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Developmental Neurogenetics and Multimodal Neuroimaging of Sex Differences in Autism

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Abstract

Examining sex differences in the brain has been contentious but is nonetheless important for advancing mental health for both girls and boys. Unfortunately, females in biomedical research remain underrepresented in most mental health conditions including autism spectrum disorders (ASD), even though equal inclusion of females would improve treatment for girls and yield benefits to boys. This review examines sex differences in the relationship between neuroanatomy and neurogenetics of ASD. Recent findings reveal that girls diagnosed with ASD exhibit more intellectual and behavioral problems compared to their male counterparts, suggesting that girls may be less likely diagnosed in the absence of such problems or that they require a higher mutational load to meet the diagnostic criteria. Thus far, the female biased effect of chromosome 4, 5p15.33, 8p, 9p24.1, 11p12-13, 15q, and Xp22.3 and the male biased effect of 1p31.3, 5q12.3, 7q, 9q33.3, 11q13.4, 13q33.3, 16p11.2, 17q11-21, Xp22.33/Yp11.31, DRD1, NLGN3, MAOA, and SHANK1 deletion have been discovered in ASD. The SNPs of genes such as *RYR2*, *UPP2*, and the androgen receptor gene have been shown to have sex-biasing factors in both girls and boys diagnosed with ASD. These sex-related genetic factors may drive sex differences in the neuroanatomy of these girls and boys, including abnormal enlargement in temporal gray and white matter volumes, and atypical reduction in cerebellar gray matter volumes and corpus callosum fibers projecting to the anterior frontal cortex in ASD girls relative to boys. Such factors may also be responsible for the attenuation of brain sexual differentiation in adult men and women with ASD; however, much remains to be uncovered or replicated. Future research should leverage further the association between neuroanatomy and genetics in girls for an integrated and interdisciplinary understanding of ASD.

Keywords

Sex Differences; Autism; Neurogenetics; Neuroimaging; Development

Potential Conflicts of Interest

The authors declare no conflicts of interest.

Introduction

Debate currently exists in the scientific research community as to the value and importance of sex differences in the brain and disorders thereof. While some authors have cautioned against exaggerating sex differences or assuming a biological explanation for sex differences in behavior and cognition (Fine 2010, Joel 2011), others have contrarily argued that striking sex differences exist in the brain on multiple levels (McCarthy and Arnold 2011), including the molecular (Jazin and Cahill 2010), genetic (Carruth, Reisert et al. 2002, Arnold 2004); hormonal (Sisk and Zehr 2005, Ahmed, Zehr et al. 2008, Peper, Hulshoff Pol et al. 2011), anatomical connectivity (Bava, Boucquey et al. 2011, Gong, He et al. 2011, Ingahalikar, Smith et al. 2014), and structural levels (Luders, Narr et al. 2004, Cahill 2014). Operating under the tacit premise that male-female differences are non-existent or unimportant has manifested in the deliberate exclusion of female subjects in various research studies with potentially adverse costs on how to interpret and act on published research findings (Cahill 2014). As noted by Eliot (2011), scientists are often in a difficult position when they research and report sex differences. For instance, many neuroscientists still only study male rodents, even to treat disorders which overwhelmingly affect women (i.e. clinical depression, post-traumatic stress disorder, Alzheimer's, fibromyalgia, eating disorders, etc.) (Cahill 2006, Beery and Zucker 2011).

Selection biases based on sex also exist in biomedical research when scientists examine male dominant neurodevelopmental disorders, such as autism spectrum disorders (ASD). For instance, given the higher prevalence of autism in males versus females (Fombonne 2002), more attention has been given to boys with ASD, at the neglect of girls. However, the inclusion of females with autism in research studies is essential to improve eventual diagnosis and treatment for girls. Additionally, gaining insight into how girls might be genetically protected from autism confers benefits to boys as well. Since girls diagnosed with ASD tend to exhibit more severe symptoms on certain autistic traits than their male counterparts, studying girls may allow scientists to understand more common occurrences of the disorder, including identifying additional genes that increase risk (Weiss 2011).

Although other reviews of the literature have assessed the hormonal, environmental, and/or genetic contributions to sex differences in autism spectrum disorders (Baron-Cohen, Knickmeyer et al. 2005, Baron-Cohen, Lombardo et al. 2011, Kirkovski, Enticott et al. 2013, Werling and Geschwind 2013, Schaafsma and Pfaff 2014, Lai, Baron-Cohen et al. 2015, Lai, Lombardo et al. 2015), a comprehensive examination is required to understand the complexity behind sexual dimorphism in diagnosis, phenotype, and brain of individuals with ASD.

Consequently, in this literature review, the main objective is to critically evaluate the existing literature on the neuroanatomical substrates and their relationship with genes which may account for these sex differences. We, moreover, make note of areas needing additional research to promote an interdisciplinary understanding of the underlying causes for sex differences in autism.

Sex Differences in Autistic Diagnosis & Phenotype

ASD comprises of a range of developmental disorders characterized by these major symptoms: 1) deficits in social interaction, communication, or language and 2) repetitive behavior or restricted interests including unusual fascination with the sensory environment (APA 2013). Sex differences in diagnosis of ASD in the U.S. are striking, with an average male to female ratio of 4.2 to 1 in the early 2000's (Fombonne 2002) and a ratio of 4.6 to 1 in recent years (Blumberg, Bramlett et al. 2013). Overall prevalence rates of ASD have been increasing due to improved recognition of the disorder and modifications to diagnostic practices over time (Blumberg, Bramlett et al. 2013). Much of this incline is driven by an increase in male diagnosis (refer to Figure 1).

Prevalence rates and sex ratios of ASD are variable depending on country, suggesting wide cultural influence (refer to Figures 2 and 3). Between 2005 and 2010, Taiwan had the highest male to female ratio of ASD (6.06 to 1 or 86% male), likely due to increases of individuals with normal intelligence more commonly found in ASD boys than girls (Lai, Tseng et al. 2012). In contrast, China had the least (2.11 to 1; 68% male) partially due to a lack of health professionals (Li, Chen et al. 2011).

Within a country, higher male to female ratios for ASD are present in samples taken from treatment facilities, as opposed to large population screenings (Lord and Schopler 1985, Volkmar, Szatmari et al. 1993, Yeargin-Allsopp, Rice et al. 2003, Kim, Leventhal et al. 2011). Thus, ASD sex ratios can vary widely within the same country. For instance, prevalence surveys conducted across multiple sites and time in the UK indicate a range of 2.6:1 to 15.7:1 (Fombonne, Quirke et al. 2009). However, the best method to obtain accurate estimates of prevalence rates is to acquire representative samples throughout the country. Taylor and colleagues report an ASD sex ratio of 4.81:1 after utilizing a longitudinal medical record system designed to be representative of the UK (Taylor, Jick et al. 2013).

In a study conducted in an U.S. metropolitan area, ASD sex ratios decrease to about 1.3:1 (or 56.5% male) in those patients having severe intellectual impairments and increases to about 7.3 to 1 (or 88% male) in those with higher cognitive functioning (refer to Figure 4) (Yeargin-Allsopp, Rice et al. 2003). Recent studies in Sweden and Finland have found no differences in sex ratios of ASD individuals with higher intellectual ability (Mattila, Kielinen et al. 2011, Idring, Rai et al. 2012). However, this may be due to low sample sizes or the failure to include subjects with severe cognitive function (IQ <20). Additionally, studies from other countries or other time periods have reported similar or higher ratios, such as the 9:1 ratio for high functioning ASD in England (Brugha, McManus et al. 2011) and the 10.8:1 ratio for Asperger's disorder in Sweden (Gillberg, Cederlund et al. 2006). This sex difference may reflect variations in underlying biology but may also be due to ascertainment bias in which girls with high cognitive abilities are less likely to be diagnosed (Werling and Geschwind 2013, Van Wijngaarden-Cremers, van Eeten et al. 2014). Furthermore, a low sex ratio of 2.1:1 was reported in autistic individuals with abnormal structural brain morphology and abnormal physical examination, while the highest sex ratio of 23:1 was reported in individuals with ASD who tested normal in both cases (Miles and Hillman 2000). Another study discovered that girls with ASD show greater signs of brain

damage and are more likely to have IQs below 50, relative to boys (Tsai, Stewart et al. 1981). Such evidence implies that girls are more likely to be diagnosed with ASD when they exhibit phenotypic or brain abnormalities.

Sex differences do not generally exist on overall autistic symptoms or severity in children or adults (Kopp and Gillberg 2011, Lai, Lombardo et al. 2011, Worley and Matson 2011, Solomon, Miller et al. 2012, Andersson, Gillberg et al. 2013, May, Cornish et al. 2014, Reinhardt, Wetherby et al. 2015), although at least one study has detected mild sex differences (Zwaigenbaum, Bryson et al. 2012). However, some studies indicate that boys and girls with ASD do differ on specific autistic domains and cognitive functioning. For instance, clinically diagnosed girls with ASD are 8.4 times more likely to display intellectual impairment or behavioral problems, compared to undiagnosed girls (Dworzynski, Ronald et al. 2012). In contrast, boys with ASD are only 1.8 times more likely to exhibit these difficulties, compared to their undiagnosed male counterparts. Girls with ASD also score higher on emotional and behavioral problems than diagnosed boys (Horiuchi, Oka et al. 2014). Furthermore, ASD girls exhibit greater internalizing disorders compared to ASD boys or typically developing girls, including greater sleeping problems, social anxiety, depression, and/or other emotional symptoms (Hartley and Sikora 2009, Solomon, Miller et al. 2012, May, Cornish et al. 2014), although one study found that girls with ASD are less likely to have a past diagnosis of anxiety (Stacy, Zablotzky et al. 2014), and a few surprisingly found greater externalizing behavior in girls rather than boys with ASD (Holtmann, Bolte et al. 2007, Frazier, Georgiades et al. 2014). They also score lower on the following aspects of the Childhood Autism Rating Scale: “Body Use,” “Object Use,” and “Activity Level” (Kumazakia, Muramatsub et al. 2015). Conversely, ASD boys demonstrate more symptoms from externalizing disorders such as aggression, hyperactivity, impulsivity, repetitive or stereotyped behaviors as well as decreased prosocial behavior (Hartley and Sikora 2009, Giarelli, Wiggins et al. 2010, Bölte, Duketis et al. 2011, Hattier, Matson et al. 2011, Sipes, Matson et al. 2011, Mandy, Chilvers et al. 2012, Frazier, Georgiades et al. 2014, May, Cornish et al. 2014, Van Wijngaarden-Cremers, van Eeten et al. 2014). Some of these sex differences do not differ from the typical population. For instance, male toddlers across both non-ASD and high ASD risk groups score lower on the Mullen Scales of Early Learning subscales (i.e. fine motor, visual reception, expressive language, and receptive language) and score higher on restricted and repetitive behavior tests than female toddlers (Messinger, 2015 #726).

On the positive side, ASD girls display better expressive actions than their male autistic peers (such as carrying a reciprocal conversation or integrating verbal with non-verbal activity) despite similar difficulties in social understanding; moreover, they have fewer and different restricted interests that are less focused on objects (Hiller, Young et al. 2014). They also exhibit better executive functioning (Bölte, Duketis et al. 2011), score higher on visual reception than ASD boys (Carter, Black et al. 2007), and possess fewer learning disabilities (Stacy, Zablotzky et al. 2014). Thus, they do not necessarily perform worse on all types of cognitive functioning. Relative to their male counterparts, they display less inattention and fewer repetitive movements (May, Cornish et al. 2012, Szatmari, Liu et al. 2012) as well as reduced stereotypical play and unusual visual responses, after IQ has been controlled (Lord, Schopler et al. 1982). They also score higher on the “Taste, Smell, and Touch Response and

Use” section of the Childhood Autism Rating Scale than boys with high functioning autism (Kumazakia, Muramatsub et al. 2015). Finally, they are less likely to be diagnosed with typical autism than their male counterparts (Mandic-Maravic, Pejovic-Milovancevic et al. 2015).

Mixed findings concerning sex differences exist for language, peer relation impairments, and social communication difficulties. Some studies indicate that ASD girls undergo more of these problems than ASD boys (Tsai and Beisler 1983, Carter, Black et al. 2007, Holtmann, Bolte et al. 2007, Hartley and Sikora 2009, Pisula, Kawa et al. 2013, Frazier, Georgiades et al. 2014), other studies indicate the reverse {Head, 2014 #430}{Lai, 2011 #456}, and the remaining studies find no sex differences especially for toddlers or preschool children (Andersson, Gillberg et al. 2013, Van Wijngaarden-Cremers, van Eeten et al. 2014, Reinhardt, Wetherby et al. 2015). Undiagnosed girls with high autistic tendencies have been shown to exhibit greater communication difficulties than their male equivalents (Dworzynski, Ronald et al. 2012). As for girls who are diagnosed, they tend to display more speech impediments than boys with ASD (Stacy, Zablotzky et al. 2014). Interestingly, ASD girls report having close and supportive friendships (Head, McGillivray et al. 2014) and engage in more pretend play than boys with ASD (Knickmeyer, Wheelwright et al. 2008). However, other studies indicate that they simply encounter different friendship problems such as initiating but poorly maintaining relationships, being unnoticed rather than spurned by others, and displaying superficial levels of closeness that is perceived by parents or teachers as better quality (Dean, Kasari et al. 2014, Hiller, Young et al. 2014). Girls with ASD have also been shown to have weaker adaptive skills (Frazier, Georgiades et al. 2014), but no sex differences in adaptive behavior have been found in very young children (Reinhardt, Wetherby et al. 2015).

While adult women and men with ASD do not differ on self-reported measures of depression, anxiety, empathy, systemizing, or OCD tendencies, women with ASD report possessing more autistic traits, display greater sensory symptoms, but have fewer social communication problems than men (Lai, Lombardo et al. 2011). ASD women with lower IQ also significantly experience greater delay in language abilities than those with higher IQ, although this pattern does not exist for ASD men. Similar to adolescent females, adult women with ASD are diagnosed at a later age, compared to the men (Begeer, Mandell et al. 2013). Restricted and repetitive behavior are significantly more present in ASD men with severe intellectual functioning than in ASD women (Hattier, Matson et al. 2011). However, most studies on ASD have examined children or adolescents; thus, additional research needs to be conducted on sex differences in the phenotype of adults with ASD to confirm these findings. Future investigations should also consider neurological reasons that account for why sex differences in ASD adults are not identical to that found in children or adolescents.

Some of the sex differences in the ASD phenotype can be explained by ascertainment bias or confounding variables. Research suggests that girls are less likely to be diagnosed in the absence of behavioral or cognitive problems or that they adopt a better compensatory strategy than boys to avoid diagnosis. For instance, although diagnosed girls display significantly greater intellectual and behavioral problems compared to undiagnosed controls who also possess high levels of autistic traits, this pattern is not as pronounced in diagnosed

boys (Dworzynski, Ronald et al. 2012). Diagnosed girls also present greater social autistic symptoms and higher levels of hyperactivity than undiagnosed girls with high autistic traits, while diagnosed and undiagnosed boys only differ on social communication deficits. Furthermore, evidence suggests that girls are less likely to be diagnosed even after controlling for cognitive impairment (Giarelli, Wiggins et al. 2010) and tend to be diagnosed at a later age (Begeer, Mandell et al. 2013). Their diagnosis of autism is often missed when they also have female dominant disorders like eating disturbances (Kirkovski, Enticott et al. 2013, Mandy and Tchanturia 2015), and once diagnosed with ASD, they are less likely to be diagnosed with comorbid conditions (Stacy, Zablotzky et al. 2014). Additionally, scientists may operate under a male-biased definition of autism, which results in biased assessment tools and further under diagnosis of girls with ASD (Dworzynski, Ronald et al. 2012, Kreiser and White 2014). Confounding variables including gender socialization (i.e. parental care and exposure to certain toys) sculpt the brain from infancy and may play a powerful role in shaping sex differences in ASD behavior (Cheslack-Postava and Jordan-Young 2012). Moreover, when boys and girls with autism are matched on age and receptive language functioning, sex differences on perceptual-motor abilities disappear (Tsai and Beisler 1983). Thus, other confounding variables such as age and language ability may influence sex differences on other ASD domains.

A few studies have concluded that no sex differences exist on some specific domains of ASD (Pilowsky, Yirmiya et al. 1998, Rivet and Matson 2011, Worley and Matson 2011, Nguyen and Ronald 2014, Reinhardt, Wetherby et al. 2015). For instance, one study discovered that no sex differences exist in psychopathology of high functioning ASD children, although the ASD group exhibited higher psychiatric symptoms than the control (Worley and Matson 2011). Another study examining predominately low functioning ASD girls and boys found no sex differences in autistic symptoms (i.e. restricted behavior, sensory over-responsivity, social cognition, and psychopathology), but did find sex differences in attention to detail (Nguyen and Ronald 2014). Several other studies have indicated that sex differences in perception, eye-hand integration, and communication disappear when IQ is controlled (Lord, Schopler et al. 1982, Banach, Thompson et al. 2009). Thus, IQ may serve as another confounding variable that influences sex differences in ASD phenotypic expression.

Sex Differences in the Neuroanatomy and Structural Connectivity of Autism

Limited research has been conducted specifically on sex differences in the neuroanatomy and brain connectivity of ASD, making this topic an exciting area of exploration (refer to studies listed in Table 1). Several studies have suggested that autistic individuals are born with an average or below average head circumference, which is indicative of reduced brain size (Courchesne, Carper et al. 2003, Redcay and Courchesne 2005). However, one study that stratified by sex indicates that this finding may only hold true for boys. In particular, eight girls diagnosed with autism exhibited significantly greater mean birth head circumference than typically developing girls, but no such difference was seen in boys with autism relative to controls (Lainhart, Piven et al. 1997). Additional research needs to be performed to confirm this finding.

After birth, those with ASD experience rapid brain growth so that by 6 to 14 months, they surpass their typically developing counterparts in head circumference (Courchesne, Carper et al. 2003). Both boys and girls with ASD from ages 1 to 5 have been shown to display total cerebrum enlargement, compared to age-matched controls (Sparks, Friedman et al. 2002, Bloss and Courchesne 2007). One study discovered that total brain volume is enlarged only in autistic males, not females (Piven, Arndt et al. 1996). However, their sample excluded toddlers and children and instead included subjects ranging from 12 to 29 years old, which may account for this sex difference in megalencephaly. Also, another more recent study confirmed that girls with ASD illustrate a 5% enlargement of total intracranial volume (Calderoni, Retico et al. 2012). Thus, increases in cerebrum volume for male and female autistic children are well documented, and this enlargement is partially due to regional brain growth. Specifically, compared to typically developing girls, girls with ASD have been shown to have increased gray matter in the right temporal-parietal junction and bilateral superior frontal gyrus (Calderoni, Retico et al. 2012), as well as in temporal gray and cingulate gray matter (Schumann, Bloss et al. 2010). Girls with autism also have greater frontal gray, temporal gray, cerebral gray, and cerebellar white matter volumes relative to typical girls, while having reduced cerebellar gray matter volumes (Bloss and Courchesne 2007). In contrast, boys with autism exhibit greater frontal gray, cerebral gray, frontal white, and cerebellar white matter volumes than typical boys. Furthermore, boys with ASD show volume enlargement in the cerebellum, hippocampus, and amygdala proportionate to cerebrum size, especially in the right amygdala which is enlarged even after controlling for cerebrum volume (Sparks, Friedman et al. 2002). In girls with ASD, no such enlargement in subcortical structures or the cerebellum is seen, a finding that jibes with the reduced gray matter in the cerebellum found in girls with autism from another study. The abnormal growth in the cerebellum for boys with autism documented in both studies may partially explain the increased motor problems that they experience relative to their female counterparts.

In general, girls with autism demonstrate very similar brain abnormality to boys with autism, such as enlarged whole brain, frontal gray, cerebral gray, and cerebellar white matter volumes; however, they also show further abnormal enlargement in temporal gray and white matter volumes and decreased cerebellar gray matter volumes (Bloss and Courchesne 2007). They also deviate more from typically developing girls than boys with autism do from typically developing boys, especially on temporal gray and white matter volumes and cerebellar gray matter volumes. In terms of the biological time course of ASD, girls with autism display size increases in the cerebral white, parietal white, frontal white, and occipital white matter volumes with increasing age. In contrast, typically developing girls only show correlations with age on the parietal and frontal white matter volumes. Furthermore, only the cingulate gray matter increases at a nonlinear rate in 1 to 5 year old boys with autism, compared to controls; however, female toddlers with autism demonstrate abnormal increases over time in many more brain regions such as total cerebrum, cerebral gray, cerebral white, temporal gray, and frontal gray matter (Schumann, Bloss et al. 2010). These findings of atypical regional brain growth in girls with ASD correspond with the fact that these girls show greater signs of many cognitive and behavioral impairments than boys. Given that striking sex differences exist in the typical neonatal, infant, and adolescent brain

as well as in brain developmental trajectories (Gilmore, Lin et al. 2007, Lenroot, Gogtay et al. 2007, Lenroot and Giedd 2010, Giedd, Raznahan et al. 2012, Knickmeyer, Wang et al. 2014), future longitudinal studies during these developmental periods are needed to confirm whether similar sex differences in ASD neuroanatomy still hold.

Regarding sex differences in white matter connectivity, a recent study found that preschool girls with ASD have smaller corpus callosum fibers projecting to the anterior frontal cortex while ASD boys have smaller fibers projecting to the orbitofrontal cortex (OFC) (Nordahl, Iosif et al. 2015). Furthermore, girls with ASD have greater mean, axial, and radial diffusivity compared to typical girls. However, these results are preliminary, and further research on sex differences in structural or functional connectivity in autistic children is essential, especially since connectivity differs between autistic and typical individuals. For instance, individuals with ASD display atypical connectivity of white matter tracts, specifically lower fractional anisotropy (FA) in the corpus callosum and right retrolenticular area of the internal capsule (Keller, Kana et al. 2007). Increased total functional connectivity in 3-month old infants at high risk for autism exists between and within the anterior and posterior regions of each hemisphere (Keehn, Wagner et al. 2013). By 12 months of age, these infants demonstrate reduced functional connectivity in those brain regions compared with their low risk peers. These results (whether they pertain to under-connectivity or over-connectivity) have been inconsistent during various ages and need to be studied more extensively across development (Rudie and Dapretto 2013, Pelphrey, Yang et al. 2014). Sex as an independent variable should be included in these future studies.

By the time those with autism reach adulthood, many typical sex differences in brain structure and connectivity are attenuated (Beacher, Minati et al. 2012). In particular, the FA of the corpus callosum, right & left cingulum (especially the anterior portion), and corona radiata is not greater for men versus women with high functioning autism, even though it is greater for male versus female controls. Gray matter volumes in the rolandic operculum and right inferior parietal lobe are larger in typical men than typical women, but not larger in men relative to women with autism. These areas are also reduced in men with autism relative to typical men. One study did find that males with autism possess enlarged temporal and parietal lobes relative to controls (Piven, Arndt et al. 1996), but the sample included adolescents, which may have distorted the findings for adults. As for women with ASD, many brain areas including the bilateral OFC, basal ganglia, and temporal lobes as well as the right medial occipital lobe and left frontal lobe are reduced in size, compared to brain areas in typical women (Craig, Zaman et al. 2007). Although women with ASD actually demonstrate increased white matter density in the projection and association fibers of the parietal, frontal, posterior temporal, and occipital lobes, the cerebellum, and the commissural fibers of the corpus callosum, they also show reduced white matter density in the bilateral brain stem and anterior temporal lobes. Despite exaggerated sex differences that take place during childhood and adolescence for patients with ASD, these gray and white matter reductions in both men and women with ASD illustrate that many typical sex differences abnormally disappear by adulthood. Nevertheless, given that women with ASD also exhibit increased white matter density in fibers of certain brain areas, differences between and within sex are still heightened in some aspects of white matter density and integrity, even for adults with autism. Recent evidence suggests that women with autism

have 2 larger clusters in the temporal-parietal-occipital regions and 2 smaller clusters in the bilateral internal capsule at the thalamus and basal ganglia regions, compared to typical women (Lai, Lombardo et al. 2013). Men with autism have 2 larger clusters in the bilateral internal capsule at the thalamus and basal ganglia, compared to typical men. These novel findings imply that despite attenuation of many sex differences, some atypical sexual dimorphism in the brain and neuroanatomical differences within sex still exist in men and women with autism.

The rapid brain growth seen in girls versus boys with autism or the white and gray matter reduction in adults with autism may be due to multiple factors. Inefficient synaptic pruning can result in an overgrowth of white matter in autistic children, since it retains (rather than eliminates) the number of synapses in the brain. Conversely, excessive synaptic pruning may be responsible for many reduced brain volumes in adults with ASD. Overproduction or underproduction of neuropil, neurons, neurotrophins, or glial cells may also be associated with the brain alterations that shape individuals with ASD throughout the lifespan. Ultimately, genes are likely responsible for the cell survival, cell proliferation, and/or dendritic branching that cause the cortical expansion seen in autistic children (Schumann, Bloss et al. 2010) or the cortical reduction seen in adults with ASD. Thus, it is imperative to investigate the genes responsible for either the excessive brain growth or the gray and white matter reductions as typified in males and females with ASD from childhood to adulthood.

Sex Differences in the Neurogenetics of Autism

Autism spectrum disorders are highly heritable, with most heritability estimates ranging from 56% to 95% (Ritvo, Freeman et al. 1985, Steffenburg, Gillberg et al. 1989, Bailey, Le Couteur et al. 1995, Taniai, Nishiyama et al. 2008, Rosenberg, Law et al. 2009, Ronald and Hoekstra 2011, Lundstrom, Chang et al. 2012). Research on autistic traits in the general population has unveiled similarly high heritability estimates and low to moderate shared and non-shared environmental influences (Scourfield, Martin et al. 1999, Constantino and Todd 2000, Constantino and Todd 2005, Ronald, Happe et al. 2005, Skuse, Mandy et al. 2005, Ronald, Happe et al. 2006). A few studies on autism and autistic traits have revealed the opposite trend: modest heritability estimates of 38%-48% and high shared and non-shared environmental factors of 52–58% (Constantino and Todd 2003, Hallmayer, Cleveland et al. 2011), but they tend to be outliers. Generally, heritability estimates are substantially higher in childhood than adulthood, either because of different autism assessments or different gene by environment interactions throughout the lifespan (Posthuma and Polderman 2013). Heritability for boys with ASD has also been shown to be around 73%, while girls with ASD have a higher heritability of 87% (Taniai, Nishiyama et al. 2008). Furthermore, ASD studies have examined concordance rates for male versus female monozygotic and dizygotic twins. For instance, Hallmayer and colleagues discovered a concordance rate of 0.77 for male monozygotic twins and 0.50 for female monozygotic twins with ASD (Hallmayer, Cleveland et al. 2011). Concordance rates for male and female dizygotic twins have been estimated to be 0.31 and 0.36, respectively. However, another study yielded lower concordance rates for both monozygotic and dizygotic twins. Lichtenstein and colleagues found a concordance rate of only 0.47 for male monozygotic twins, 0.14 for male dizygotic twins, and 0.20 for female dizygotic twins (Lichtenstein, Carlstrom et al. 2010). Future

studies are needed to reconcile these differences. In addition, recurrence risk for boys with autism is about two to three times greater than girls with autism (Ozonoff, Young et al. 2011, Werling and Geschwind 2015).

Most copy number variants (CNVs; deletions, duplications, etc.) associated with ASD arise *de novo* and can disrupt gene function (Sanders, Murtha et al. 2012). *De novo* single nucleotide variants (SNVs) mutations are also linked to ASD (Iossifov, Ronemus et al. 2012). Generally, a large number of genes (around 384–821) are responsible for the disorder, rather than one specific gene (O’Roak, Vives et al. 2012), and these genetic variants additively contribute to ASD in small increments (Klei, Sanders et al. 2012). As a likely consequence of these genetic mutations, neuronal abnormalities including atypical neuronal migration, axon pathfinding, synaptogenesis, and pruning emerge and impact mental health. For example, autism has been typified as a “developmental disconnection syndrome” proposed to be due to the disconnection between frontal and temporal lobe association cortices (Geschwind and Levitt 2007). This disconnection can involve the severing of already developed connections or the failure for these connections to form as the result of neuronal and genetic abnormalities. One such gene variant that may play a role in autism risk disconnections includes the Met Receptor Tyrosine (MET) kinase gene, which is expressed in the occipital, temporal, and parietal cortices that process social information in humans (Mukamel, Konopka et al. 2011). Evidence suggests that variant in the MET gene predicts decreased structural and functional connectivity in the temporal-parietal cortices of ASD subjects (Rudie, Hernandez et al. 2012). Furthermore, adult men with ASD demonstrate reduced *MET* expression in the temporal neocortex, while adult women with ASD do not have patterns of gene expression different from controls (Plummer, Evgrafov et al. 2013). These findings suggest that autistic individuals may have disrupted *MET* signaling that impact temporal circuit formation in a sex specific fashion. How these autism risk genes impact sexual dimorphism in the brain on both neuronal and anatomical levels remains to be investigated.

Although sex differences in the genetic basis of autism have not been well studied, some evidence suggests that girls may be genetically more protected from autism (refer to Table 2) (Robinson, Lichtenstein et al. 2013, Werling and Geschwind 2013, Jacquemont, Coe et al. 2014, Werling and Geschwind 2015). For instance, recurrence rates are higher in siblings of female versus male probands, which is predicted by the female protective model (Werling and Geschwind 2015). Furthermore, autistic females exhibit greater number of detrimental autosomal CNVs and SNVs, compared to males (Jacquemont, Coe et al. 2014), indicating that females may require a higher mutational load to be susceptible to autism. From analysis of whole exome sequencing data, female probands also possess a higher burden of *de novo* frameshift indels than males and these indels arise mostly from the paternal chromosome (Dong, Walker et al. 2014). This female protective effect is not likely to be regulated by one locus but possibly by many genes and environmental factors, since no single SNP in the X chromosome or the whole genome reached significance after a targeted as well as full genome wide association study (GWAS) analysis (Gockley, Willsey et al. 2015). Once girls are diagnosed with autism, they also demonstrate lower cognition than boys, most likely because of the extra mutations (Jacquemont, Coe et al. 2014). Other evidence suggests that the greater mutational load hypothesis for girls with autism may not be completely

substantiated. For instance, the prevalence rate of these girls' relatives has been found to not be significantly different from that of their male counterparts' relatives, a result that contradicts what is predicted by the hypothesis (Goin-Kochel, Abbacchi et al. 2007). However, many other studies do support the hypothesis that greater genetic disruption is necessary for females to be diagnosed compared to males (Zhao, Leotta et al. 2007, Gilman, Iossifov et al. 2011, Levy, Ronemus et al. 2011, Szatmari, Liu et al. 2012, Robinson, Lichtenstein et al. 2013). For example, more autistic females carry de novo CNV mutations than autistic males (Sebat, Lakshmi et al. 2007, Levy, Ronemus et al. 2011), and these affected females have larger sized CNVs that include more genes linked to ASD than males (Gilman, Iossifov et al. 2011). CNVs in autistic females disturb the functional network of genes involved in synaptogenesis, neuronal motility, and axon guidance to a greater degree than autistic males (Gilman, Iossifov et al. 2011).

Linkage signal at 1p31.3 (Werling, Lowe et al. 2014), 5q12.3 and 9q33.3 (Szatmari, Paterson et al. 2007), 13.16 cM on chromosome 7q (Schellenberg, Dawson et al. 2006), 11q13.4 (Schellenberg, Dawson et al. 2006), 16p (Lamb, Barnby et al. 2005), 17q11 (Stone, Merriman et al. 2004), 17q21 (Cantor, Kono et al. 2005), as well as microdeletion at SHANK1 are linked to ASD in males (refer to Figure 5), whereas microdeletion at the same site is associated with anxiety in females (Sato, Lionel et al. 2012). However, at least one study did not find a male biased linkage for chromosome 17 (Schellenberg, Dawson et al. 2006). DRD1, which encodes the dopamine D1 receptor, is associated with an increased susceptibility to ASD in sibling pair families (Hettinger, Liu et al. 2008). In particular, these male-only ASD families display an over-transmission of the DRD1 polymorphisms (rs4532-A and rs265981-C) as well as the rs265981-C / rs-4532-A / rs686-T (C-A-T) haplotype, and individuals with this genotype demonstrate greater stereotypical behavior, difficulties in non-verbal communication, and social interaction. Furthermore, using a family-based GWAS, Chang and colleagues discovered that 5 SNPs on chromosome 13q33.3 and paternal transmission of SNPs rs2535443, rs311150, and rs311149 in the pseudoautosomal region of the XG gene on chromosome Xp22.33/Yp11.31 are significantly associated with male-only ASD families (Chang, Pauls et al. 2013). In addition, a case-control association analysis revealed that at the NLGN3 gene, common variants at the SNP rs4844285 and the XA-XG-XT (rs11795613-rs4844285-rs4844286) haplotype are associated with a male bias in ASD (Yu, He et al. 2011). Possession of the monoamine oxidase (MAOA) marker rs6323 with T alleles increases risk of ASD in males, and owning rs1137070-C results in GATA-2 binding site deletion, which potentially causes sex differences in ASD because GATA-2 acts on the SRY gene (Verma, Chakraborti et al. 2014). In another study, 9 of the ten 16p11.2 CNVs existed in autistic males, indicating that this locus may be sex-biased (Levy, Ronemus et al. 2011). One twin study demonstrated that the genetic overlap between social and communication impairment is greater for males with extreme autistic-like traits and for males in the typical population, compared to females (Robinson, Koenen et al. 2012). Finally, novel rare variants in the *TMLHE* gene have been identified via next generation sequencing in male patients with ASD but not in controls (Nava, Lamari et al. 2012). Since next generation sequencing has yielded discoveries of at least 9 to 33 novel autism risk genes (Iossifov, Ronemus et al. 2012, Neale, Kou et al. 2012, O'Roak, Vives et al. 2012, Sanders, Murtha et al. 2012, De Rubeis, He et al. 2014, Iossifov, O'Roak et al. 2014, De

Rubeis and Buxbaum 2015), future research should assess the role of sex on novel gene variants in autism by utilizing this genomic approach.

Deletion at chromosome Xp22.3 has been seen in 3 females with autism (Thomas, Sharp et al. 1999). Linkage signals at chromosome 4 (Schellenberg, Dawson et al. 2006), 8p12 and 8p21.2 (Werling, Lowe et al. 2014), 5p15.33, 9p24.1, and 11p12-13 (Szatmari, Paterson et al. 2007), and 15q (Lamb, Barnby et al. 2005) have been discovered in female containing sibling pairs with ASD. Moreover, a case-control association analysis has unveiled that females with ASD have a higher prevalence of SNP rs6152-A as well as short CAG alleles of the androgen receptor gene, compared to controls; meanwhile, a family-based association analysis uncovered that the 23-repeat GGN allele is over-transmitted to females with ASD, while the 20-repeat GGN allele is under-transmitted to males (Henningsson, Jonsson et al. 2009). In a GWAS analysis, two SNPs (rs6683048-G of the *RyR2* gene and rs17420138-T of the *UPP2* gene) have been found to be over-transmitted in both male only and female containing ASD families (Lu and Cantor 2012). Another study using GWAS and convergent functional genomics found that the 133 common variants identified in or close to functionally relevant genes for autism explained 5% of the genetic variance in females with ASD and 1% of the variance in males (Carayol, Schellenberg et al. 2014). However, despite these genetic findings, several twin studies have not found sex-specific genetic factors in autism or autistic traits (Hoekstra, Bartels et al. 2007, Taniai, Nishiyama et al. 2008). More research needs to be conducted to reconcile the difference in these results from those of non-twin studies.

SNP rs2747648 on the *ESR1* (which encodes estrogen receptor alpha) is significantly associated with boys with high levels of autistic traits, while SNP rs523349 on the *SRD5A2* (which encodes 5-alpha-reductase) is linked to girls with autistic-like traits (Zettergren, Jonsson et al. 2013). This finding implies that sex steroid related genes influence gene expression and hormone regulation that serve as risk factors for autistic-like behavior. Furthermore, androgens and estrogens have been shown to differentially affect the *RORA* (retinoic acid-related orphan receptor-alpha) gene, which regulates aromatase, the enzyme responsible for converting testosterone to estradiol (Sarachana, Xu et al. 2011). Specifically, estrogen upregulates the gene, while testosterone suppresses it. The negative feedback mechanism of testosterone on *RORA* leads to decreases in aromatase, which then results in an accumulation of testosterone that further diminishes *RORA* gene expression. Such reductions in aromatase and *RORA* proteins as the result of hormonal regulation have been demonstrated in the frontal cortex of autistic individuals and may be a reason behind the sex bias in ASD. Furthermore, a recent study indicates that female controls have higher levels of *RORA* proteins than males and that ASD females have greater aromatase levels than ASD males, which suggests that females may utilize better compensatory strategy that counters aromatase deficiency caused by down regulation of *RORA* expression and dysregulation of androgen and estrogen (Hu, Sarachana et al. 2015). Thus, steroid hormones have a significant influence on sex differences in autistic-like behavior, as predicted by fetal testosterone theory, and may be responsible for the impaired empathizing and intact systemizing skills seen in autistic individuals (Baron-Cohen, Lombardo et al. 2011). However, much still remains to be studied on the interaction between hormones and genes. For example, while oxytocin is estrogen-dependent and vasopressin is androgen-dependent

(Carter, Black et al. 2007) and at least one study has found sex differences in plasma oxytocin and vasopressin levels in ASD (Miller, Bales et al. 2013), no studies thus far have researched whether variants of the oxytocin and vasopressin receptor genes contribute to sex differences in ASD. Additionally, another study has found an association between 2 SNPs in the *PITX1* gene (which regulates hormones in the hypothalamic-pituitary-adrenal axis) and autism (Philippi, Tores et al. 2007); however, despite previous studies indicating sex differences in these hormones (Majchrzak and Malendowicz 1983, Handa and Weiser 2014), no studies have yet shown how the *PITX1* gene affects sex differences in the brain and behavior of individuals with ASD.

All these sex-specific genetic factors have implications on brain development. For instance one study discovered that a 17q21.31 microdeletion is linked to mental retardation (Koolen, Vissers et al. 2006) and triventricular ventriculomegaly in the fetus (Egloff, Encha-Razavi et al. 2014). Other mutations in the same chromosome region can damage the fronto-temporal regions that lead to dementia (Cruts, Gijselinck et al. 2006, Mackenzie, Baker et al. 2006). Furthermore, microdeletions of 16p11.2-p12.2 have been found in some individuals with developmental delay (Ballif, Hornor et al. 2007), whereas 13q deletion (Brown, Gersen et al. 1993) and 11p12-p15.4 duplication (Coppola, Striano et al. 2010) have been associated with mental retardation. Chromosome Xp22.3 deletion has been discovered in a boy with cerebral cortical heterotopias and mental retardation (van Steensel, Vreeburg et al. 2008). While chromosome 8p21.1-q11.23 is linked to basal ganglia calcification (Dai, Gao et al. 2010), 8p23.1-p11.1 duplications as well as 1p31.3-p31.1 deletions have been observed in patients with corpus callosum agenesis (Sajan, Fernandez et al. 2013). Duplication of 15q has also been found in those with hippocampal dysplasia and heterotopias, hippocampal sclerosis and malformation, corpus callosum hypoplasia and thinning, as well as greater pericerebral spaces (Boronat, Mehan et al. 2015). Furthermore, a 15q trisomy has been seen in 2 boys with mesial temporal lobe malformation (i.e. fusiform and parahippocampal gyri, hippocampus, etc.) (Kobayashi, Facchin et al. 2002), whereas a 5p anomaly is associated with periventricular heterotopia (Sheen, Wheless et al. 2003). ASD risk gene *MET* (specifically, the “C” variant of rs1858830 promoter allele) has been shown to predict lower fractional anisotropy in major tracts of the temporal-parietal-occipital lobes, such as the superior and inferior longitudinal fasciculus, cingulum, and the splenium of the corpus callosum (Rudie, Hernandez et al. 2012). Dysfunction in MAOA markers can lead to MAOA deficiency, which is affiliated with corpus callosum thinning, disturbed cerebellum microarchitecture, and greater dendritic arborization in the prefrontal cortex (Bortolato, Godar et al. 2013). Other genes such as NLGN and SHANK operate at a molecular level, with NLGN involved in synapse formation (Kim, O’Sullivan et al. 2011) and SHANK functioning as a molecular scaffold (Lim, Naisbitt et al. 1999). DRD1 gene encodes D1 receptors, which are regionally distributed in the striatum, substantia nigra, and olfactory bulb (Levey, Hersch et al. 1993), among many other regions such as the frontal cortex and are involved in synaptogenesis, neurite outgrowth, and connectivity (Money and Stanwood 2013). The RORA gene plays a critical role in cerebellar development and Purkinje cell differentiation (Sarachana, Xu et al. 2011). Generally, male-biased genes have been shown to be involved in cell cytoskeleton, immune response, glycoproteins or extracellular matrix formation, and chromatin, all of which may be implicated in ASD (Ziats and Rennert 2013).

Autism is not simply an X-linked disorder (Hallmayer, Spiker et al. 1996, Pickles, Starr et al. 2000); however, a second X chromosome (especially from the father) may still provide protection from autism. For instance, mice with only one X chromosome are less social on social preference tasks and dyadic interaction tests and spend less time at the distal ends of an elevated plus maze (Cox, Quinlivan et al. 2015). Furthermore, genomic imprinting impacting the X chromosome may explain sex differences in autism, since all males possess X chromosomes derived from the maternal line. In a study that investigated 5 cases of autism in a sample of 150 individuals with Turner syndrome (XO), all the autistic individuals feature a maternal X-chromosome or an abnormal paternal X-chromosome (Creswell and Skuse 1999). Another study examining a female with autism and Turner syndrome confirms that her X chromosome was maternally inherited (Donnelly, Wolpert et al. 2000). Girls with Turner syndrome, which is highly comorbid with autism, tend to be more socially adjusted with better verbal and executive function if they possess a paternal derived X chromosome (Skuse, James et al. 1997). Additionally, girls with Turner syndrome have lower levels of vasopressin in the plasma, relative to controls (Cox, Quinlivan et al. 2015). These findings support the idea that those with fewer number of X chromosomes (especially of maternal origin) are at greater risk of developing social deficits similar to autism. Further evidence to substantiate this idea comes from sex chromosome aneuploidy cases, such as Turner syndrome (XO) in which the risk of autism increases by 3% compared to those with their sex chromosomes intact (Skuse, James et al. 1997, Creswell and Skuse 1999, Donnelly, Wolpert et al. 2000). Additionally, presence of the Y chromosome may increase the risk for autism. For instance, in those with Klinefelter syndrome (XXY), there is about a 10% greater risk for autism, while in 47, XYY syndrome, the risk increases to ~20% (Jha, Sheth et al. 2007, Bishop, Jacobs et al. 2011, Ross, Roeltgen et al. 2012, van Rijn, Bierman et al. 2012). No such increase in autism has been seen in X chromosome trisomy cases (Bishop, Jacobs et al. 2011).

Future Research Directions

Studying sex differences in ASD may, in fact, be paramount for advancing treatment for both boys and girls diagnosed as having autism. Both boys and girls with ASD show rapid increases in total cerebrum and regional brain areas, relative to controls. Yet, girls with ASD display further enlargement in the temporal volume and abnormal reduction in the cerebellum and some corpus callosum fibers, compared to boys with ASD. Female toddlers with autism also exhibit atypical enlargement over time in many brain regions, while male toddlers with autism display atypical increases in only the cingulate, compared to controls. By the time these girls and boys with ASD reach adulthood, sex differences in many brain regions and connections are attenuated.

The greater brain abnormalities seen in girls with ASD supports a female protective model, which states that a higher mutational threshold is required for girls to be diagnosed with ASD. However, it is worth noting that ascertainment bias (in which girls with severe phenotypes and low cognitive functioning are more likely to be diagnosed with ASD) may partially contribute to the greater neural abnormalities and excess deleterious mutations seen in the profile of diagnosed girls. Still, higher CNV burden is seen in females even after controlling for IQ (Jacquemont, Coe et al. 2014). Furthermore, many neuroanatomical

studies investigating sex differences in autism have controlled or matched for IQ (Piven, Arndt et al. 1996, Sparks, Friedman et al. 2002, Bloss and Courchesne 2007, Craig, Zaman et al. 2007, Schumann, Bloss et al. 2010, Tepest, Jacobi et al. 2010, Calderoni, Retico et al. 2012, Lai, Lombardo et al. 2013, Nordahl, Iosif et al. 2015). Hence, sex is likely to still play a role in the neuroanatomical and some genetic differences between girls and boys with ASD, regardless of IQ. Thus far, chromosome 4, 5p15.33, 8p, 9p24.1, 11p12-13, 15q, and Xp22.3 have been linked to girls with ASD. Meanwhile, 1p31.3, 5q12.3, 7q, 9q33.3, 11q13.4, 13q33.3, 16p11.2, 17q11-21, Xp22.33/Yp11.31, DRD1, NLGN3, MAOA, and SHANK1 deletion are associated with boys with ASD. The SNPs of *RYSR2*, *UPP2*, and the androgen receptor gene also have sex-biasing factors in both girls and boys with ASD. Other genes such as *PITX1*, *MET*, and *TMLHE* need to be assessed in girls with ASD to see whether variants in these genes yield sex differences in autistic brain or phenotype. All of these genes may play an integral role on brain development; however, much remains to be replicated and discovered in this area of research that has been historically neglected. Although some studies have examined sex differences in brain structure and others have investigated sex differences in genes of ASD, future studies need to integrate the two disparate approaches and analyze how genes affect brain sexual differentiation in neuroanatomy and connectivity of ASD. Furthermore, future research should examine how changes in brain structure relate to different types of cognitive and behavioral outcomes for males and females with ASD. Additionally, given the recent separation of social communication disorder from autism spectrum disorders in DSM-V (APA 2013), examining how sex differences in diagnosis and phenotype have changed in these two disorders is critical.

Investigating these research questions will require larger and equal sample sizes for ASD boys and girls in multiple sites across the nation. Thus far, most studies include small, non-representative samples of girls or women, and scientists should be more proactive in recruiting girls with ASD to their research studies. Given that evidence exists for sex differences in the autistic phenotype, it may be necessary to devise and use sex-based tests for diagnosis to fully capture ASD in girls (Head, McGillivray et al. 2014). Additionally, since the neural profile of males and females with ASD look differently across age, longitudinal studies need to be implemented to track changes across time.

While it is vital to probe the neural and genetic underpinnings of sex differences in the autistic brain, experience with the external world also play a powerful role in shaping brain architecture during infancy and sensitive periods of development that may lead to mental disorders (Greenough and Black 1992, Nelson 2014). Failure to integrate appropriate experiences early in life may lead to social dysfunction characteristic of autism, and such dysfunction appears to be unmalleable. These details highlight the importance of researching the impact that environment has on genes and neurodevelopment that may contribute to sexual dimorphism in the brains of patients with autism.

Conclusions

Our literature review aims to provide the most current scientific knowledge regarding sex differences in ASD and to emphasize the fundamental gap in understanding the genetic,

neural, and phenotypic profile of girls diagnosed with ASD. Autism represents not only a heterogeneous group of mental disorders but one in which vast sex differences in diagnosis exist. Given the difficulty of recruiting girls with ASD, none of the studies documented here include adequate sample sizes of girls with ASD. Furthermore, no experiments detailed in this review have followed girls and boys with ASD longitudinally from early childhood to late adolescence to establish the developmental milestones by which various types of sex differences in ASD begin to emerge. Complicating these problems, current research in ASD has only examined the disorder from narrow and isolated perspectives, focusing either on genetics or neuroanatomy of ASD. These serious methodological issues of all studies thus far need to be remedied. Specifically, future interdisciplinary studies (intertwining genetics, neuroimaging, and psychology) are essential for scientists to advance a more complete framework for understanding a disorder as complex as ASD. Results from these future studies will be crucial for informing sex-specific intervention strategies that target precise genes and neuroanatomical pathways to reduce severity in ASD phenotype. Our review is a critical first step towards this seamless integration of disparate fields and calls for visionary research that sheds new light on the interactions of genes, brain, and behavior underlying sex differences in ASD.

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Figure 1.

Overall prevalence rate of ASD is increasing over time in the U.S., and this increase is mainly driven by male diagnosis. Data are from the U.S. Center for Disease Control, Autism and Developmental Disabilities Monitoring Network (CDC 2007, CDC 2007, CDC 2009, CDC 2009, CDC 2012, CDC 2014). Information for 2012 is not included because diagnostic method is different from previous years.

Figure 2.

The graph displays overall, male, and female prevalence rates of ASD in South Korea (Kim, Leventhal et al. 2011), the U.S.(CDC 2014), Canada (NEDSAC 2013), Australia (ABS 2011), the U.K. (Taylor, Jick et al. 2013), Taiwan (Lai, Tseng et al. 2012), Venezuela (Montiel-Nava and Peña 2008), Iran (Samadi, Mahmoodizadeh et al. 2012), China (Li, Chen et al. 2011), and Oman (Al-Farsi, Al-Sharbati et al. 2011) from 2005 to 2010.

Underdeveloped countries such as Oman and Iran tend to have the lowest prevalence rates because of minimal attention to diagnosing the disorder (Al-Farsi, Al-Sharbati et al. 2011, Samadi, Mahmoodizadeh et al. 2012). Reasons for the high prevalence rate in South Korea are unknown, although usage of Western diagnostic tools may have introduced cultural biases. Limitation of this graph includes different sampling methods among countries.

Figure 3. Percentage of males with ASD (relative to females) varies by country depending on economic development (higher prevalence for developed countries), but in all locations, male prevalence is substantially higher than female prevalence.

Figure 4.

In the U.S., the greatest sex differences in prevalence occur in ASD individuals with normal or high intellectual ability (Yeargin-Allsopp, Rice et al. 2003). For those with very low intelligence, there is about equal representation of males and females diagnosed with ASD. Other countries like Sweden and England show similar trends, although a few recent studies do not, most likely because of low sample sizes or failure to test individuals with the most severe intellectual functioning.

Figure 5.

Loci highlighted in red indicates susceptibility to ASD for males, while loci highlighted in yellow indicates susceptibility to ASD for females. Loci colored in blue signifies risk for either males or females depending on hormonal levels. Source of images comes from National Institute of Health's NCBI Map Viewer. RYR2 = 1q43, SRD5A2 = 2p23, UPP2 = 2q24.1, DRD1 = 5q35.1, ESR1 = 6q25.1, RORA = 15q21-22, SHANK1 = 19q13.33, MAOA = Xp11.3, androgen receptor gene = Xq12, NLGN3 = Xq13.1.

TABLE 1

Sex Differences in Structural and Neural Connectivity in Autism

Author	Year	Area	Country	Method	Sample Size
Piven et al	1996	Iowa	USA	sMRI	*26 males & 9 females with autism *20 males & 16 females as typical controls
Lainhart et al	1997	Baltimore	USA	sMRI	*70 males & 21 females with autism *used a reference sample of 354 volunteers from Britain for typical controls
Sparks et al	2002	Seattle Bethesda	USA	sMRI	*38 boys & 7 girls with ASD *18 boys & 8 TD girls *6 boys & 8 girls with DD
Bloss & Courchesne	2007	San Diego	USA	sMRI	*9 girls & 27 boys with autism *14 girls & 13 TD boys
Craig et al	2007	London	UK	sMRI VBM	*14 women with ASD *19 women as typical controls
Tepest et al (Tepest, Jacobi et al. 2010)	2010	Cologne	Germany	sMRI	*18 men & 11 women with high functioning autism *18 men & 11 women as typical controls
Schumann et al	2010	San Diego	USA	sMRI Longitudinal	*32 boys & 9 girls with autism *32 boys & 12 TD girls
Calderoni et al	2011	Pisa	Italy	sMRI VBM SVM-RFE	*19 girls with ASD *19 DD girls *19 TD girls
Beacher et al	2012	Brighton	UK	sMRI DTI	*13 women & 15 men with high functioning autism *15 women & 15 men as typical controls
Lai et al	2013	Cambridge	UK	sMRI VBM	*30 women & 30 men with autism *30 women & 30 men as typical controls
Nordahl et al	2013	Davis	USA	DTI Longitudinal	*112 pre-school ASD boys & 27 preschool ASD girls *53 boys and 29 TD girls

Diagnostic Criteria	Age	Brain Regions
*ADI	Autistic subjects: 12 – 29	Enlarged TBV in autistic males, not females.
*DSM-III-R	Typical subjects: 13 –	Autistic vs. typical males; Enlarged temporal and parietal lobes in autistic males, compared to typical males.

Diagnostic Criteria	Age	Brain Regions
*ADI *Clinical Observation	28	
	3–38	<p>8 autistic females vs. typical females from reference sample – greater mean birth head circumference in autistic females.</p> <p>37 autistic males vs. typical males from reference sample – no significant difference in head circumference.</p>
*MSEL *VABS *ADI-R *ADOS-G *DSM-IV	3–4	<p>Both ASD girls and boys exhibited cerebellum enlargement, relative to controls.</p> <p>ASD vs. TD boys – Enlarged cerebellum, hippocampus, & amygdala, proportionate to cerebellum size. Enlarged right amygdala, controlling for cerebellum volume.</p> <p>ASD vs. TD girls – No such enlargement in cerebellum or subcortical structures.</p>
		<p>Autistic vs. TD girls: Enlarged intracranial, whole brain, cerebral GM, frontal GM, temporal GM, & cerebellar WM volumes. Reduced cerebellar GM.</p> <p>Autistic vs. TD boys: Enlarged whole brain, cerebral GM, frontal WM, frontal GM, & cerebellar WM volumes.</p> <p>Autistic boys vs. autistic girls: Enlarged cerebral WM, cerebellar GM, frontal GM, & temporal GM volumes.</p>
	Autistic girls: 2.35 – 4.97 Autistic boys: 1.92 – 5.08	<p>TD boys vs. TD girls: Enlarged frontal GM & parietal WM volumes.</p> <p>Autistic boys over age: No relationship between age & any brain structure.</p> <p>TD boys over age: Correlations with age on almost all brain structures assessed.</p>
	*CARS *ADOS *ADI	<p>Autistic girls over age: Cerebral WM, parietal WM, frontal WM, and occipital WM volumes increased with age.</p> <p>TD girls over age: Correlations with age on only the frontal WM and parietal WM volumes.</p>
*ICD-10 *ADI-R *ADOS	ASD women: 37.9 ± 11.4 Typical women: 35.0 ± 14	<p>ASD vs. typical women – GM. Reduced bilateral OFC, basal ganglia, & temporal lobes. Smaller R medial occipital lobe & L frontal lobe.</p> <p>ASD vs. typical women – WM: Reduced density in bilateral brain stem and anterior temporal lobes. Increased density in the projection & association fibers of parietal, frontal, posterior temporal, & occipital lobes, in the cerebellum, & the commissural fibers of the CC.</p>
	Autistic subjects: 20.9 – 53.3 Typical subjects: 20.3 – 55.2	<p>Both high functioning autistic and typical women had significantly larger ratio of CC / TBV than the men – but this was explained by brain size.</p>
	Autistic boys: 22–67 months Autistic girls: 26–58 months TD boys: 12–63 months TD girls: 12–61 months	<p>Autistic vs. TD boys: Enlarged temporal & frontal GM. Cingulate GM increased at a nonlinear rate, compared to controls.</p> <p>Autistic vs. TD girls: Enlarged temporal & cingulate GM. Total cerebrum, cerebral GM, cerebral WM, temporal GM, and frontal GM increased at an abnormal rate, compared to controls.</p>
	*DSM-IV-TR *ADOS *CARS	<p>ASD vs. TD girls: 5% enlargement of total intracranial volume. Increased GM in bilateral SFG and R TPJ.</p>
*DSM-IV *AAA *DISCD	Autistic women: 32 ± 7 Autistic men: 32 ± 10 Typical women: 32 ± 8	<p>Typical men vs. typical women: Enlarged GM volumes in the Rolandic operculum & R inferior parietal lobe</p> <p>Autistic men vs. autistic women: No such enlargement.</p>

Diagnostic Criteria	Age	Brain Regions
Typical men: 28 ± 8		Autistic men vs. typical men: No such enlargement.
		Typical men vs. typical women: Higher FA in the CC, R & L cingulum (i.e. the anterior portion), & corona radiata
		Autistic men vs. autistic women: No sex differences in FA.
*ICD-10 *DSM-IV *ADI-R *ADOS *ASQ *AAA	18–49	Autistic and typical men vs. women – WM: Larger in 6 clusters in occipital, frontal, & TPOJ regions.
		Autistic and typical women vs. men – WM: Larger in 3 clusters in cerebellum / brain stem, internal capsule, and fibers from CC.
		Autistic vs. typical women – WM: Larger in 2 clusters in TPOJ regions (posterior cingulum, CC, inferior longitudinal fasciculus, and R arcuate fasciculus). Smaller in 2 clusters in bilateral internal capsule at thalamus and basal ganglia.
		Autistic vs. typical men – WM: No difference in size in TPOJ regions. Larger in 2 clusters in bilateral internal capsule at thalamus and basal ganglia.
		Autistic and typical men vs women – GM: Larger in 6 clusters in DMPFC, frontal & occipital poles, sensory motor cortices, Heschl gyri, superior temporal gyri, lingual and calcarine gyri, lateral temporal regions, temporo-occipital regions, precuneous, superior cerebellar hemispheres, posterior cingulate cortices, & brainstem.
		Autistic and typical women vs. men – GM: Larger volumes in 9 clusters in supplementary motor area, L DLPFC, primary somatosensory cortex, caudate, thalamus, bilateral OFC, fusiform, parahippocampal, hippocampal gyri, & cerebellar vermis and hemispheres.
		For autistic females, abnormal brain regions overlapped with sexually dimorphic GM & WM regions in typical controls; however, this was not the case for autistic males.
		ASD boys vs. girls – smaller CC region projecting to the OFC.
		ASD girls vs. boys – smaller CC region projecting to the anterior frontal cortex
*ADOS-G	3–5	ASD girls vs. TD girls – greater MD, AD, & RD
*ADI-R		ASD boys vs. TD boys – no difference
Sample Size		
TTD = typically developing, DD = developmental delay		
Diagnostic Criteria		
AAA = Adult Asperger Assessment, ABC = Aberrant Behavior Checklist, ADI-R = Autistic Diagnostic Interview-Revised, ADOS-G = Autism Diagnostic Observation Schedule – Generic, ASQ = Autism Spectrum Quotient, AGRE = Autism Genetic Resource Exchange, AT = Autism-Tics, CARS = Childhood Autism Rating Scale, BAPQ = Broad Autism Phenotype Questionnaire, DISCD = Diagnostic Interview for Social & Communication Disorders, DSF = Diagnosis Summary Form, DSM = Diagnostic Statistical Manual, ICD-10 = International Statistical Classification of Diseases-10, MSEL = Mullen Scales of Early Learning, RBS-R = Repetitive Behavior Scale-Revised, VABS = Vineland Adaptive Behavior Scales		
Brain Regions		
GM = gray matter, WM = white matter, FA = fractional anisotropy, R = right, L = left, CC = corpus callosum, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, OFC = orbitofrontal cortex, SFG = superior frontal gyrus, TBV = total brain volume, TPJ = temporal-parietal junction, TPOJ = temporal-parietal-occipital junction, MD = mean diffusivity, AD = axial diffusivity, RD = radial diffusivity.		

Table 2

Sex Differences in the Neurogenetics of Autism

Author	Year	Area	Method	Sample Size	Diagnostic Criteria	Genetics
Thomas et al	1999	UK	Fluorescence in situ hybridization (FISH) analysis PCR Cytogenetic analysis	8 patients with Xp22 deletions, 3 with autistic symptoms	*ADOS	Female: Xp22.3 deletion
Stone et al	2004	USA	Complete genome linkage scans	257 nuclear families, With 2 or more ASD children	--	Male linkage: Linkage peak at 17q11
Cantor et al	2005	USA	Full-genome linkage scan	109 sibling pairs with ASD	--	Male linkage: 17q11-17q21 Linkage peak at 17q21
Lamb et al	2005	UK	Linkage analysis	420 individuals with autism 219 sibling pairs	*ADI-R *ADOS *ADOS-G *VABS	Male linkage: 16p Female containing linkage: 15q
Schellenberg et al	2006	USA	Genome-wide linkage scan	222 families with 2 or more ASD children	*ADI-R *ADOS-G *DSM IV	Male linkage: 11 Male linkage: 133.16 cM on chromosome 7 Female linkage: 4
Szatmari et al	2007	North America Europe	Linkage analysis CNV assessment	1,496 ASD families 7,917 family members	*ADI-R *ADOS *Clinical evaluation	Male linkage: 5q12.3 & 9q33.3 Female containing linkage: 5p15.33, 9p24.1, & 11p12-13
Hettinger et al	2008	Canada UK	Single marker & haplotype case-control comparisons; Family-based association tests; Genotype-phenotype assessments	112 ASD sibling pairs, Families with 2 or more ASD children	*ADI-R *ADOS *AGRE defined categories	Male association: DRD1 (over-transmission of rs265981-C, rs4532-A, & C-A-T haplotype)
Henningsson et al	2009	France Sweden	Case-control association analysis; Family-based association analysis	267 subjects with ASD	*DSM-IV	Female association: short CAG alleles, greater SNP rs6152-A, the 23-repeat GGN allele is over-transmitted in females Male association: rare 20-repeat GGN allele is under-transmitted

Author	Year	Area	Method	Sample Size	Diagnostic Criteria	Genetics
Levy et al	2011	USA Canada	Five state model Probe mappings Trio analysis CNV analysis	1000 ASD simplex families; 10 cases of 16p11.2 CNVs	*ADI-R *ADOS *BAPO *RBS-R *VABS *DSF *ABC	Male: 16p11.2 CNV
Yu et al	2011	China	Case-control association analysis	229 ASDs cases 184 control individuals	*DSM-IV *ICD-10	Male association: intronic variant, SNP rs4844285 in NLGN3 gene 3-marker haplotype XA-XG-XT (rs11795613-rs4844285-rs4844286)
Sato et al	2012	Canada France Sweden Germany Finland UK	Microarray	1,158 Canadian and 456 European individuals with ASD	*ADI-R *ADOS *DISC	Males: SHANK1 deletion
Lu and Cantor	2012	USA	GWAS	990 nuclear families, with 2 or more ASD children	*ADI-R	Male & female association: rs6683048-G of the RYR2 gene and rs17420138-T of the UPP2 gene are over-transmitted
Chang et al	2013	USA	Family-based genome-wide association study approach	801 ASD nuclear families	*ADI-R *ADOS *AGRE defined categories	Male association: 13q33.3, pseudoautosomal boundary on Xp22.33/Yp11.31
Zettergren et al	2013	Sweden	Association analysis	1771 subjects with ASD or autistic like traits	*AT	Male association: rs2747648 SNP located in the 3'-UTR of ESR1 Female association: rs523349 (Leu89Val) located in SRD5A2 Encoding 5-alpha-reductase, type 2
Werling et al	2014	USA	Genome-wide, Non-parametric linkage analysis	1,008 ASD multiplex families	*ADI-R *ADOS *DSM-V	Male linkage: 1p31.3 Female containing linkage: 8p21.2 and 8p12
Verma et al	2014	West Bengal	Genotyping analysis (PCR); Bioinformatics analysis; Single marker & haplotype association analysis; Linkage disequilibrium	194 ASD cases 227 control cases	*CARS	Male association: MAOA marker, rs6323 (low activity T allele), rs1137070-C causes GATA-2 binding site deletion (GATA-2 interacts with SRY) Female haplotype association: rs6323G + rs5905809-C

<u>Author</u>	<u>Year</u>	<u>Area</u>	<u>Method</u> analysis	<u>Sample Size</u>	<u>Diagnostic Criteria</u>	<u>Genetics</u>
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Male / Female linkage = the gene was linked to males / females with ASD

Female containing linkage = the gene was linked to male-female and female-female sibling pairs Male / Female association = the gene was associated with autistic males / females in a GWAS (or other association) analysis

Genome-wide association study = GWAS CNV = copy number variant