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Sex differences in autism spectrum disorders

Donna M Werling[a,b] and **Daniel H Geschwind**[b,c]

[a]Neuroscience Interdepartmental Program, Brain Research Institute, University of California-Los Angeles

[b]Semel Institute, University of California-Los Angeles

[c]Department of Neurology, Center for Neurobehavioral Genetics, Neurogenetics Program, Center for Autism Research and Treatment, David Geffen School of Medicine, University of California-Los Angeles

Abstract

Purpose of review—A strong male bias in autism spectrum disorder (ASD) prevalence has been observed with striking consistency, but no mechanism has yet to definitively account for this sex difference. Toward the pursuit of a more complete understanding of the biological basis for sex-differential risk, this review explores the current status of epidemiological, genetic, and neuroendocrinological work addressing ASD prevalence and liability in males and females.

Recent findings—Recent studies continue to report a male bias in ASD prevalence, but also suggest that sex differences in phenotypic presentation, including fewer restricted and repetitive behaviors and externalizing behavioral problems in females, may contribute to this bias. Genetic studies demonstrate that females are protected from the effects of heritable and *de novo* ASD risk variants, and compelling work suggests that sex chromosomal genes and/or sex hormones, especially testosterone, may modulate the effects of genetic variation on the presentation of an autistic phenotype.

Summary—ASDs affect females less frequently than males, and several sex-differential genetic and hormonal factors may contribute. Future work to determine the mechanisms by which these factors confer risk and protection to males and females is essential.

Keywords

autism spectrum disorders; sex differences; hormones; sex chromosomes; genetic liability

Introduction

Sexually dimorphic disease prevalence is well recognized, but poorly understood. For example, many disorders with autoimmune etiologies, such as multiple sclerosis and systemic lupus erythematosis, are female predominant [1], whereas some neurodevelopmental disorders, such as attention deficit hyperactivity disorder and language

Correspondence to Dr. Daniel Geschwind, MD/PhD, Department of Neurology, David Geffen School of Medicine, University of California-Los Angeles, 2506 Gonda Bldg, 695 Charles E. Young Dr. South, Los Angeles, CA 90095-1761. Tel: 310-794-6570; Fax: 310-267-2401; dhg@mednet.ucla.edu.

impairment show a male bias [2,3,4]. Autism spectrum disorders (ASDs) are prototypical in this regard, as they show a striking male bias in prevalence, with approximately 4 affected males for every 1 affected female. The consistency of this observation across time and populations strongly implicates the involvement of sex-specific biological factors in ASD etiology. However, we have yet to definitively identify the underlying mechanism through which these pathways interact to give rise to the male preponderance among individuals with ASDs. In recent years, increased priority has been placed on the inclusion and study of autistic females, while geneticists have made considerable headway in identifying novel genetic risk variants for ASD, putting us now in a position to assess relationships between genetic risk factors, hormones, and observed patterns of sex-differential vulnerability to ASDs. Toward this goal, here we review patterns of sex bias in ASD prevalence and phenotypic presentation, and evaluate the evidence for several hypotheses that could explain the biological basis of the male bias in ASD. We also identify areas of research where additional work is needed to advance our understanding of the interactions between sex-differential biology and risk factors for ASD.

ASD prevalence in males and females

From the first published descriptions of autism, it has been a male-typical disorder: 8 of the 11 cases described by Kanner [5], and all 4 cases described by Asperger [6], were male. Prevalence surveys conducted since have reported a range of male biases from 1.33:1 male:female (M:F) to 15.7:1 [7], and a commonly referenced consensus ratio of ~4:1. Intelligence level affects this sex ratio: males are substantially over-represented among high-functioning cases, and males and females are more equally represented among cases with severe intellectual disability (ID) [8,9,10,11]; a 1999 review reported median sex ratios of 6:1 among normal-functioning subjects and 1.7:1 among cases with moderate to severe ID [11].

Several biological factors could explain this relationship between IQ and the sex ratio, but it should also be recognized that this could also, at least partially, reflect ascertainment bias. Co-morbid ID increases females' likelihood of acquiring an ASD diagnosis, and conversely high-functioning females may go undiagnosed. The wide variation in the sex ratio reported by different sites in the Autism and Developmental Disabilities Monitoring (ADDM) Network and findings from large-scale population screening for ASD in a South Korean community where clinically ascertained samples show higher M:F ratios than less biased population screening are consistent with this hypothesis [12**,13**]. Generally, high sex ratios have been found by studies that predominantly identified subjects via treatment facilities or disability registries [8,9,14], including more recent studies of records from Boston area hospital records [15*] and Taiwanese disability registries [16*]. In contrast, low sex ratios between 1.7:1 in high-functioning ASD cases, and 2.3:1 in cases with ASD and co-morbid ID were found in an epidemiological, population-screening study for ASDs in Finland [17*], although the same trend was not found in England, where a 9 to 1 M:F ratio was observed in high functioning individuals with an ASD [18*]. Overall, prevalence studies demonstrate that ASD is consistently over-represented in males as compared to females. But, we currently do not understand the extent of this over-representation, or the degree to which this male bias in prevalence is related to intellectual functioning or

ascertainment methods in addition to the influence of sex-differential genetic or hormonal factors.

Presentation of ASD symptoms and related phenotypes in males and females

In contrast with the higher proportion of diagnosed autistic females than males with ID, many studies find no sex differences in overall composite ASD severity as measured on several standard assessment tools [16,19,20,21*,22*,23**]. This suggests that among those who meet diagnostic criteria, females are not more severely affected. However, differences emerge when each core symptom domain of ASD is considered separately, and sex differences observed in cases tend to reflect sex differences observed in the typical population. Males with ASD are found to show more externalizing behavior problems than females, such as aggressive behavior, hyperactivity, reduced prosocial behavior, and increased repetitive/restricted behaviors and interests [24*,25*,26**,27*,28]. Females with ASD show greater internalizing symptoms than boys, including anxiety, depression, and other emotional symptoms as reported by parents [25*,29*]; parents also more frequently endorse the item “avoids demands” for female cases on the Autism Spectrum Screening Questionnaire (ASSQ) [19], perhaps reflecting girls’ tendency to misbehave passively, as opposed to acting out. The observed sex differences raise the possibility that male-typical externalizing behaviors are more disruptive in the home or school setting than female-typical internalizing behaviors, preferentially prompting evaluation and diagnosis for boys, especially as compared to high-functioning girls. For girls then, ID may be more likely the secondary issue prompting evaluation and diagnosis. This scenario further implies that some proportion of the sex difference in ASD prevalence is attributable to biases inherent in the diagnostic process.

A recent study from the UK addressed this potential diagnosis gap by characterizing children with high autistic traits who met or fell short of the threshold for ASD diagnosis [30**]. A significantly smaller proportion of high-scoring girls met full ASD diagnostic criteria than males (38% versus 56%) whereas ASD-diagnosed girls had a higher mean total problem score (hyperactivity, anxiety, and conduct, peer, and prosocial problems) and a higher frequency of low IQ than ASD-diagnosed boys. Girls without diagnoses showed increased communication difficulties, but reduced social impairments as compared to non-diagnosed boys. Thus, it may be that relatively higher levels of social ability in females preclude full diagnosis of ASD, particularly for those who are high-functioning. Nevertheless, whether the male-skewed prevalence of ASD is due to biased diagnosis of sex-differential presentations of the disease or to true sex differences in prevalence (or both), sex-specific biology is likely to play a role. For the remainder of this review, we discuss the relationships between ASD and the two major drivers of sex-specific biology: genetics and hormones.

Sex differences in genetic contributions to ASD risk

Biological theories for the sex difference in ASD prevalence most frequently take the form of a multiple-threshold multifactorial liability model [31], in which females have a higher

threshold for reaching affection status than males (Figure 1A). Thus, genetic studies operating under this model hypothesize that females with ASD are likely to be carrying a higher heritable mutational "load" than affected males. This model predicts that relatives of female probands should be at increased risk for ASD as compared with relatives of male probands, which is supported by a recent twin study [32]. In contrast, other studies have failed to support the genetic loading hypothesis, including a study of 882 families [33] and another recent study of high risk siblings of autistic probands that found that only the sex of the sibling was a significant predictor of their future ASD status [34**]. However, a new study of more than 9000 dizygotic twin pairs from population-based cohorts provides the most conclusive demonstration of female-protective factors to date, showing that siblings of autistic females exhibit significantly greater autistic impairments than siblings of autistic males (Angelica Ronald, December 13, 2012). This finding also supports a role for heritable variation in ASD liability under the threshold model.

There is additional experimental evidence for heritable loci with sex-differential penetrance. In one approach, multiplex family samples are divided into two groups for analysis: those with only affected male children ("male-only"), and those with at least one affected female child ("female-containing") to identify sex-differential genetic variation at several loci in male-only and female-containing families [35,36,37,38,39,40]. However, only the male-only linkage signal at 17q21 has been successfully replicated, and the exact risk genes or variants responsible for these linkage peaks remain unknown. Other approaches have identified more defined sex related risk loci. For example, Lu and Cantor used a case-pseudocontrol genome-wide association test with sex as a factor to find two genome-wide significant single nucleotide polymorphisms (SNPs) within genes RYR2 (Ryanodine receptor 2) and UPP2 (uridine phosphorylase 2) [41*]. Also, a study of rare copy number variants (CNVs) in ASD identified the first inherited autosomal variant with clear male-biased penetrance: males carrying a microdeletion in SHANK1 had high-functioning autism, while female relatives carrying the same microdeletion showed anxiety but did not meet diagnostic criteria for ASD [42**]. While they cannot fully explain the male bias in ASD, these sex-differential linkage peaks, SNPs, and the SHANK1 microdeletion represent promising starting points for further work to elucidate the mechanism by which these inherited variants confer sex-differential ASD risk.

Aside from heritable variation, it is also plausible that some of females' hypothesized higher genetic load is caused by de novo variation [43*] and is therefore not shared with relatives. In fact, close to 90% of ASD families have only one affected member [44], suggesting that de novo variants of large effect may contribute significantly to ASD liability. This is supported by studies of chromosomal structural variation that indicate that a higher proportion of female cases carry a de novo CNV than male cases and that these CNVs disrupt a greater number of genes than those from males [45,46*,47*]. An elevated rate of de novo single nucleotide variants (SNVs) is also observed in exome sequences from autistic females [48**,49**], especially the most deleterious SNVs (nonsense, splice site, some missense) [50**,51**]. One study also observed a trend towards increased de novo CNV rate in unaffected female siblings [47*], consistent with the hypothesis that females can withstand more significant mutations than males before being affected with ASD. Taken together with studies of familial recurrence rate, it appears that regardless of whether risk

variants are inherited or de novo, in the face of a comparable degree of genetic liability, males are at increased risk for and females are protected from manifesting ASD symptoms that meet diagnostic criteria.

Sex chromosomal genes have been proposed to be key players in molecular mechanisms driving females' protection from ASD liability conferred by specific risk loci and/or by genome-wide mutational load (Figure 1B). An early theory proposed that ASD might be an X-linked disorder, in which females are protected from deleterious effects of X chromosomal mutations by compensatory transcription from their intact, second X chromosome. However, ASD transmission in most families does not follow an X-linked pattern, and while several ASD risk genes have been identified on the X chromosome (e.g. FMRP, MECP2, NLGN3, NLGN4X), all cause significant ID, indicating a more general role for X chromosome gene dosage in neural development.

Although ASD may not be X-linked in the Mendelian sense, sex chromosome complement may still modulate ASD risk. Sex chromosome aneuploidies provide test cases for this hypothesis, with an increased rate of ASD diagnosis in Turner syndrome (TS, XO, ~3% ASD) [52,53,54], Klinefelter syndrome (KS, XXY, ~10% ASD) [55,56*], and 47,XYY syndrome (~20% ASD), but no increased rate in X chromosome trisomy [57,58**]. In addition to the general association of aneuploidy with ID, these observations suggest several intriguing possibilities: 1) the Y chromosome is a risk factor for ASD, and 2) a second X chromosome is protective, possibly via genes that escape X-inactivation. Interestingly, the reported TS cases with co-morbid ASD predominantly carry an intact maternal X chromosome, which led Skuse and colleagues to propose the theory that imprinted genes expressed only from the paternal X protect against ASD [59]. Since 40-50% of KS cases arise from maternal nondisjunction of the X, this subset of cases also lacks putative protective paternally expressed X genes, as do all 47,XYY cases. In combination with the presence of a Y chromosome, this lack of paternal X expression could then raise ASD risk for both syndromes, and for a higher proportion of XYY cases as is observed. However, larger epidemiological studies are needed to more accurately establish ASD prevalence in aneuploid individuals, and the parental origin of all sex chromosomes and patterns of escape from X-inactivation must be determined to better assess the validity of this model.

Sex hormonal contributors to ASD risk

One major theory that invokes a broad role for testosterone in ASD etiology is the Extreme Male Brain theory, which proposes that ASD arises from hypermasculinization of the brain [60]. A theory born from cognitive-behavioral observations, this masculinization is conceptualized along two cognitive dimensions: 1) empathizing, the drive to perceive others' feelings and thoughts and respond appropriately, and 2) systemizing, the drive to interact with and understand rule-based systems. Early work convincingly demonstrated that typical females score significantly higher on measures of empathizing and value placed on meaningful relationships with others [61,62], whereas typical males score significantly higher on measures of systemizing [63]. In these studies, high-functioning ASD cases scored lower than typical males on measures of empathy and friendship, and higher than typical males on measures of systemizing.

Given that testosterone secreted by fetal testes during gestation drives human sexual differentiation to the male phenotype, Baron-Cohen and colleagues have proposed that fetal testosterone (FT) levels may also drive cognitive hypermasculinization in ASD. Findings of significant positive correlations between FT levels and measures of systemizing [64] and autistic traits [65], and negative correlations with measures of empathizing [66] and the quality of social relationships [67] are consistent with this hypothesis. Recent work has even found a correlation between increasing FT and volume of sexually dimorphic brain regions, specifically increased volume of the right temporoparietal junction/posterior superior temporal sulcus and decreased volume of the planum temporale/parietal operculum and posterior lateral orbitofrontal cortex volume [68*]. These results suggest that increased FT levels predispose the differentiating brain to a hypermasculine cognitive and neuroanatomical phenotype.

Interestingly, work from other investigators have suggested that testosterone beyond fetal development may also play a role in ASD pathophysiology. For example, levels of testosterone and its precursors were found to be significantly elevated in a sample of ASD cases, with 57 of the 70 subjects having at least one androgen metabolite measuring above the upper limit of sex- and age-matched reference ranges [69]. Subsequent studies have found increased androstenedione in serum from adults with ASD compared to controls irrespective of sex [70*], and a higher free androgen index in females with Asperger's syndrome versus controls [71*], although a study of unaffected Japanese adults found no correlation between salivary testosterone levels and autistic-like traits [72]. These findings were recently reviewed in detail by Geier et al. [73*], collectively suggesting that hyperandrogenism may be a significant risk factor for ASD, and that more frequent assessment of testosterone levels in ASD cases is warranted to determine how prevalent this risk factor may be.

One potential pathway by which testosterone influences ASD risk may involve RORA (retinoic acid-related orphan receptor-alpha), a gene down-regulated in ASD lymphoblastoid cell lines [74]. RORA regulates expression of aromatase, the enzyme that converts androgens to estrogens, and is reciprocally activated by estradiol and inhibited by testosterone [75*]. These regulatory relationships may create a feedback loop that further elevates testosterone levels, but it may have more specific effects on brain as well, since RORA has a role in cerebellar and Purkinje cell development, and neuroprotection from oxidative stress. Another potential mechanism may involve immune system functioning in the brain, as a co-expression module of genes involved in immune system and glial function was observed to be up-regulated in adult autistic cortex [76**], and sex hormones, particularly estradiol, have been shown to affect glial-neuronal interactions [77*,78]. Thus, it may not be the absolute levels of androgens or estrogens, but the balance between them that influences ASD risk.

Sex hormones are attractive candidates for sex-biased ASD risk and protective factors in that they raise the possibility for the development of treatments that cut across individuals' specific genetic liability. However, much work remains to determine the precise cellular and molecular mechanisms by which testosterone interacts with neurodevelopmental pathways and genetic risk loci to increase liability for autistic behavior, so that future treatments may

specifically target these interactions. For example, in addition to the liability conferred directly to neural development by sex chromosomal genes, it also should be noted that sex chromosomal abnormalities frequently affect gonadal function. In fact, gonadal dysgenesis is common in TS and KS, causing abnormally low postnatal estrogen and testosterone levels, respectively, whereas testosterone levels are normal prenatally in KS and throughout life in 47,XYY cases [79,80]. While this more male-like hormonal environment may contribute to increased ASD risk in TS, hypogonadism in XXY males in the face of a nearly 10-fold increase in ASD prevalence suggests that the role of the hormonal milieu in ASD liability is likely complex and may be mediated by other risk factors.

Conclusion

ASD prevalence remains highly biased toward males, although more recent population screens have identified a higher proportion of autistic females relative to males than past work on clinically ascertained samples. Discussion continues as to whether females present the autistic phenotype differently than males, and further work is needed to determine if currently undiagnosed females would benefit from standard ASD services, and if diagnostic criteria need to be adjusted to effectively identify these girls. ASD risk is likely to be multifactorial, with many different genetic variants and environmental factors contributing to liability, and still other sex-differential genetic and hormonal factors acting to potentiate risk to males and/or attenuate risk to females (Figure 1B). Evidence suggests that sex chromosomal gene dosage and sex hormone levels may be involved in setting sex-specific liability thresholds, but much future work is needed to definitively identify the most critical players at hand and to elucidate the precise mechanisms by which these sex-specific factors modulate presentation of the ASD phenotype.

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Key points

- The prevalence of ASDs is strongly male-biased, affecting 4 times as many males as females, on average.
- Little attention has been paid to understanding if ASD in females differs from that in males.
- Sex differences in behavior, or the presentation of autistic symptoms and co-morbid intellectual disability may contribute to the male bias in diagnoses.
- There is evidence for a greater “genetic load” in females with ASD, consistent with the idea of female protective factors.
- The potential role of sex hormones in modulating ASD risk warrants further study.

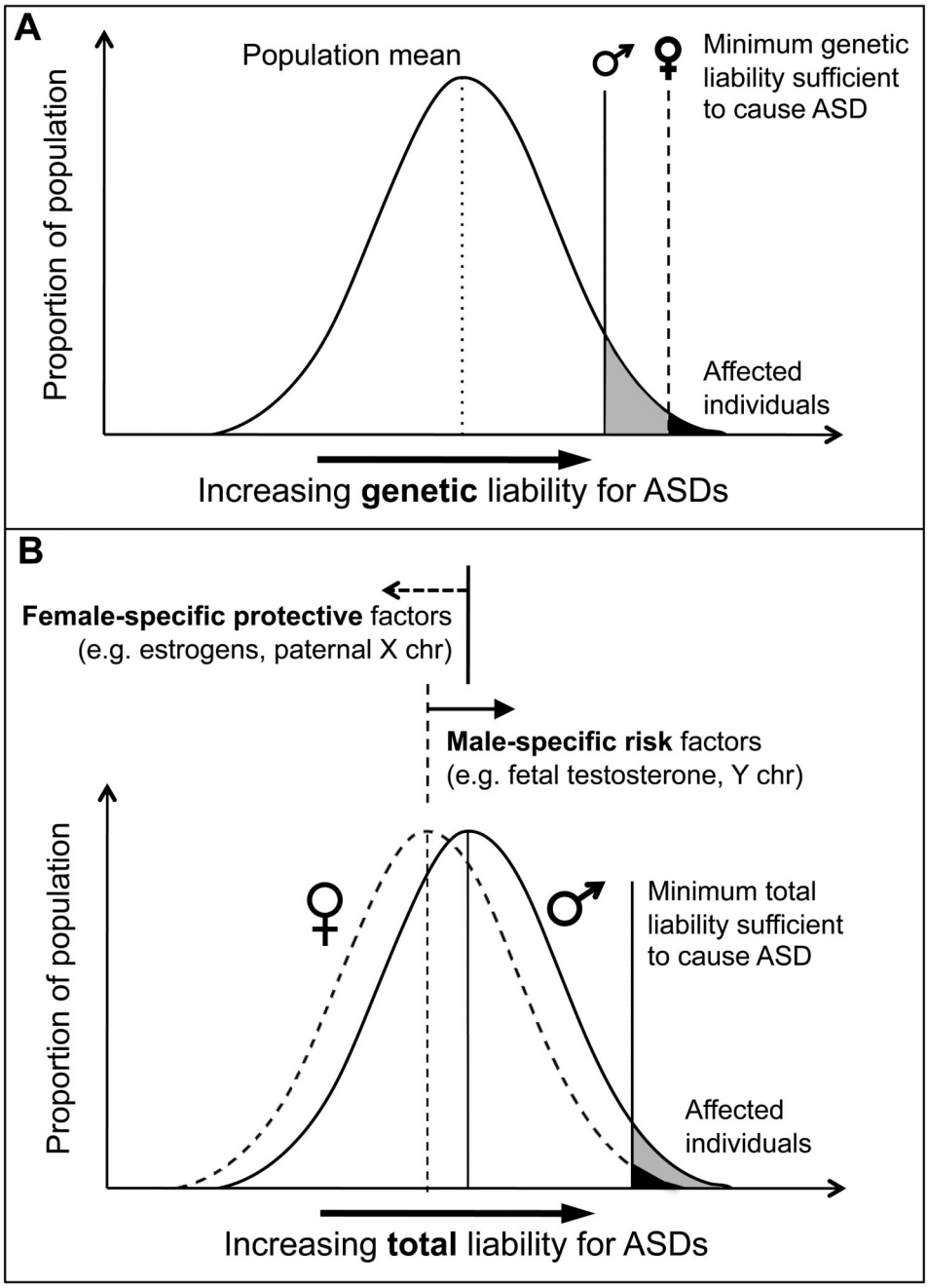

Figure 1.

Multifactorial liability models for ASDs. A) Multiple-threshold model in which genetic liability for ASD is normally distributed in the population and the minimum genetic liability sufficient to cause ASD (liability threshold) in females is greater than in males. B) Multifactorial liability model in which total liability for ASD, including contributions from genetic variation, environment, and other biological factors, is distributed in the population; female-specific factors shift females' total liability distribution away from, and male-

specific factors shift males' distribution toward, a single threshold. Figure adapted from Reich et al. [31]