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Male gender bias in autism and pediatric autoimmunity

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Abstract

Lay Abstract—Males have a higher incidence of autism than females by approximately 4 to 1. Similarly, males have a higher incidence of some pediatric autoimmune diseases as compared to females. The basis for these disparities is largely unknown. In recent years there is growing evidence that immune and autoimmune dysregulation may be involved in autism. It is suggested here that the hormonal and immune processes that may contribute to a male preponderance in some pediatric autoimmune disorders may play a role in the male preponderance in autism.

Scientific Abstract—Male bias in both autism and pediatric autoimmune disease is thought to involve hormonal perturbations in pregnancy or early childhood in the context of genetic control. These early molecular events, at a time of rapid development, are intimately linked to concurrent development in the brain and immune system. It is suggested here that these early regulatory events may overlap between autism and autoimmunity in determining male sex bias and may provide evidence of an etiological link between autism, immune dysregulation, and autoimmune disease.

Introduction

One of the striking and consistent features of autism and autistic spectrum disorders (ASD) is the preponderance of males versus females. For example, the male to female ratio in autism has been reported at 2-1(Levy, Mandell, & Schultz, 2009) and 6-1(Windham et al., 2010), with an average of 4.2-1 (Fombonne, 2002). The basis for this male bias is unknown with theories including the “extreme male brain” (Baron-Cohen, 2002), hormonal theories (Baron-Cohen, Knickmeyer, & Belmonte, 2005), stress and anxiety theory(Pfaff, Rapin, & Goldman, 2011) and genetic influences contributing to male sex bias. Similarly, a male bias is common in pediatric autoimmune disorders, with evidence for hormonal and genetic contributions to male sex bias in autoimmunity and certain autoimmune diseases. Given the growing evidence of immune dysregulation in autism and ASDs, it is suggested that the origins of the male bias in autism may share etiological features with male gender bias in pediatric autoimmune disease.

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Autism and autoimmune disease

Autism and ASDs have been shown to have numerous characteristics in common with autoimmune and inflammatory disorders at the genetic, molecular, cellular, histological, and epidemiological level(Atladottir et al., 2009; Comi, Zimmerman, Frye, Law, & Peeden, 1999; Croen, Grether, Yoshida, Odouli, & Van de Water, 2005; Enstrom, Van de Water, & Ashwood, 2009; Keil et al., 2010; Mouridsen, Rich, Isager, & Nedergaard, 2007; Sweeten, Bowyer, Posey, Halberstadt, & McDougle, 2003). These include shared genetic associations(Becker, 2007), altered immune pathways at the RNA level(Lintas, Sacco, & Persico, 2010; Voineagu et al.), imbalances in cytokine, chemokine, and antibody profiles(Ashwood et al., 2010; Grether, Croen, Anderson, Nelson, & Yolken, 2010), variations in T cells, macrophages, and mast cells(Grigorenko et al., 2008; Mostafa, Al Shehab, & Fouad, 2010; Theoharides et al., 2010), as well as activation of glial cells in the brain(Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Immune allergic response has been reported to be increased in Asperger syndrome as well(Magalhaes et al., 2009).

One hallmark of autoimmune disorders is an increase in the frequency of other autoimmune and inflammatory disorders, not necessarily the patient's specific disease, in family members of the patient(Anaya, Gomez, & Castiblanco, 2006; Barcellos et al., 2006; Prahalad, Shear, Thompson, Giannini, & Glass, 2002). This is thought to represent an underlying shared genetic susceptibility and a broad dysregulation of immune pathways in autoimmunity and inflammation(Anaya et al., 2006; Becker et al., 1998). While many genes have been associated with autoimmune disease, they are almost exclusively genes of immune regulation. There is little evidence that disease target organ specificity (i.e. MS, brain; type 1 diabetes, pancreas; etc.) in autoimmune disease is genetically determined while there is evidence that infection, lack of early immune challenge, or other environmental factors drive tissue disease specificity in the context of a genetically determined susceptible immune system.

Importantly, autism and ASDs have been shown to have an increased frequency of autoimmune disorders in family members of autistic patients in multiple studies in different populations(Atladottir et al., 2009; Becker 2012; Comi et al., 1999; Croen et al., 2005; Keil et al., 2010; Mouridsen et al., 2007; Sweeten et al., 2003), suggesting an underlying genetic basis of immune dysregulation. In particular, both type 1 diabetes and autoimmune thyroid disease have been shown to be significantly increased in families with autism and ASDs (Atladottir et al., 2009; Comi et al., 1999), and a link between type 1 diabetes and autism has been suggested(Freeman, Roberts, & Daneman, 2005).

Male gender bias in pediatric autoimmune disease

Classical *adult* autoimmune disorders are well known to often have a strong female sex bias. This female gender bias generally begins at puberty and is most pronounced in early adulthood and may decline after menopause. However, what is not well appreciated is that prior to puberty, in pediatric or juvenile autoimmune disease, sex bias is often reversed with a clear male sex bias.

Table 1 shows reported male female ratios and age ranges for selected autoimmune disorders. A male bias has been shown in juvenile type 1 diabetes in Denmark (Christau et al., 1977), Sardinia (Songini & Muntoni, 1992), and Sweden (Ostman et al., 2008) and in 21 other populations, with no evidence for female predominance in type 1 diabetes in any population(Ostman et al., 2008). Moreover, a male sex bias has been shown in asthma with a preponderance of boys before puberty followed by a reversal of the sex ratio during puberty, with girls having more asthma and atopy throughout the reproductive years(Osman, 2003). In Crohn's disease, a skewed male-female ratio has been described in children and adults (Ishige et al., 2010). Although early onset juvenile autoimmune disease is rare, male bias has been noted in immune thrombocytopenia(Sutor, Harms, & Kaufmehl, 2001), Goodpasture's syndrome(Beeson, 1994), IgA nephropathy(Wyatt et al., 1998), pediatric primary sclerosing chloangitis(Miloh, Arnon, Shneider, Suchy, & Kerkar, 2009), and juvenile multiple sclerosis(Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007; Haliloglu et al., 2002; Hanefeld, 1995; Ruggieri, Polizzi, Pavone, & Grimaldi, 1999) Interestingly, the peak of the highest male bias often tends to be at approximately ages 2–6, the typical age of onset for autism and ASDs. This bias tends to decline and invert at puberty, leading to a strong female preponderance post puberty and into adulthood. A male bias in pediatric autoimmune disorders is not universal, with a female bias having been demonstrated for juvenile psoriatic arthritis (Stoll & Nigrovic, 2006), juvenile dermatomyositis (Pachman et al., 2005), and juvenile thyroid autoimmunity (Kaloumenou et al., 2008).

Hormones and sex bias in autoimmune disease and autism

Hormonal influences on adult female sex bias in autoimmunity are complex and highly variable between different autoimmune disorders(Fairweather, Frisancho-Kiss, & Rose, 2008; Lockshin, 2002; McCombe, Greer, & Mackay, 2009) and little is known about the role of hormonal mechanisms in pediatric autoimmune disease. Estrogen has generally been shown to enhance immune responses including altering cytokine and chemokine levels as well as the levels of important immune transcriptional regulators such as NFkB and FOXP3. Androgens tend to have immunosuppressive effects(Cutolo et al., 2006; Rubtsov, Rubtsova, Kappler, & Marrack, 2010; Voskuhl, 2011) with hormonal changes during puberty and young adulthood contributing to sex bias in autoimmunity. These effects on disease are often altered by infection, pregnancy, and menopause(Cutolo et al., 2006; Rubtsov et al., 2010; Voskuhl, 2011). Testosterone has been shown to have an immunosuppressive effect experimentally in animal models(Voskuhl, 2011), as well as clinically. In type 1 diabetes and asthma, it has been suggested that the immunosuppressive and immunomodulatory effects of testosterone may play a role in altering disease course and influencing the male-female disease ratio(Osman, 2003). Moreover, androgen anomalies have been found in adolescents and adults with type 1 diabetes.(Codner & Escobar-Morreale, 2007; Danielson, Drum, & Lipton, 2008; Meyer et al., 2000)

Similarly, testosterone is thought to play a key role in autism during fetal and postnatal development. Increased levels of testosterone have been correlated with autistic traits in toddlers and young children(Auyeung et al., 2009; Auyeung, Taylor, Hackett, & Baron-Cohen, 2010) and in women with autistic traits(Ingudomnukul, Baron-Cohen, Wheelwright, & Knickmeyer, 2007), with the suggestion that testosterone may have a direct effect on

brain development and may influence male gender bias(Baron-Cohen et al., 2005; Chura et al., 2010). Other reports of testosterone and testosterone precursor anomalies have been described in the context of autism and autistic traits as well(Manning, Baron-Cohen, Wheelwright, & Sanders, 2001) (Croonenberghs et al., 2010; Ingudomnukul et al., 2007; Ruta, Ingudomnukul, Taylor, Chakrabarti, & Baron-Cohen, 2011; Takagishi et al., 2010).

At the level of molecular regulation, the effects of testosterone have been associated with both autism and immune regulation through the same signaling molecules. Recently, a new candidate gene in autism, retinoic acid related orphan receptor alpha (*RORA*) has been shown to be under positive and negative feedback by androgens and estrogen through its gene target aromatase (*CYP19A1*), which is responsible for the conversion of testosterone to estrogen(Sarachana, Xu, Wu, & Hu, 2011). *RORA* has also been shown to be reduced in cells lines and in the brains of autism patients(Nguyen, Rauch, Pfeifer, & Hu, 2010). Importantly, RORA, which is phosphorylated by ERK2 (see below), is a key regulator in autoimmune and inflammatory processes and is required for TH17 differentiation and IL17 expression through a mechanism involving STAT3 and interaction with FOXP3(Du, Huang, Zhou, & Ziegler, 2008; Jetten, 2009) (see below).

In addition, the extracellular signal-regulated kinases (ERKs) have been suggested to be central to neurodevelopmental anomalies in autism(Levitt & Campbell, 2009) and have been shown to be upregulated in both a mouse model of autism(Zou H, 2011) as well as in the brains of autistic patients(Yang K, 2011). Anomalous regulation of ERKs lead to altered immune regulation(Gorelik & Richardson, 2010) while testosterone activation of ERKs has been shown to be differentially regulated in neutrophils between males and females, leading to gender dependent production of 5-Lipoxygenase (Pergola et al., 2008), a key enzyme in leukotriene biosynthesis and inflammation(Radmark & Samuelsson, 2010). This has been suggested as a molecular basis for differences in male sex bias in inflammation and asthma.

The influence of the X chromosome in sex bias in autism and autoimmune disease

The influence of the X chromosome in autism and male sex bias in autism has been described by multiple groups. Genetic evidence of loci on the X chromosome has been shown for phenotypes including autism, autistic features, intellectual disability, and speech delay. Recently, genetic mutations in the gene *PTCHD1* at chromosome Xp22.11 have been suggested as a basis for this male bias in autism and intellectual disability(listed, 2010; Noor et al., 2010) although mutations at this locus comprised less than 1% of affected patients tested(Noor et al., 2010).

Likewise, differences in immune function and immune disorders between males and females are profoundly influenced by the X chromosome(Libert, Dejager, & Pinheiro, 2010). Anomalies in X inactivation, haploinsuficiency, hormonal variability regulated by the X chromosome, as well as X chromosome microRNAs may play a role in male-female immune differences at different developmental stages and in different disease contexts(Libert et al., 2010).

The short segment of the X chromosome, Xp11.21-23, has been a focus of mapping in autism and intellectual disability as well as in autoimmunity and autoimmune disease. Giorda(Giorda et al., 2009) reported segmental duplications at Xp11.22-p11.23 associated with intellectual disability, speech delay and EEG anomalies in males and females. Additionally, complex rearrangements at Xp11.23-p11.3(Bonnet et al., 2006; El-Hattab et al., 2010; Giorda et al., 2009; Marshall et al., 2008; Monnot et al., 2008; Qiao et al., 2008) (Chung et al., 2011; Edens, Lyons, Duron, Dupont, & Holden; Holden ST, 2010; Marshall et al., 2008) have been noted in individuals with autism, autistic like features, speech delay, and/or intellectual disability. Similarly, type 1 diabetes and autoimmune thyroid disease, both of which have been shown to be overrepresented in families with autistic children(Keil et al., 2010; Molloy et al., 2006), have both been linked to Xp11.23 (Villano et al., 2009)and have been suggested to play a role in male gender bias(Cucca et al., 1998).

Importantly, the gene *FOXP3*, in Xp11.23, maps to the small region described for autism, autistic features and intellectual disability (Bonnet et al., 2006; Giorda et al., 2009). FOXP3 is a central regulator of immune function and autoimmunity(Buckner, 2010; Campbell & Koch, 2011; Gambineri, Torgerson, & Ochs, 2003; Lourenco & La Cava, 2011) with $FOXP3^+$ regulatory T cells playing a key role in T cell homeostasis(Mai, Wang, & Yang, 2010). Skewed X inactivation has been shown to alter FOXP3 levels in the autoimmune disease systemic sclerosis(Broen et al., 2010). Polymorphisms in *FOXP3* have been associated with multiple autoimmune disorders including type 1 diabetes(Bassuny et al., 2003), autoimmune thyroid disease(Inoue N, 2010), lupus(Lin et al., 2011), vitiligo(Birlea et al., 2011), psoriasis(Gao et al., 2010), and allergic rhinitis(Zhang et al., 2009), although other studies found no association(Zavattari et al., 2004). Moreover, a mouse model of brain inflammation has been demonstrated to be mediated through Hepatocyte Growth Factor (HGF) and c-MET (the HGF receptor), an autism associated gene, resulting in induction of $FOXP3^+$ regulatory T cells(Benkhoucha et al., 2010).

Limitations and Conclusions

The suggestions made here regarding male gender bias in autism and autoimmunity are speculative. They reflect the complex and variable nature of molecular, cellular, and hormonal processes in development and disease. Moreover, attributing disease relevance to individual features of specific genetic regions, as in the example of FOXP3, is quite speculative given that CVNs, deletions, and amplifications, may affect many genes or regulatory elements in those regions.

However, evidence is mounting that immune dysregulation and autoimmunity are fundamental aspects of autism and ASDs. Prenatal and postnatal hormonal fluctuations that have been associated with both autism and autoimmunity are in the context of a nascent and rapidly developing brain and immune system and both autism and autoimmune disease may be influenced by hormonal fluctuations through shared transcriptional and regulatory interactions. Likewise, the molecular and genetic basis of the male sex bias in both autism and autoimmune disorders is unclear. It is suggested here that the underlying determinants of male sex bias in autism and pediatric autoimmune disorders overlap and may manifest themselves through shared molecular mechanisms and common hormonally driven immune

processes, in the context of genetic background, and may provide clues to the etiology of both types of disorders.

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References

Anaya JM, Gomez L, Castiblanco J. Is there a common genetic basis for autoimmune diseases? Clin Dev Immunol. 2006; 13(2–4):185–195. [PubMed: 17162361]

Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, Van de Water J. Altered T cell responses in children with autism. Brain Behav Immun. 2010

Atladottir HO, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, et al. Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics. 2009; 124(2): 687–694. [PubMed: 19581261]

Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G. Fetal testosterone and autistic traits. Br J Psychol. 2009; 100(Pt 1):1–22. [PubMed: 18547459]

Auyeung B, Taylor K, Hackett G, Baron-Cohen S. Foetal testosterone and autistic traits in 18 to 24-month-old children. Mol Autism. 2010; 1(1):11. [PubMed: 20678186]

Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. Lancet Neurol. 2007; 6(10):887–902. [PubMed: 17884679]

Barcellos LF, Kamdar BB, Ramsay PP, DeLoa C, Lincoln RR, Caillier S, et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. Lancet Neurol. 2006; 5(11):924–931. [PubMed: 17052659]

Baron-Cohen S. The extreme male brain theory of autism. Trends Cogn Sci. 2002; 6(6):248–254. [PubMed: 12039606]

Baron-Cohen S, Knickmeyer RC, Belmonte MK. Sex differences in the brain: implications for explaining autism. Science. 2005; 310(5749):819–823. [PubMed: 16272115]

Bassuny WM, Ihara K, Sasaki Y, Kuromaru R, Kohno H, Matsuura N, et al. A functional polymorphism in the promoter/enhancer region of the FOXP3/Scurfin gene associated with type 1 diabetes. Immunogenetics. 2003; 55(3):149–156. [PubMed: 12750858]

Becker KG. Autism, asthma, inflammation, and the hygiene hypothesis. Med Hypotheses. 2007; 69(4): 731–740. [PubMed: 17412520]

Becker KG. Autism, autoimmune disease, and socioeconomic status. Autism-Open Access. 2012 in press.

Becker KG, Simon RM, Bailey-Wilson JE, Freidlin B, Biddison WE, McFarland HF, et al. Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases. Proc Natl Acad Sci U S A. 1998; 95(17):9979–9984. [PubMed: 9707586]

Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med. 1994; 96(5):457–462. [PubMed: 8192178]

Benkhoucha M, Santiago-Raber ML, Schneiter G, Chofflon M, Funakoshi H, Nakamura T, et al. Hepatocyte growth factor inhibits CNS autoimmunity by inducing tolerogenic dendritic cells and CD25+Foxp3+ regulatory T cells. Proc Natl Acad Sci U S A. 2010; 107(14):6424–6429. [PubMed: 20332205]

Birlea SA, Jin Y, Bennett DC, Herbstman DM, Wallace MR, McCormack WT, et al. Comprehensive association analysis of candidate genes for generalized vitiligo supports XBP1, FOXP3, and TSLP. J Invest Dermatol. 2011; 131(2):371–381. [PubMed: 21085187]

Bonnet C, Gregoire MJ, Brochet K, Raffo E, Leheup B, Jonveaux P. Pure de-novo 5 Mb duplication at Xp11.22-p11.23 in a male: phenotypic and molecular characterization. J Hum Genet. 2006; 51(9): 815–821. [PubMed: 16900295]

Broen JC, Wolvers-Tettero IL, Geurts-van Bon L, Vonk MC, Coenen MJ, Lafyatis R, et al. Skewed X chromosomal inactivation impacts T regulatory cell function in systemic sclerosis. Ann Rheum Dis. 2010; 69(12):2213–2216. [PubMed: 20699236]

Buckner JH. Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases. Nat Rev Immunol. 2010; 10(12):849–859. [PubMed: 21107346]

Campbell DJ, Koch MA. Phenotypical and functional specialization of FOXP3(+) regulatory T cells. Nat Rev Immunol. 2011; 11(2):119–130. [PubMed: 21267013]

Christau B, Kromann H, Andersen OO, Christy M, Buschard K, Arnung K, et al. Incidence, seasonal and geographical patterns of juvenile-onset insulin-dependent diabetes mellitus in Denmark. Diabetologia. 1977; 13(4):281–284. [PubMed: 913920]

Chung BH, Drmic I, Marshall CR, Grafodatskaya D, Carter M, Fernandez BA, et al. Phenotypic spectrum associated with duplication of Xp11.22-p11.23 includes Autism Spectrum Disorder. Eur J Med Genet. 2011; 54(5):e516–e520. [PubMed: 21689796]

Chura LR, Lombardo MV, Ashwin E, Auyeung B, Chakrabarti B, Bullmore ET, et al. Organizational effects of fetal testosterone on human corpus callosum size and asymmetry. Psychoneuroendocrinology. 2010; 35(1):122–132. [PubMed: 19833443]

Codner E, Escobar-Morreale HF. Clinical review: Hyperandrogenism and polycystic ovary syndrome in women with type 1 diabetes mellitus. J Clin Endocrinol Metab. 2007; 92(4):1209–1216. [PubMed: 17284617]

Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol. 1999; 14(6):388–394. [PubMed: 10385847]

Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med. 2005; 159(2):151–157. [PubMed: 15699309]

Croonenberghs J, Van Grieken S, Wauters A, Van West D, Brouw L, Maes M, et al. Serum testosterone concentration in male autistic youngsters. Neuro Endocrinol Lett. 2010; 31(4):483–488. [PubMed: 20802443]

Cucca F, Goy JV, Kawaguchi Y, Esposito L, Merriman ME, Wilson AJ, et al. A male-female bias in type 1 diabetes and linkage to chromosome Xp in MHC HLA-DR3-positive patients. Nat Genet. 1998; 19(3):301–302. [PubMed: 9662410]

Cutolo M, Capellino S, Sulli A, Serioli B, Secchi ME, Villaggio B, et al. Estrogens and autoimmune diseases. Ann N Y Acad Sci. 2006; 1089:538–547. [PubMed: 17261796]

Danielson KK, Drum ML, Lipton RB. Sex hormone-binding globulin and testosterone in individuals with childhood diabetes. Diabetes Care. 2008; 31(6):1207–1213. [PubMed: 18346991]

Du J, Huang C, Zhou B, Ziegler SF. Isoform-specific inhibition of ROR alpha-mediated transcriptional activation by human FOXP3. J Immunol. 2008; 180(7):4785–4792. [PubMed: 18354202]

Edens AC, Lyons MJ, Duron RM, Dupont BR, Holden KR. Autism in two females with duplications involving Xp11.22-p11.23. Dev Med Child Neurol. 53(5):463–466. [PubMed: 21418194]

El-Hattab A, Bournat J, Eng P, Wu J, Walker B, Stankiewicz P, et al. Microduplication of Xp11.23p11.3 with effects on cognition, behavior, and craniofacial development. Clin Genet. 2010

Enstrom AM, Van de Water JA, Ashwood P. Autoimmunity in autism. Curr Opin Investig Drugs. 2009; 10(5):463–473.

Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol. 2008; 173(3):600–609. [PubMed: 18688037]

Fombonne E. Epidemiological trends in rates of autism. Mol Psychiatry. 2002; 7(Suppl 2):S4–S6. [PubMed: 12142931]

Freeman SJ, Roberts W, Daneman D. Type 1 diabetes and autism: is there a link? Diabetes Care. 2005; 28(4):925–926. [PubMed: 15793197]

Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol. 2003; 15(4):430–435. [PubMed: 12819471]

Gao L, Li K, Li F, Li H, Liu L, Wang L, et al. Polymorphisms in the FOXP3 gene in Han Chinese psoriasis patients. J Dermatol Sci. 2010; 57(1):51–56. [PubMed: 19880293]

Giorda R, Bonaglia MC, Beri S, Fichera M, Novara F, Magini P, et al. Complex segmental duplications mediate a recurrent dup(X)(p11.22-p11.23) associated with mental retardation, speech delay, and EEG anomalies in males and females. Am J Hum Genet. 2009; 85(3):394–400. [PubMed: 19716111]

Gorelik G, Richardson B. Key role of ERK pathway signaling in lupus. Autoimmunity. 2010; 43(1): 17–22. [PubMed: 19961364]

Grether JK, Croen LA, Anderson MC, Nelson KB, Yolken RH. Neonatally measured immunoglobulins and risk of autism. Autism Res. 2010; 3(6):323–332. [PubMed: 21182209]

Grigorenko EL, Han SS, Yrigollen CM, Leng L, Mizue Y, Anderson GM, et al. Macrophage migration inhibitory factor and autism spectrum disorders. Pediatrics. 2008; 122(2):e438–e445. [PubMed: 18676531]

Haliloglu G, Anlar B, Aysun S, Topcu M, Topaloglu H, Turanli G, et al. Gender prevalence in childhood multiple sclerosis and myasthenia gravis. J Child Neurol. 2002; 17(5):390–392. [PubMed: 12150589]

Hanefeld F. Characteristics of childhood multiple sclerosis. Int MSJ. 1995; 1:91–97.

Holden ST CA, Thomas NS, Abbott K, James MR, Willatt L. A de novo duplication of Xp11.22-p11.4 in a girl with intellectual disability, structural brain anomalies, and preferential inactivation of the normal X chromosome. Am J Med Genet A. 2010; 152A(7):1735–1740. [PubMed: 20578133]

Ingudomnukul E, Baron-Cohen S, Wheelwright S, Knickmeyer R. Elevated rates of testosterone-related disorders in women with autism spectrum conditions. Horm Behav. 2007; 51(5):597–604. [PubMed: 17462645]

Inoue N WM, Morita M, Tomizawa R, Akamizu T, Tatsumi K, Hidaka Y, Iwatani Y. Association of functional polymorphisms related to the transcriptional level of FOXP3 with prognosis of autoimmune thyroid diseases. Clin Exp Immunol. 2010; 162(3):402–406. [PubMed: 20942809]

Ishige T, Tomomasa T, Takebayashi T, Asakura K, Watanabe M, Suzuki T, et al. Inflammatory bowel disease in children: epidemiological analysis of the nationwide IBD registry in Japan. J Gastroenterol. 2010; 45(9):911–917. [PubMed: 20232217]

Jetten AM. Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism. Nucl Recept Signal. 2009; 7:e003. [PubMed: 19381306]

Kaloumenou I, Mastorakos G, Alevizaki M, Duntas LH, Mantzou E, Ladopoulos C, et al. Thyroid autoimmunity in schoolchildren in an area with long-standing iodine sufficiency: correlation with gender, pubertal stage, and maternal thyroid autoimmunity. Thyroid. 2008; 18(7):747–754. [PubMed: 18631003]

Keil A, Daniels JL, Forssen U, Hultman C, Cnattingius S, Soderberg KC, et al. Parental autoimmune diseases associated with autism spectrum disorders in offspring. Epidemiology. 2010; 21(6):805–808. [PubMed: 20798635]

Levitt P, Campbell DB. The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders. J Clin Invest. 2009; 119(4):747–754. [PubMed: 19339766]

Levy SE, Mandell DS, Schultz RT. Autism. Lancet. 2009; 374(9701):1627–1638. [PubMed: 19819542]

Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. Nat Rev Immunol. 2010; 10(8):594–604. [PubMed: 20651746]

Lin YC, Lee JH, Wu AS, Tsai CY, Yu HH, Wang LC, et al. Association of single-nucleotide polymorphisms in FOXP3 gene with systemic lupus erythematosus susceptibility: a case-control study. Lupus. 2011; 20(2):137–143. [PubMed: 21078762]

Lintas C, Sacco R, Persico AM. Genome-wide expression studies in Autism spectrum disorder, Rett syndrome, and Down syndrome. Neurobiol Dis. 2010

listed, n.a. Why being XY increases risk of autism. Perspect Public Health. 2010; 130(6):242.

Lockshin MD. Sex ratio and rheumatic disease: excerpts from an Institute of Medicine report. Lupus. 2002; 11(10):662–666. [PubMed: 12413063]

Lourenco EV, La Cava A. Natural regulatory T cells in autoimmunity. Autoimmunity. 2011; 44(1):33–42. [PubMed: 21091291]

Magalhaes ES, Pinto-Mariz F, Bastos-Pinto S, Pontes AT, Prado EA, deAzevedo LC. Immune allergic response in Asperger syndrome. J Neuroimmunol. 2009; 216(1–2):108–112. [PubMed: 19840888]

Mai J, Wang H, Yang XF. Th 17 cells interplay with Foxp3+ Tregs in regulation of inflammation and autoimmunity. Front Biosci. 2010; 15:986–1006.

Manning JT, Baron-Cohen S, Wheelwright S, Sanders G. The 2nd to 4th digit ratio and autism. Dev Med Child Neurol. 2001; 43(3):160–164. [PubMed: 11263685]

Marshall CR, Noor A, Vincent JB, Lionel AC, Feuk L, Skaug J, et al. Structural variation of chromosomes in autism spectrum disorder. Am J Hum Genet. 2008; 82(2):477–488. [PubMed: 18252227]

McCombe PA, Greer JM, Mackay IR. Sexual dimorphism in autoimmune disease. Curr Mol Med. 2009; 9(9):1058–1079. [PubMed: 19747114]

Meyer K, Deutscher J, Anil M, Berthold A, Bartsch M, Kiess W. Serum androgen levels in adolescents with type 1 diabetes: relationship to pubertal stage and metabolic control. J Endocrinol Invest. 2000; 23(6):362–368. [PubMed: 10908163]

Miloh T, Arnon R, Shneider B, Suchy F, Kerkar N. A retrospective single-center review of primary sclerosing cholangitis in children. Clin Gastroenterol Hepatol. 2009; 7(2):239–245. [PubMed: 19121649]

Molloy CA, Morrow AL, Meinzen-Derr J, Dawson G, Bernier R, Dunn M, et al. Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: a CPEA Study. J Autism Dev Disord. 2006; 36(3):317–324. [PubMed: 16598435]

Monnot S, Giuliano F, Massol C, Fossoud C, Cossee M, Lambert JC, et al. Partial Xp11.23-p11.4 duplication with random X inactivation: clinical report and molecular cytogenetic characterization. Am J Med Genet A. 2008; 146A(10):1325–1329. [PubMed: 18412111]

Mostafa GA, Al Shehab A, Fouad NR. Frequency of CD4+CD25high regulatory T cells in the peripheral blood of Egyptian children with autism. J Child Neurol. 2010; 25(3):328–335. [PubMed: 19713552]

Mouridsen SE, Rich B, Isager T, Nedergaard NJ. Autoimmune diseases in parents of children with infantile autism: a case-control study. Dev Med Child Neurol. 2007; 49(6):429–432. [PubMed: 17518928]

Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. FASEB J. 2010; 24(8):3036–3051. [PubMed: 20375269]

Noor A, Whibley A, Marshall CR, Gianakopoulos PJ, Piton A, Carson AR, et al. Disruption at the PTCHD1 Locus on Xp22.11 in Autism spectrum disorder and intellectual disability. Sci Transl Med. 2010; 2(49) 49ra68.

Osman M. Therapeutic implications of sex differences in asthma and atopy. Arch Dis Child. 2003; 88(7):587–590. [PubMed: 12818904]

Ostman J, Lonnberg G, Arnqvist HJ, Blohme G, Bolinder J, Ekbom Schnell A, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983–2002. J Intern Med. 2008; 263(4):386–394. [PubMed: 18205768]

Pachman LM, Lipton R, Ramsey-Goldman R, Shamiyeh E, Abbott K, Mendez EP, et al. History of infection before the onset of juvenile dermatomyositis: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Research Registry. Arthritis Rheum. 2005; 53(2): 166–172. [PubMed: 15818654]

Pergola C, Dodt G, Rossi A, Neunhoeffer E, Lawrenz B, Northoff H, et al. ERK-mediated regulation of leukotriene biosynthesis by androgens: a molecular basis for gender differences in inflammation and asthma. Proc Natl Acad Sci U S A. 2008; 105(50):19881–19886. [PubMed: 19064924]

Pfaff DW, Rapin I, Goldman S. Male predominance in autism: neuroendocrine influences on arousal and social anxiety. Autism Res. 2011

Prahalad S, Shear ES, Thompson SD, Giannini EH, Glass DN. Increased prevalence of familial autoimmunity in simplex and multiplex families with juvenile rheumatoid arthritis. Arthritis Rheum. 2002; 46(7):1851–1856. [PubMed: 12124869]

Qiao Y, Liu X, Harvard C, Hildebrand MJ, Rajcan-Separovic E, Holden JJ, et al. Autism-associated familial microdeletion of Xp11.22. Clin Genet. 2008; 74(2):134–144. [PubMed: 18498374]

Radmark O, Samuelsson B. Regulation of the activity of 5-lipoxygenase, a key enzyme in leukotriene biosynthesis. Biochem Biophys Res Commun. 2010; 396(1):105–110. [PubMed: 20494120]

Rubtsov AV, Rubtsova K, Kappler JW, Marrack P. Genetic and hormonal factors in female-biased autoimmunity. Autoimmun Rev. 2010; 9(7):494–498. [PubMed: 20144912]

Ruggieri M, Polizzi A, Pavone L, Grimaldi LM. Multiple sclerosis in children under 6 years of age. Neurology. 1999; 53(3):478–484. [PubMed: 10449107]

Ruta L, Ingudomnukul E, Taylor K, Chakrabarti B, Baron-Cohen S. Increased serum androstenedione in adults with autism spectrum conditions. Psychoneuroendocrinology. 2011

Sarachana T, Xu M, Wu RC, Hu VW. Sex hormones in autism: androgens and estrogens differentially and reciprocally regulate RORA, a novel candidate gene for autism. PLoS One. 2011; 6(2):e17116. [PubMed: 21359227]

Songini M, Muntoni S. High incidence of type 1 diabetes in Sardinia. Gruppo Collaborativo per l'Epidemiologia dell'IDDM in Sardegna. Ann Ig. 1992; 4(3):179–190. [PubMed: 1284518]

Stoll ML, Nigrovic PA. Subpopulations within juvenile psoriatic arthritis: a review of the literature. Clin Dev Immunol. 2006; 13(2–4):377–380. [PubMed: 17162381]

Sutor AH, Harms A, Kaufmehl K. Acute immune thrombocytopenia (ITP) in childhood: retrospective and prospective survey in Germany. Semin Thromb Hemost. 2001; 27(3):253–267. [PubMed: 11446659]

Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. Pediatrics. 2003; 112(5):e420. [PubMed: 14595086]

Takagishi H, Takahashi T, Yamagishi T, Shinada M, Inukai K, Tanida S, et al. Salivary testosterone levels and autism-spectrum quotient in adults. Neuro Endocrinol Lett. 2010; 31(6):837–841. [PubMed: 21196912]

Theoharides TC, Angelidou A, Alysandratos KD, Zhang B, Asadi S, Francis K, et al. Mast cell activation and autism. Biochim Biophys Acta. 2010

Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol. 2005; 57(1):67–81. [PubMed: 15546155]

Villano MJ, Huber AK, Greenberg DA, Golden BK, Concepcion E, Tomer Y. Autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. J Clin Endocrinol Metab. 2009; 94(4):1458–1466. [PubMed: 19141582]

Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature. 474(7351):380–384. [PubMed: 21614001]

Voskuhl R. Sex differences in autoimmune diseases. Biol Sex Differ. 2011; 2(1):1. [PubMed: 21208397]

Windham GC, Anderson MC, Croen LA, Smith KS, Collins J, Grether JK. Birth Prevalence of Autism Spectrum Disorders in the San Francisco Bay Area by Demographic and Ascertainment Source Characteristics. J Autism Dev Disord. 2010

Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. J Am Soc Nephrol. 1998; 9(5):853–858. [PubMed: 9596083]

Yang K SA, Malik M, Wen G, Zou H, Brown WT, Li X. Up-regulation of Ras/Raf/ERK1/2 signaling and ERK5 in the brain of autistic subjects. Genes Brain Behav. 2011

Zavattari P, Deidda E, Pitzalis M, Zoa B, Moi L, Lampis R, et al. No association between variation of the FOXP3 gene and common type 1 diabetes in the Sardinian population. Diabetes. 2004; 53(7): 1911–1914. [PubMed: 15220219]

Zhang L, Zhang Y, Desrosiers M, Wang C, Zhao Y, Han D. Genetic association study of FOXP3 polymorphisms in allergic rhinitis in a Chinese population. Hum Immunol. 2009; 70(11):930–934. [PubMed: 19679154]

Zou H YY, Sheikh AM, Malik M, Yang K, Wen G, Chadman KK, Brown WT, Li X. Association of upregulated Ras/Raf/ERK1/2 signaling with autism. Genes Brain Behav. 2011; 10(5):615–624. [PubMed: 21595826]

Table 1

Male-Female Ratios of selected autoimmune disorders

Disease	Country/Region	Male-Female ratio	age range	Reference
type 1 diabetes	Sardinia	1.4-1	overall	Songini & Muntoni, 1992
	Sardinia	1.8-1	ages 10–14	Songini & Muntoni, 1992
	Sweden	1.8-1	overall	Ostman et al., 2008
	Denmark	3.7-1	overall	Christau et al., 1977
asthma and atopy	Scotland	~2-l	age 2	Osman 2003
	Scotland	1-1	age 10	Osman 2003
	Scotland	~l–2	ages 15–60	Osman 2003
Crohn's disease	Japan	1.7-1	children	Ishige et al., 2010
	Japan	2.6-1	adults	Ishige et al., 2010
immune thrombocytopenia	Germany	1.7-1	<age 6	Sutor et al 2001
	Germany	1–2.1	ages 14–16	Sutor et al 2001
IgA nephropathy	Kentucky, USA	2.7-1	overall	Wyatt RJ et al 1997
juvenile multiple sclerosis	multiple countries	1.2-1	<age 6	Banwell, Ghezzi, et al 2007
	multiple countries	1–1.6	ages 6–10	Banwell, Ghezzi, et al 2007
	multiple countries	1–2.13	> age 10	Banwell, Ghezzi, et al 2007
	Turkey	2.3-1	< age 10	Haliloglu et al., 2002
	Germany	4-1	<age 6	Hanefeld F 1995
	Italy	1.6-1	<age 2	Ruggierie M 1999
	Italy	1-3.0	ages 6–15	Ruggierie M 1999
primary sclerosing cholangitis	New York, USA	1.6-1	ages 2–20	Miloh et al. 2009