TET expression in mouse hippocampal tissue [101]. Nonetheless, unravelling the dynamics of DNMTs and TETs in both sexes is warranted to reveal the nature of DNA methylation in exercise adaptations.

A recent study is the first to thoroughly investigate DNA methylation sex differences in human skeletal muscle myoblasts and myotubes (13 men, 13 women). Genome-wide DNA methylation and gene expression (measured with microarrays) were performed on the autosomes and the X-chromosomes. Several pathways related to the cell cycle and energy, protein and fatty acid metabolism were enriched in females while pathways mostly related to cell-cell communication (e.g. transforming growth factor-beta, TGF-beta, signalling) were enriched in males. They confirmed the direct DNA methylation effect on gene expression using the luciferase assay method. They found sex differences in both DNA methylation and gene expression for 40 genes in myoblasts (including *LAMP2* and *SIRT1*), 9 in myotubes (*KDM6A*), and 5 in both myoblasts and myotubes (*CREB5, RSP4X, SYAP1, XIST, ZRSR2*). Furthermore, this study found more DNA methylation differences during cell differentiation in females compared to males on the autosomes. These intrinsic differences may contribute to the sex-specific differences observed in muscular phenotypes [102]. These findings highlight the importance of taking sex into account in biomedical research, as future medicine will further benefit from such findings. Furthermore, it reinforces the importance of investigating whether sex differences in DNA methylation are also involved in the adaptation to exercise.

A meta-analysis of 16 studies identified 478 loci (307 in skeletal muscle) that undergo methylation changes following either acute (one bout) or chronic exercise (walking, cycling, and tai-chi). DNA

methylation changed to a larger degree (i.e., larger effect size) in females than males following exercise, suggesting sex differences in the epigenetic response to training [31]. However, a sex comparison was not the focus of this study, so specific DNA methylation differences between males and females were not investigated. Additional studies have found that long-term exercise is associated with changes in DNA methylation in human skeletal muscle [29,97]. After 3 months of one-legged knee extensor exercise training in men and women, 4919 loci were differentially methylated in the exercised leg, compared with the control leg. Training and sex were identified as major determinants of variability in methylation on autosomal DNA. Sex was treated as a confounder, but no statistical analysis was performed to determine whether males and females differed in their DNA methylation response to exercise and which specific methylation sites were altered in each sex [29]. Of note, most of the aforementioned studies have uploaded their raw DNA methylation data on the Gene Expression Omnibus (GEO) platform, making it possible to explore potential sex differences in epigenetic response to exercise.

The meta-analysis by Brown also highlights the importance of identifying sex-differences in exercise-induced methylation of genetically imprinted genes [31]. We typically inherit two working copies of a gene from each parent; however, close to 100 human genes are imprinted [103], meaning that only one allele is expressed in a parent-specific manner. These loci are conserved among humans, meaning that a maternal locus will always express the inherited maternal allele [104,105]. Imprinted genes are of great medical significance since they are essential for healthy offspring development, and imprinting dysregulations may lead to metabolic and neurodevelopmental disorders [31,106]. Five loci that underwent DNA methylation changes following training (chronic exercise) were imprinted loci (two loci in skeletal muscle) [31], however sex differences in those genes were not investigated. No study, to date, has investigated whether there are sex-specific differences in DNA methylation changes at imprinted genes following exercise. An editorial on the topic calls for exercise studies to investigate the effect of timing and dosage of maternal exercise on methylation of imprinted genes in offspring. It is currently hypothesized that the dosage of maternal exercise will influence the offspring epigenome in a dose-dependent manner (i.e., positive effects at low/moderate doses and negative effects at high doses) [107]. Since exercise is a gestational stressor (that leads to epigenetic changes in the gamete) and the susceptibility to gestational stressors differs between the sexes [108,109], it is likely that maternal exercise affects the gamete epigenome differently between the sexes.

Histone modifications

DNA coils around histone proteins for structural and functional reasons. The amino acid residues within histone tails can be modified by acetylation, phosphorylation, methylation, ubiquitination, sumoylation, or ADP ribosylation. These modifications alter histone-DNA interactions and promote recruitment and access of major transcriptional regulators to DNA [40,110]. Like many other post-translational modifications, histone modification is a dynamic process and controlled by numerous enzymes that both add and remove these post-translational modifications. For example, histone acetyltransferases (HATs) add acetyl groups to histone lysine residues, which is a common mechanism to induce transcriptional activation. Histone acetylation generally neutralises electrostatic interactions between histones and DNA, which exposes promoter and gene body regions to transcriptional activators, such as RNA polymerase. Conversely, histone deacetylases (HDACs) remove acetyl groups from histone proteins, resulting in transcriptional silencing. The localisation of HATs and HDACs to particular chromatin regions is highly dependent on DNA bound transcription factors. Reviews have outlined the effect of acute exercise on histone modifications [40,88,111]. For example, skeletal muscle contractions induce phosphorylation and nuclear export of the class IIa HDACs, resulting in the relaxation of chromatin regulatory regions in exercise-related genes [112,113]. Acute exercise typically induces nuclear export of HDACs 4 and 5, causing hyperacetylation of some histone residues. This results in increased glucose transporter type 4 (*GLUT4*) expression, which supports enhanced energy consumption [114,115]. Histone deacetylation may therefore regulate the response to exercise. Indeed, genetic disruption of the class IIa HDAC corepressor complex induces exercise-like transcriptional and metabolic adaptive responses [116]. Sex-specific differences in

the class IIa HDAC signalling and function in response to exercise have been explored in humans, however no differences were observed [117].The effect of sex hormones on sex-specific histone modifications and transcriptional responses to exercise is an area that is yet to be explored in any detail. Activated estrogen receptors (ERs) regulate gene expression by altering the balance of HAT and HDAC enzymes at specific chromatin regions, resulting in increased histone acetylation and transcriptional activation [118,119]. Exercise and ERs regulate a number of common gene programs involved in skeletal muscle metabolism [120] but whether there are sex-specific differences in the ER responses to exercise has not been established. Sex-specific differences in substrate utilisation could also impact on histone acetylation responses, with females having a greater reliance on fatty acid oxidation at any particular submaximal power output. It has recently emerged that fatty acids play an important role in providing the acetyl-CoA required for acetylation reactions, with up to 90% of acetylation at specific histone acetylation marks being from carbon derived from fatty acids [121]. The greater reliance on fatty acid oxidation for ATP generation in females could suggest that the availability of free acetyl-CoA for acetylation reactions is reduced, which in turn would impact gene expression responses. These mechanisms have not yet been investigated in well-controlled studies allowing the analysis of sex-specific responses.

Although histone acetylation is important for transcriptional initiation, a plethora of other histone post-translational modifications play a role in transcriptional responses. Beyond acetylation, there are no studies that have examined histone modifications in response to exercise, yet alone in a sex-specific manner. Understanding the histone modifications evoked by exercise will be important for deciphering sex-specific responses to exercise, as well as understanding interactions with other epigenetic process such as DNA methylation and how they together impact the adaptive response to exercise.

MicroRNA

MiRNAs are derived from double-stranded hairpin loops of about 70 nucleotides, which are cleaved by Dicer protein into single strands of ~22 nucleotides. These small, noncoding RNAs inhibit the translation of specific mRNA targets by either inducing degradation of the mRNA transcript or physically inhibiting the access of translational machinery to the mRNA, ultimately decreasing the expression levels of the targeted mRNA [122–124]. The network dynamics of miRNAs is complex since many miRNAs may work together to repress a certain gene and many genes can be regulated by the same miRNA [125]. Several reviews have summarized the effects of exercise on miRNA expression [90,126–128]. Briefly, specific miRNAs are upregulated and downregulated with both acute and chronic exercise in humans [27,129,130]. Russell *et al.* reported an increase in miR-1, −133a, −133b and −181a, as well as key components of the miRNA biogenesis pathways and a decrease in miR-9, −23a, −23b and −31 three hours after a single bout of high-intensity interval endurance exercise in human males [27]. Additionally, they found that after 10 days of training, miR-1 and −29b were increased, while miR-31 remained decreased (as in the acute testing) [27]. Using reporter assays, this study validated some of the associations of the miRNAs with predicted targets HDAC4 and nuclear respiratory factor 1 (NRF1), both of which are regulated during exercise and are thought to contribute to exercise adaptive responses [41,115]. Acute and short-term exercise regulate several miRNAs that are potentially involved in the regulation of skeletal muscle regeneration, gene transcription, and mitochondrial biogenesis, suggesting that miRNAs play a role in exercise adaptation. However, no studies investigated the potential differences between males and females in skeletal muscle miRNA activity following exercise. One study investigated the differences in muscle-specific miRNAs, termed myomiR (miR), between males and females at rest [86]. They found sex differences in two (miR-133a and b) of four miRNAs (miR-1, miR-133a, miR-133b, and miR−206) that are crucial for the regulation of skeletal muscle development and function and are known to change following exercise [86]. One study found sex differences in miRNAs in saliva that changed following one bout of long distance running [79]. While those sex-differentially expressed miRNAs are inferred to be involved in fatty acid biosynthesis pathways, targets were not validated. Further research is therefore needed to determine whether miRNA regulation of gene expression contributing to exercise adaptation differs between males and females.

Conclusion and recommendations for future research

Males and females performing similar endurance training can have comparable relative improvements in fitness, but the underlying molecular mechanisms may be different. GWASs have identified that some SNPs or SNP scores are associated with exercise adaptations differently between males and females [72,73]. Studies on the correlation between genotype and phenotype are controversial for the well-known exercise SNPs in *ACTN3* and *ACE*, which might partially be attributed to sex differences. Despite the multitude of research conducted on exercise genomics, there is still a lack of knowledge on specific genes. This is reasonable given that exercise-related phenotypes are polygenic and influenced by many other factors, which make it challenging to identify genes with large effect sizes. Therefore, future studies in the field should aim for larger sample sizes and perform sex-specific analyses. Currently, consortia and large-scale studies are underway to advance exercise genomics. The recently established Athlome consortium project (www.athlomeconsortium.org), led by members of our group, is comprised of 15 research groups that are combining genomic, epigenomic, transcriptomic, proteomic, and metabolomic data to uncover the 'omics' basis of elite performance, training response, and predisposition to exercise-related injuries [24]. Future studies in this field should take into consideration the sex of the participants, given some of the sex-specific exercise genomics discussed in this review. Males and females differ in exercise-related skeletal muscle gene expression [39]. Additionally, studies have suggested that males and females may differ in exercise-induced DNA methylation changes following endurance exercise [29,31], but no detailed analysis has been performed. No studies to date have investigated whether there are skeletal muscle sex differences in histone modification and miRNA activity following exercise. Given that gene-environment interactions are likely to explain many of the observed phenotypic sex differences in complex traits [74], it is crucial to identify the epigenetic differences between males and females following exercise. A recent study has found sex differences in DNA methylation in human skeletal muscle myotubes and myoblasts [102], reinforcing the need to determine whether skeletal muscle DNA methylation sex differences exist in exercise adaptations as well. Additionally, studies have found transcriptome-wide sex differences in exercise-related gene expression at rest [35,39], and only one study has investigated transcriptome-wide sex differences in the response to exercise and did not find sex differences [47]. Furthermore, the field is lacking protein expression verification.

As we continue to expand our knowledge on the underlying mechanisms of exercise adaptations, we recommend that researchers consider the potential sex-specific differences involved. Recent mice studies have also found sex differences in exercise adaptations, highlighting the sex gap in both human and animal exercise research [131]. Major findings on the effect of genetic variants, the genes undergoing epigenetic regulation, and the downstream protein and gene expression should not only perform experiments on both males and females, but should also split them into two separate cohorts to obtain reliable results. Females are under-represented in sports and exercise medicine research [132]. While controlling for the female hormonal cycle may be challenging for research, there are many ways to take those fluctuations into consideration; therefore females should be included in exercise studies. Future studies related to exercise adaptations should integrate genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics to reveal the underlying molecular mechanisms of sex-specific exercise adaptations. Additionally, future studies should validate their targets/pathways to confirm their findings. Current efforts are being made to elucidate the exercise adaptations in both males in females in a tightly controlled study, the Gene SMART (Skeletal Muscle Response to Training) study [133]. This study is exploring 'omics' data to understand the potential sex differences following acute and long-term high-intensity interval training. Altogether, taking sex into consideration in biomedical research is imperative, as it can be of further importance for future medicine. Elucidating the genetic and epigenetic sex-specific adaptations to exercise is expected to bring highly innovative fundamental knowledge on how individuals respond to exercise, as well as pave the way for future translational studies that are likely to provide evidence-based recommendations regarding personalised health-related interventions.

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