Review

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Sex differences in disease genetics: evidence, evolution, and detection

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Understanding the genetic architecture of disease is an enormous challenge, and should be guided by evolutionary principles. Recent studies in evolutionary genetics show that sexual selection can have a profound influence on the genetic architecture of complex traits. Here, we summarise data from heritability studies and genome-wide association studies (GWASs) showing that common genetic variation influences many diseases and medically relevant traits in a sex-dependent manner. In addition, we discuss how the discovery of sex-dependent effects in population samples is improved by joint interaction analysis (rather than separate-sex), as well as by recently developed software. Finally, we argue that although genetic variation that has sex-dependent effects on disease risk could be maintained by mutation–selection balance and genetic drift, recent evidence indicates that intra-locus sexual conflict could be a powerful influence on complex trait architecture, and maintain sex-dependent disease risk alleles in a population because they are beneficial to the opposite sex.

Can sex differences explain the missing heritability?

Heritable diseases are loosely classified as being rare or common (prevalence >0.1%). Rare diseases have a monogenic aetiology, whereas common diseases are caused by multiple genetic variants, each with high population frequency but small individual contribution to disease risk [1,2]. For the latter, GWASs (see Glossary) have been successful at identifying contributing loci, but the heritability accounted for by main effects, and by polygenic risk score, remains conspicuously low [3,4]. This deficit (generally referred to as 'missing heritability') is stimulating integration of other evidence-based factors such as the environment, epigenetics, and epistasis into analyses [5]. Here, we consider the role of sex (gender) in the genetic architecture of common, heritable medical disorders.

The difference in gamete size between males and females is a fundamental property of almost all sexual species. Sexual dimorphism also exists throughout the body in cellular and anatomical specialisation, secondary sexual traits such as ornamentation and behaviour, and in gene coexpression networks [6–8]. It is therefore unsurprising that in the field of medicine males and females frequently differ in core phenotypic features of disease [9]. Appreciating the magnitude and extent of these sex differences is important for the effective design of therapies, but at a fundamental level, it would also add to our understanding of how these differences evolve.

The simplest way in which a sex-dependent disease risk allele can be maintained in frequency is through mutation–selection balance and genetic drift. Selection alone is not a necessary condition, because a new allele can easily have a sex-dependent effect regardless of the selection on the trait that it might affect. An alternative mechanism for the maintenance of sex-dependent risk alleles is sexual antagonism, whereby an allele that is deleterious to one sex is maintained because it is beneficial to the other sex (Box 1) [10,11]. We refer here to intra-locus sexual conflict because it occurs across a single locus, in contrast with inter-locus sexual conflict, which concerns conflict between different

Glossary

Fitness: an evolutionary concept, applicable to individuals, comprised of (i) the ability to survive, and (ii) the number of offspring produced (fecundity). It is ideally measured as lifetime reproductive success.
Genetic architecture: the number, allele frequency in the population, and effect size of genetic variants that contribute toward phenotypic variance of a particular trait.
Genome-wide association study (GWAS): a method for identifying molecular genetic variation controlling heritable traits in a population sample. It involves assessing the correlation between allele frequencies and phenotype value, at millions of markers of common genetic variation across the genome.
Intra-locus sexual conflict: opposing direction of selection between males and females for a particular locus or single trait, for instance, where a sequence variant improves the fitness of one sex but reduces fitness in the other.
Sex-specific selection: difference in magnitude but not direction of selection between the sexes, for example, if a trait experiences stronger selection in one sex, or if a trait is sex-limited and therefore only subject to selection in one sex. Compare with sexually antagonistic selection.
Sexual antagonism: opposing direction of selection between males and females for a particular heritable trait that has a positive genetic correlation between the sexes. In contrast to intra-locus sexual conflict, sexual antagonism can involve different traits in each sex, and is therefore a more inclusive term.
Sexual dimorphism: a statistical difference between males and females in a population for the value of a particular trait. It may include anything from anatomical measurements to the expression level of a gene.
Sexually antagonistic selection: difference in direction (and possibly magnitude) of selection between the sexes, for example, if a trait experiences positive selection in one sex and negative selection in the other.
Single nucleotide polymorphism (SNP): DNA sequence variation occurring in multiple unrelated individuals in a population; stably inherited and caused by replacement of a nucleotide base with one of the remaining three. Depending on the exact location within the functional DNA sequence, SNPs can alter biological metrics, and contribute to complex traits and disease susceptibility.

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Box 1. Sexual antagonism and its role in the maintenance of genetic variation

Sexual antagonism results from sexually discordant (antagonistic) selection acting on a shared genome. Sexual antagonism has now been demonstrated in a wide variety of taxa, including plants, birds, mammals, and insects [11,94]. Anisogamy (difference in gamete size) is considered to be the ultimate source of sex-specific selection [95,96], although ecological factors can also play a role in shaping patterns of sex-specific selection [97]. Sex-specific selection is thought to result in the evolution of sexual dimorphism [98]. However, these divergent phenotypes must be developed from a shared gene pool, making it difficult to simultaneously achieve optimum trait values in both sexes. Thus, for certain traits, a conflict will be maintained and the sexes will be displaced from their optimum phenotypes. For example, in fruit flies (*Drosophila melanogaster*), when selection on females was removed, they became more masculinized, demonstrating that males had previously been displaced from their phenotypic optimum by counter-selection in females [99]. Pedigree analysis of wild animal populations has also demonstrated a negative intersexual genetic correlation for fitness, that is, genotypes producing successful males produce unsuccessful females and vice versa [100,101].

More formally, sexual antagonism occurs when genetically correlated traits have opposite effects on male and female fitness. In the simplest case, increasing values of a single trait would increase fitness in one sex and decrease it symmetrically in the other sex (Figure IA). In this case, it is assumed that the trait is positively correlated between the sexes. However, more complicated patterns are also possible, such as opposite fitness effects of different correlated traits (Figure IB,C) or asymmetric patterns of selection (Figure ID). Consistent with this, a recent study demonstrated that human height was likely to be subject to sexual antagonism: within sibling pairs, men of average height had higher fitness while shorter women had higher fitness [13]. This means that the fitness effect of a given height-determining allele will be context-dependent in terms of sex, and that the population as a whole will be unlikely to evolve towards a shorter phenotype, despite directional selection in females, because of counter-selection in males. Sexual antagonism has also been observed for tolerance to infection in the fruit fly *D. melanogaster* [102]. One of the major evolutionary implications of sexual antagonism is the maintenance of genetic variation that is deleterious to one sex. Although this has not been fully demonstrated at the molecular level, the population dynamics of a synthetic sexually antagonistic allele in a laboratory *D. melanogaster* study accurately follows predictions [65,66].

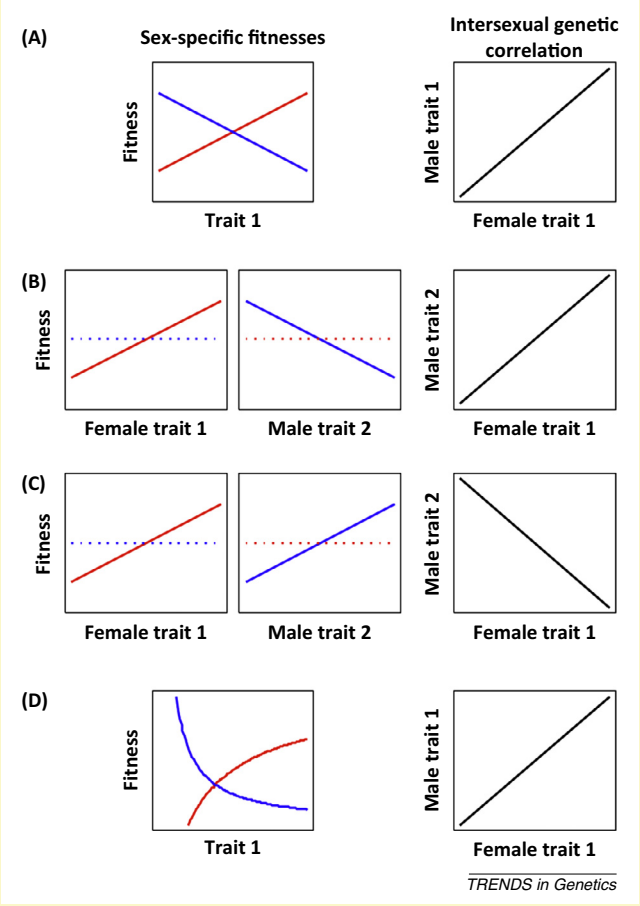

Figure I. The different forms of sexual antagonism. Female fitness functions are shown with red lines, male with blue lines, and the intersexual genetic correlation with black lines. **(A)** The simplest case (also known as intra-locus sexual conflict) is where the same trait has opposite and approximately symmetric fitness effects on males and females. The intersexual genetic correlation for the traits is high and positive. **(B)** Sexual antagonism can also occur when different traits have a high positive intersexual genetic correlation, but are selected in opposite directions in males relative to females. In the unselected sex (broken lines), selection for the trait in question might be weakly positive, neutral, or even absent if the trait is sex-limited. **(C)** Although no empirical examples of this type have yet been demonstrated, it is also possible that traits with a strong negative intersexual genetic correlation could be subject to sexual antagonism, assuming both traits are selected concordantly across the sexes. A negative intersexual genetic correlation could occur when the same gene product is incorporated in competing alternative pathways. **(D)** It should also be pointed out that selection pressures need not be completely symmetric. Non-linear relationships are also possible.

sets of genes in males and females, for example, competition between the seminal fluid and the female immune system in *Drosophila melanogaster* [12]. An example of intra-locus sexual conflict in humans is relative body height, which is positively selected in men, yet negatively selected in women despite being controlled by the same molecular genetic variation [13].

Insights from evolutionary biology are of great value here because theory about the ultimate origin and evolution of sex differences is well developed, both on the phenotypic and on the genetic level. Asymmetrical selection pressures operating between the sexes on genetic variants offer a long-term, evolutionary explanation for the existence of sexually dimorphic phenotypes, including those identified in human diseases. Sex differences in the genetic architecture of common diseases have been known for some time [14], and recent analysis of large GWAS datasets has resulted in an unprecedented rise in the identification of sex-specific loci for human diseases and quantitative traits (Table 1). While this fact alone should encourage further investigation, evolutionary theory also predicts the existence of sex-specific genetic architecture for complex traits via sex-specific or sexually antagonistic selection.

In this review, we summarise recent evidence for the sex-specific genetic architecture of common diseases and offer guidelines for the identification of sex-specific genetic effects in population-based samples. We also discuss the relationship between sexual antagonism and sexual dimorphism, and propose new mechanisms through which the genetic architecture of disease might be determined by the