EUROPEAN ACADEMIC RESEARCH
Vol. VI, Issue 6/ September 2018

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

X-Linked Gene Effects on Offspring of Autism Spectrum Disorders

URMI RAHMAN RINIK[1]
ASIF AHMED
Biotechnology and Genetic Engineering Discipline
Khulna University, Khulna

Abstract:

Systematic literature search was performed regarding autism spectrum disorder in offspring and abnormalities in X –chromosome of parents due to their advanced age. Although no diagnostic tests are specified for identifying this disorder, several behavioral experiments are carried out for ensuring autistic syndromes in children. Several individual genes are contributing to autism spectrum disorders due to inactivation by point mutation such as deletions or duplications, copy number variations as well as in case of chromosomal abnormality especially in women with advanced age. Autism has been identified as highly heritable and genetically heterogeneous in some studies. The more commonly observed copy number variants as well as significant candidate genes for ASD are NRXN1, CNTNAP2, NLGN4X, RBOX1, CNTN4 and CDH18.Truncating mutations of chromo domain helicase DNA-binding protein 8(CHD8) represents one of the strongest known risk factors for ASD. Mutations in genes of X-chromosome result from advanced parental age which causes autism spectrum disorder in their offspring that is focused in this study. In the current study, contribution and relation of mutation in x chromosome in the case of Autism spectrum disorders (ASDs) have been explored and reviewed.

Key words: X-chromosome, Autistic disorder, Chromosomal abnormality, Mutation, CHD8

[1] Corresponding author: rinikbgeku130701@gmail.com

1 INTRODUCTION:

Individuals with Autism spectrum disorders (ASDs) of 5-15% have an identifiable genetic etiology which corresponds to known chromosomal rearrangements by high resolution karyotyping or single gene disorders (Devlin and Scherer 2012). There is an increased assessment of the performance of *de novo* and inherited copy number variation (Abrahams and Geschwind 2008). Rare *de novo* and inherited copy number variations (CNVs) are too small to be tracked out by karyotyping (Cook Jr and Scherer 2008). Screening for CNVs has proven to be a rapid method to identify both large as well as small changes that are associated with ASD susceptibility (Devlin and Scherer 2012).

Small percentage of autism cases because of mutations in *MECP2 , PTEN , SHANK3 ,NLGN4X* genes (Beaudet 2007). Several significant genes located on the X-chromosome, responsible for autism spectrum disorders that have been identified across several studies will be discussed in another chapter. Parental age whether it is teenage or advanced is the responsible factor for autism spectrum disorders (ASDs) will be discussed in this review in the form of epidemiological studies. Genes of X- chromosome are mainly focused in this study according to their categorisation because of their roles in the risk of ASD. Single gene mutations which results from independent studies of advanced paternal and maternal ages have been established as a main risk factor for ASD will be discussed here.

1.1 Objectives

- To find out the relationship of advanced aging and mutation in human
- To establish that mutations in X-chromosome of parents causes ASD in offsprings

2. GENETIC CAUSES OF ASDS:

The genetic structure of autism spectrum disorders (ASDs) is complex and heterogeneous (Sugathan et al. 2014). The root cause of autism involves multiple genes , possibly varying in expression and in combination with external factors (Newschaffer et al. 2007, Lauritsen and Ewald 2001, Folstein and Rutter 1988). Although mutation causes autism , mutations are not inherited (Beaudet 2007). It is established that de novo germline mutation is a more significant risk factor for autism spectrum disorders (Sebat et al. 2007). Individual genes that contribute to ASD when they suffer heterozygous inactivation by coding mutation, copy number variations and balanced chromosomal abnormalities has been identified in recent discoveries (Sugathan et al. 2014). Because of many more germ cell divisions in male , mutation rate in germline is much higher in older males than older females (Crow 2000). The female germ cells undergo mutation at an accelerated rate with increasing age whereas mutation rate in father increases at a constant rate (Wong et al. 2016).

Sebat et al. seeked out de novo copy number changes in children using an oligonucleotide array that is of 10% from simplex families(i.e., autism in a single family member) as well as 2% from multiplex families (i.e., autism in multiple family members) than 1% in controls (Miles 2011). Marshall et al. discovered unbalanced CNVs in 44% of 427 unrelated families with autism using a dense genome-wide single nucleotide polymorphism array that were absent in control families (Miles 2011). Many of these CNVs were inherited as well as only 7% were de novo in autistic persons of unknown cause (Miles 2011). However, significant limitations exist to our current understanding of CNVs as causes of ASD because unaffected parents as well as families may carry the same CNV as the ASD proband (Miles 2011).

A list of rare and highly penetrated copy number variants(CNVs) and single nucleotide variants(SNVs) related with ASDs have been unveiled by genome-wide copy number variant and sequence analyses (Jiang et al. 2014).

However, patients with autism spectrum disorders could be diagnosed with four separate disorders : autistic disorder, Asperger's syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS), and childhood disintegrative disorder (Jiang et al. 2014) as well as genetic analysis of ASD can be carried out. Advanced paternal age (Reichenberg et al. 2006, Croen et al. 2007) and advanced maternal age (Croen et al. 2007, Kolevzon, Gross, and Reichenberg 2007) have been shown to be associated with an increased risk of having offspring with ASDs , possibly because of de novo spontaneous mutations and alterations in genetic imprinting. Imprinting is the process of methyl groups that is used to mark genes according to the parent from where they are inherited (Hall and Kelley 2014). It is easier to be controlled by imprinting whether maternal or paternal gene will be expressed in the offspring (Hall and Kelley 2014). There are possibilities of creation of disorders in offspring when loss of functions occur in paternally or maternally imprinted copy of gene (Hall and Kelley 2014). Some researchers have suggested that an epigenetic mechanism (heritable changes in gene expression that occur without changes in DNA sequence) may be responsible (Lopez-Rangel and Lewis 2006).

Candidate genes for ASDs such as NRXN1, CNTNAP2, NLGN4X, A2BP1(RBOX1), CNTN4, CDH18 , TMEM195 are the more commonly observed copy number variants detected in the cohort of a study (Jiang et al. 2014) that are shown in figure 1. CNV studies have also led to the identification of autism candidate genes which are named SHANK3 (MIM 606230) and NRXN1 (MIM 600565) (Noor et al. 2010).

Mutations in SHANK3 gene (chromosomal location 22q13.3) can cause severe verbal and social deficits in ASD children (Moessner et al. 2007).

Rare and common genetic variants in **contactin-associated protein-like 2 (*CNTNAP2*),** that is another member of the neurexin superfamily are also associated with ASDs (Fassio et al. 2011).

Copy Number Variants		
NRXN1 CNTNAP2 NLGN4X	A2BP1(RBOX1) CNTN4 GRIK4 SHANK3	CDH18 TMEM195 NRXN1

Figure 01: List of Copy Number Variants

2.1 X-chromosome:

The human X-chromosome refers to the sex chromosome being shared by both males and females that was shaped by it's evolution (Ross et al. 2005). Females inherit two X-chromosomes from their parents (one from mother and one from father) , but male inherit one X-chromosome from mothers (Ross et al. 2005). Through the process of X-chromosome inactivation , gene expression on one of the female X-chromosome remains silence early in the development and in female germline, the reactivation of this inactive X-chromosome occurs through meiotic recombination with the second X-chromosome (Ross et al. 2005). The male X-chromosome is restricted to such a kind of recombination , instead short regions at the tips of the X-chromosome arms recombine with equivalent segments on the Y-chromosome (Ross et al. 2005).

The X-linked susceptibility genes are present in people with ASD (Chung et al. 2011b). An X-chromosome duplication was inherited from a healthy 'carrier' mother to her offspring with ASD (Beaudet 2007). Genome-wide linkage studies have smeared regions on the X-chromosome as well as marking off structural variants in genes for example neuroligin 4 , X-linked

(NLGN4X) manifest the potential role of X-linked genes in autism (Chung et al. 2011b).

Deletions in the Xp22.2 to Xp22.3 distal region contain *NLGN4* and *TBL1X* genes that are associated with autism have been shown by multiple studies (Chung et al. 2011b). Two other SNPs (rs5934665 and rs2188766) in the *TBL1X* gene that were identified , close to the chromosome-wide significance in the meta-analysis for males (Chung et al. 2011b). One intronic SNP , rs17321050 , in *TBL1X* was found that manifested chromosome-wide evidence of association in the meta- and joint analyses , strongly supporting *TBL1X* as a risk factor for ASD (Chung et al. 2011b).

2.2 Description of located genes on the X-chromosome and their roles in the risk of ASDs:

Genes that are located on the X-chromosome as well as their roles are descriped below according to their genetic categorization. ASD is genetically categorised into four major groups: syndromic , rare single gene variant , functional and genetic association (figure 2).

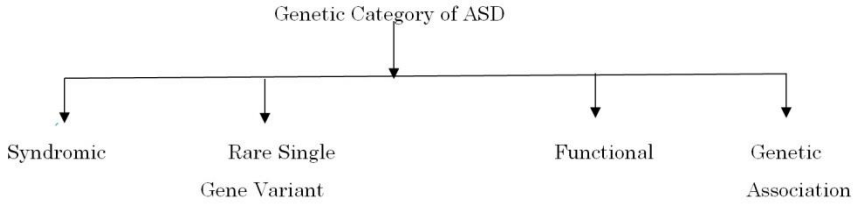


Figure 02: Categorisation of Autism Spectrum Disorders Genetically

2.2.1 Syndromic ASDs:

ASD is syndromic if autistic diagnosis is part of the clinical presentation of a known genetic syndrome and when the cause is unknown that is idiopathic (Jiang et al. 2014). When autism is associated with malformations or dysmorphic features it is called syndromic (Beaudet 2007). In the case of idiopathic ASD , the maternally inherited duplication of the chromosomal

15q11-q13 Angelman and Prader-Willi syndrome region observed using traditional chromosome analysis is the best example of an associated chromosomal rearrangements (Jiang et al. 2014).

IQSEC2 , KDM5C , KDM6A , OCRL , PCDH19 , **PHF8** , RPS6KA3 , SLC9S6 , **UPF3B** , ATRX , AFF2 , AP1S2 , CASK , CDKL5 , CNKSR2 , DMD , HUWE1 , HCFC1 , **MECP2**

Figure 03: The List of Genes that are Located on X-Chromosome Involving Syndromic ASDS.

IQSEC2: Two truncating mutations in IQSEC2 namely two de novo intragenic duplication mapped to the Xp11.22 region and a nonsense mutation in exon 7 are characterized using array CGH(Comparative Genomic Hybridization) and exome sequencing (Tran Mau-Them et al. 2014). Truncating mutations in IQSEC2 are responsible for syndromic severe ID in male patients (Tran Mau-Them et al. 2014), encoding a guanine nucleotide exchange factor for the ADP-ribosylation factor family of small GTPases, caused this disorder (Shoubridge et al. 2010).

UPF3B: Mutations in the *UPF3B* gene , which encodes a protein involved in non-sense mediated mRNA decay (NMD), have recently been described in four families with specific, non-specific X-linked autism (Laumonnier et al. 2010). NMD is a surveillance pathway that exists in all eukaryotes. Its main function is to reduce errors in gene expression by eliminating mRNA transcripts that contain premature stop codons.

Besides, we cannot omit a contribution of **PHF8** deletion to the autism phenotype (De Wolf et al. 2014).

MeCP2 : Methyl CpG binding protein 2 . Chromosome location Xq28 . De novo mutations in the MeCP2 gene were found in two autistic disorder females (Carney et al.). MeCP2 is a key player

in epigenetic processes and these proteins facilitate silencing genes by binding to the methylated regions of DNA (Hall and Kelley 2014). It is reported that MeCP2 mutations are incredibly rare in autism but some studies pointed their role in autism through epigenetic processes (Hall and Kelley 2014).

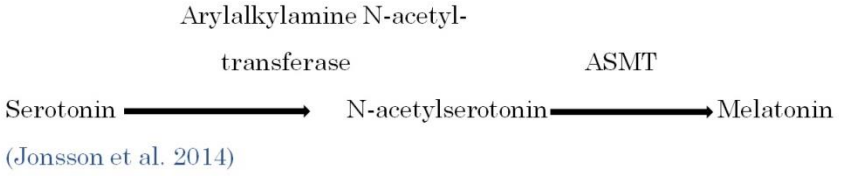
2.2.2 Genetic Association:

The following genes have genetic association with autism spectrum disorder. One or more alleles will be seen more in an individual carrying the trait than expected by chance if genetic association is present. One of a pair , or series , of variant forms of a gene that occur at a given locus in a chromosome. In a normal diploid cell there are two alleles of any one gene (one from each parent) which occupy the same relative locus. Within a population there may be more than two alleles of a gene that arise by mutation.

Androgen receptor(AR) is encoded by a gene located on the X-chromosome(Xq11-12) (Henningsson et al. 2009). It has been suggested that prenatal brain exposure to androgens may be of importance for the development of autism because of the higher prevalence of autism in men than in women (Henningsson et al. 2009). In addition,both autism and autism related trait had been suggested to be associated with elevated levels of testosterone in fetus (Henningsson et al. 2009). Variation in the androgen receptor gene for the susceptibility of autism may play an important role in this case (Henningsson et al. 2009). Genotyping for three polymorphisms in exon 1(which encodes amino terminal end of the AR gene) of the AR gene: the CAG repeat,GGN repeat and rs6152 SNP was held verified in case(withASD)-control groups (Henningsson et al. 2009). These three polymorphisms are situated close to each other and are in linkage disequilibrium that were not considered independent (Henningsson et al. 2009). In addition, a higher manifestation of short CAG alleles as well as of the A allele of the rs6152 SNP

in female cases was appeared in case-control comparisons and mean length of the CAG allele was shorter in patients than controls (Henningsson et al. 2009). Short CAG repeats are associated with higher testosterone levels in women (Henningsson et al. 2009). It was not provided any support regarding the influence of CAG repeat in the AR on the risk of autism in males (Henningsson et al. 2009).

Association between Acetylserotonin O-methyltransferase (ASMT) and autistic like traits:
The low activity of acetylserotonin o-methyltransferase (ASMT) enzyme decrease the levels of melatonin in individuals with autism spectrum disorders because of variations within the ASMT gene (Jonsson et al. 2014). Melatonin is involved in the regulation of immune responses and neurodevelopmental processes (Jonsson et al. 2014).



(Jonsson et al. 2014)

The study showed correlation with autism:
•Mutations in the ASMT gene
•Promoter region of ASMT influence mRNA transcription (Jonsson et al. 2014)

CD99L2: 2,012 genes of known immune –function were identified via Ingenuity Pathway Analysis, a bioinformatics database (Ramos et al. 2012). It was observed that there was significant associations in the CD99 molecule- like 2 region (*CD99L2*), in the jumonji AT rich interactive domain 2 (*JARID2*) gene and in the thyroid peroxidase gene (TPO) (Ramos et al. 2012).

IL1RAPL1: One patient study showed *IL1RAPL1* gene disruption would be predicted to result in a truncated protein and may account for autism (Figure 4) , but further studies is needed to be confirmed (Bhat et al. 2008). *IL1RAPL1* is a gene related to ASD candidate gene (Griswold et al. 2015).

MAOA: Meta-analysis demonstrated that across studies , the association between maltreatment as well as mental health problems is effectively stronger in the group of males with the genotype conferring low vs. high MAOA activity (Kim-Cohen et al. 2006).

Mediator of RNA Polymerase II transcription (MED)12 (HOPA) is a 25-kb Xq13 member of the mediator complex which plays a crucial role in the complex as well as directly moderates receptor tyrosine kinase, nuclear receptor ,Wnt and participates in the recognition of certain members of the SOX family of genes (Philibert and Madan 2007).

MED12 is sided centromerically by the IL-2 receptor gamma chain, a gene that is mutated in X-linked severe combined immunodeficiency as well as telomerically by Neuroligin-3 (NLGN3), a gene in which variations linked to autism have been noticed (Philibert and Madan 2007). Sequence variation in MED12 has been determined to two forms of X-linked mental retardation and a form of positive-syndrome psychosis (Philibert and Madan 2007).

TBL1X gene is transducin(beta) like 1 x-linked whose location is Xp22.31-p22.2 and it has been described in 4.1 of this cahapter. The region containing TBL1X carries CNVs that have been involved with a diverse range of neurodevelopmental phenotypes (Chung et al. 2011a).

2.2.3 Rare Single Gene Variant:

Rare variants are alternative forms of a gene that are present with a minor allele frequency (MAF) of less than 1%. Rare variants play a significant role in complex disease as well as some Mendelian conditions. Rare single gene variant alters the specific function of a single gene which results in neurodegenerative diseases like autism.
Several rare single gene variants are followings:

ARHGEF9: An 8-year- old female with autism spectrum disorder(ASD) was reported to carry a de novo 82 kb deletion of chromosome Xq11.1-11.2 involving the ARHGEF9 gene on chromosomal microarray (Bhat et al. 2016).

HNRNPH2: is situated at Xq22.1 that encodes a member of a family of ubiquitous heterogeneous nuclear ribonucleoproteins (HNRNP) (Bain et al. 2016). The HNRNPs are a large group of RNA binding proteins having distinct nucleic acid binding properties that act as a shuttle between the nucleus and the cytoplasm as well as act on pre-mRNA to positively or negatively affect spliceosome assembly at nearby splice sites, thereby controlling pre- mRNAsplicing (Bain et al. 2016). These proteins play a crucial role in controlling gene expression (Bain et al. 2016). The failure to recognize affected males, the severity of the neurodevelopmental phenotype in females, as well as the fundamental role of this gene suggests that male concept uses with these variants may be impossible (Bain et al. 2016).

As genes from the GABAergic pathway have previously been thought to be associated in the pathophysiology of ASD , there is a report of ASD patients with truncating mutations in GABA receptors genes (Piton et al. 2013).

KIAA2022: The study showed the patient of only mild ID with severe language delay and repetitive behaviors as a result of decreased KIAA2022 expression that is falling in the range of

an autism spectrum disorder(ASD) (Van Maldergem et al. 2013).

PTCHD1: Mutations in the X-chromosome PTCHD1(patched-related) gene were reported in seven families with autism spectrum disorder (Noor et al. 2010). Recent studies of sub-microscopic genomic copy number variation (CNV) have identified several loci which are associated with Autism Spectrum Disorder (Noor et al. 2010). The 167 kb deletion at PTCHD1 was found to be transmitted from a heterozygous unaffected mother to two affected dizygotic twin sons ,also to an unaffected daughter (Noor et al. 2010).

RAB39B: RAB39B, which is one of the RAB GTPase proteins of unknown function , as well as understanding how the absence of RAB39B involved in the pathology of XLMR associated with autism spectrum disorder and macrocephaly is therefore particularly connate for understanding the pathogenesis of the disease (Giannandrea et al. 2010).

SYN1: an X-linked gene encoding for a neuron -specific phosphoprotein involved in the regulation of neurotransmitter release and synaptogenesis in which a Q555X mutation is reported that is associated with ASD (Fassio et al. 2011).

SLC7A3 gene is located on the X-chromosome and encodes cationic amino acid transporter(CAT-3) (Nava et al. 2015). The patient carrying most deleterious SLC7A3 variant had high-functioning autism as well as carries a de novo 16p11.2 duplication possibly contributing to his phenotype (Nava et al. 2015).

An analysis revealed a paternally inherited two-exon intragenic deletion of NRXN3 and a de novo missense mutation of ***NLGN2*** in proband 13367.pl (Krumm et al. 2015). Both of genes are ASD risk factors (Krumm et al. 2015).

TSPAN7: A 121-kb duplication was identified spanning seven exons of TSPAN7 in an affected son that is inherited from an unaffected mother in a family from Newfoundland (Noor et al. 2009). Mutations in TSPAN7 may be the causal agent of autism was hypothesized in this study, but no coding mutations were identified among the probands(a person serving as the starting point for the genetic study of a family) (Noor et al. 2009). However , the involvement of TSPAN7 mutations in a very small fraction of autism patients can not be cropped (Noor et al. 2009).

TMLHE: A deletion of exon 2 of the trimethyllysine hydroxylase epsilon (TMLHE) gene in a proband with autism was reported (Celestino-Soper et al. 2012). TMLHE deficiency results in the loss of ability to make carnitine in the body and this common inborn error of metabolism may be significantly frequent in male- male sib pairs (Celestino-Soper et al. 2012). Carnitine biosynthesis is a method for the endogenous production of L-carnitine, a molecule that is essential for energy metabolism (Celestino-Soper et al. 2012). In humans and many other animals, L-carnitine is obtained from both diet and by biosynthesis (Celestino-Soper et al. 2012). The TMLHE gene is on the X-chromosome so that it is sex- linked and occurs predominantly in males and encodes the first enzyme in carnitine biosynthesis, 6-N-trimethyllysine dioxygenase (Celestino-Soper et al. 2012). However, the carnitine pathway may provide a novel target for therapy or prevention of autism (Celestino-Soper et al. 2012).

WNK3: Duplication or deletion of the genomic location surrounding the WNK3 gene has been found in individuals with ASD (Lee et al. 2012).

2.2.4 Functional ASDs :

Gene Name		Chromosome Band
SLC25A14	Solute carrier family 25(mitochondrial carrier brain)member 14	Xq26.1
FMR1	Fragile X mental retardation 1	Xq27.3

FAM120C: *FAM120C* belongs to a novel family of putative N-glycosylated transmembrane proteins , including *FAM120A* (9q22.31) and *FAM120B* (6q27) (De Wolf et al. 2014). *FAM120C* is identified as a novel X-linked candidate gene for autism for two reasons: first , a larger deletion encompassing *FAM120C* segregates with autism in a previously reported family and second , there is recent evidence that *FAM120C* interacts with CYFIP1, part of the FMRP (Fragile X Mental Retardation Protein) network (De Wolf et al. 2014).

The Fragile X syndrome is a familiar genetic reason of ASD , involving by mutations in FMR1 , resulting in a loss of function of FMRP (De Wolf et al. 2014).

2.3 Others:

Engrailed 2 **(EN2)** is a Wnt target gene that has been involved with autism in several studies (Chung et al. 2011b). The WNT2 gene (Wingless-type mouse mammary tumor virus integration site family, member 2) is identified as a candidate gene for autism (Chung et al. 2011b) .

There are insufficient data to carry out a similar analysis specially for **DMD** and ASD (Pagnamenta et al. 2011).

All mutations or copy number variants (CNVs) associated so far with ASD have been uncommon, with minor allele frequencies <1% (Nava et al. 2012). A few *de novo* or inherited CNVs , some of which are frequent , such as duplications of the 15q11-q13 or 7q11.23 as well as deletions of 16p11.2 regions ,were found to confer a highly penetrant risk of autism (Nava et al. 2012).

Truncating mutations of **chromodomain helicase DNA-binding protein 8(CHD8)** represents one of the strongest known risk factors for ASD (Sugathan et al. 2014). A protein is shortened by a truncation mutation which specially induces premature termination of messenger RNA translation. CHD8 regulates in neural progenitor cells by reducing its expression and trancriptome sequencing with genome wide CHD8 binding (Sugathan et al. 2014). Genes indirectly down –regulated(i.e. without CHD8 binding sites) involve in the pathways of brain development including synapse formation, neuron differentiation, cell adhesion, axon guidance, whereas CHD8 bound genes are strongly associated with chromatin modification and transcriptional regulation. Genes associated with ASD were present in down-regulated loci (Sugathan et al. 2014).

It has been shown that common variants of ***GRM3*** (Metabotropic glutamate receptor 3) have association with ASD while rare copy number variants in *GRIK4*(glutamate receptor , ionotropic , kinate 4) have been employed (Griswold et al. 2015). **Chromodomain helicase DNA-binding protein 8 (CHD8**) insufficiency may be a central hub in neuronal development and ASD risk (Wilkinson et al. 2015).

2.3.1 Angiotensin Receptor 2 (AGTR2) and X-linked mental retardation:

The study showed the expression of the AGTR2 gene that had been absent in a female patient with mental retardation(MR), who had a balanced X (Vervoort et al. 2002). Additionally , one frameshift and three missense mutations in AGTR2 gene (Figure 4) had been found in 8 of 590 unrelated male patients with MR (Vervoort et al. 2002). The study findings suggested that there is a role of AGTR2 in brain development and cognitive function (Vervoort et al. 2002).

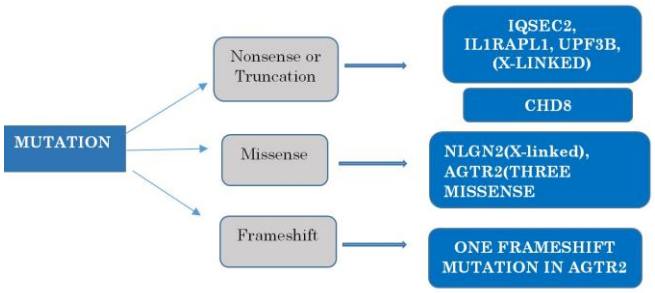


Figure 04: Occurrence of Three Significant Mutations on these Represented Genes Causing the Risk of Autism Spectrum Disorders.

2.3.2 Detection of a 17q12 recurrent microduplication in a patient with ID and Autism:

Bold chromosomal aberrations detected by rapid cytogenetic analysis responsible for about 6-7% of ASDs (Brandt et al. 2012). Copy number variants(CNVs) or submicroscopic chromosome aberrations account for an additional 10% of patients identified by array comparative genomic hybridization(aCGH) and confirmed by fluorescence in situ hybridization(FISH) (Brandt et al. 2012). In array comparative genomic hybridization , a normal control DNA as well as a patient DNA are labeled with different coloured fluorescent dyes which are then hybridized to cloned DNA fragments or oligonucleotides on a glass slide (Beaudet 2007).The relative intensity of two dyes identifies variations in genomic copy number between two samples (Beaudet 2007).

Recurrent microdeletion at chromosome 17q12,which ranges in size from 1.4 to 1.8Mb is one of the such copy number variants(CNVs) (Brandt et al. 2012). Microduplication formed de novo as a result of maternal interchromosomal event that was indicated by parental analysis (Brandt et al. 2012). In a study, Affymetrix 6.0 SNP microarray analysis was accomplished to designate the parent of origin of this de novo 17q12 microduplication and stated that the aberration was formed maternally (Brandt et al. 2012). At SNP loci in which parents were each homozygous for a different allele, patient

consistently inherited a third allele from his mother and the results were consistent with an interchromosomal event generating aberration when the father is homozygous and the mother is heterozygous at SNP loci (Brandt et al. 2012).

It is reported in a study that a Chinese newborn had dismorphic features,microcephaly and valvar aortic stenosis,who was confirmed to have a 790kb microduplication in chromosome 17p13.3 by array comparative genomic hybridization(aCGH) (Ho et al. 2012).

Lessons that are learned from the large CNVs:

• Gene dosage imbalance-Heterozygous sporadic mutations

• Individually rare,but collectively common(de novo and inherited)

• Large CNVs account for 14.2% intellectual disability-7 to8% autism spectrum disorders

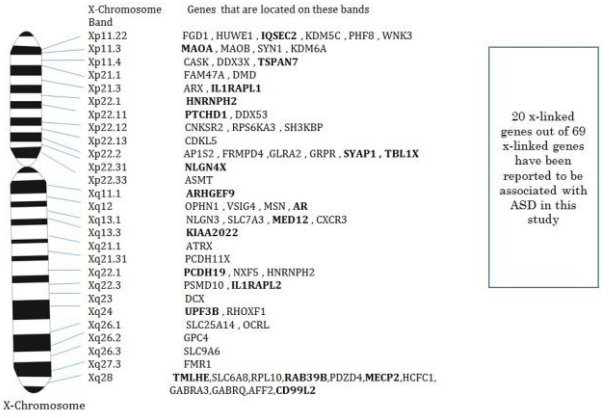
• Importance of genome –wide discovery followed by more detailed phenotyping

- **Problems**
- CNVs identify regions of genic imbalance but in most cases not specific genes
- Most CNVs are of unknown significance

2.3.3 Cryptic gain of proximal 15q causing autism in a multiplex family:

In approximately 1% of cases, duplication of the 15q11-13 region has been reported as a strong etiology of autism spectrum disorders in a study (Koochek et al. 2006). Two individuals from a multiplex family demonstrate autism due to a maternally inherited gain of 15q11-13 through clinical, array –comparative genomic hybridization (CGH) and cytogenetic evaluation (Koochek et al. 2006). Chromosome 15q11.2-13 is detected as a hotspot for rearrangements including deletions, duplications, triplications, inversions, translocations due to the large number of low copy repeat sequences in this region

(Koochek et al. 2006). However, these rearrangements are primarily intrachromosomal with deletions and duplications involving only the altered 15 homolg(12) (Koochek et al. 2006). Chromosome 15's long arm has been implicated with findings of micro-duplications in the so called "autism candidate region" amongst many reports (Simic and Turk 2004).



The bold genes are more significant

Figure 05: X-Chromosome with Bands and the Relative Genes Located on these Bands are Represented.

3. DISCUSSION:

Whole genome sequencing studies joining older fathers to higher rates of de novo mutations in some genes and the risk of ASD in offspring which gives special attention to paternal age (Beaudet 2007). These differences in studies are likely due to issues such as sample size and characteristics , missing data , case ascertainment , covariate adjustment (Lee and McGrath 2015). It should be inferred the contribution of rare de novo copy number variations(CNVs) and transmitted duplications with ASD. There are several observations such as a higher incidence of de novo copy number variations in children with ASDs from simplex families (a single member of families with a specific disease) than in their siblings as well as ASDs children

from multiplex families(multiple members from families with a specific disease) , duplications outweigh deletions in case of transmitted rare variants but deletions outweigh duplications in de novo events in children with ASDs , evidence of transmission distortion to offspring with ASDs for ultrarare events , bias arises due to reported unaffected male sibling , detectable de novo copy number variants are higher in females with ASDs than ASD males but females are less likely to be diagnosed with ASDs than males (Pinto, Pagnamenta, Klei, Anney, Merico, Regan, Conroy, Magalhaes, Correia, Abrahams, et al. 2010, Marshall et al. 2008, Zhao et al. 2007, Sebat et al. 2007). Female children seem to be more resistant in the development of ASDs than male children as well as harmful large copy number events are noticed more frequently in affected females , because there are lesser target genes for inducing ASDs in females than males (Gilman et al. 2011). A faster motion of development might mirror a robustness that offers protection in females , for example speaking their first words at an earlier age generally (Richler et al. 2010, Roze et al. 2010). There is lack of evidence under reasonable prediction of the rate of observable contributory transmitted CNVs(7%) as well as a robust bias toward transmission from mothers of contributory events(75%) (Levy et al. 2011). However , it is worth considering that male and female children with higher risk genotypes may face difficulties in later stages of their lives or may be not.

The genetic basis of autism may be explained by dominant acting genetic variants but certainly not all. A genetic model that assumes about half of the ASDs result from new mutations as well as high penetrance of a selected set of single mutational hits (Levy et al. 2011). There are large number of inevitable target loci for ASDs but small number of recurrent loci has been detected from several events such as *NRXN1* (encoding neurexin 1) which is a well-established candidate gene for ASDs as well as schizophrenia (Pinto,

Pagnamenta, Klei, Anney, Merico, Regan, Conroy, Magalhaes, Correia, and Abrahams 2010, Kim et al. 2008, Ching et al. 2010) , maternally inherited deletions at the X-linked *DDX53* locus (encoding a DEAD-box RNA helicase of unknown function) have been associated with ASDs in males (Pinto, Pagnamenta, Klei, Anney, Merico, Regan, Conroy, Magalhaes, Correia, and Abrahams 2010). The linkage of the X-chromosomal *NLGN3* locus (encoding neuroligin 3) to ASDs has not been somewhat clear , but first independent confirmation for a role of *NLGN3* mutations in the pathogenesis of ASDs was provided by the 33 kb deletion in *NLGN3* from 11689 families that was discovered in a study (Levy et al. 2011).

The risk of a de novo CNV is not related to the age of either parent that has been reported in a study (Beaudet 2007). Approximately 10% of the ASD individuals have been identified with Mendelian condition or genetic syndrome (Devlin and Scherer 2012).The ratio of *de novo* CNVs which is three-fold to five-fold higher in ASD families than controls (Devlin and Scherer 2012). Fathers of autistic individuals carry traits such as shyness as well as aloofness related with the autism phenotype which may limit interaction with women leading to late paternity (Hultman et al. 2010). Mutation was considered to be paternal in origin because of the transmission of the paternal haplotype of the proband to his or her child as well as the child carries mutation (Kong, Frigge, Masson, Besenbacher, Sulem, Magnusson, Gudjonsson, Sigurdsson, Jonasdottir, Jonasdottir, et al. 2012). It is guessed that mutation presents on the maternal chromosome of the proband if the child carrying the paternal haplotype was inherited from the parent who does not have the mutation (Kong, Frigge, Masson, Besenbacher, Sulem, Magnusson, Gudjonsson, Sigurdsson, Jonasdottir, Jonasdottir, et al. 2012).

Copy number variations may not be enough to achieve clarity as well as looking for deletions , duplications are not adequate to explain the majority of gene mutations because of

that further deeper understandings will be demanded at the mechanistic level (Levy et al. 2011). There are several limitations in this study such as absence of genetical data and family history of ASDs children because of unavailable information regarding linkage of X-chromosome mutation and older parental age in the poor and developing countries.

Autism is linked with a high degree of heritability but a small number of specific mutations have been reported that are accounted for minority of cases (Stephan 2008, Sykes and Lamb 2007, Wang et al. 2009, Aso et al. 1996, Zoghbi 2005) while the most of the cases are scattered (Alter et al. 2011). Older fathers might increase the risk of autism in their offspring as a result of transmission of an effect on global levels of gene expression regulation (Alter et al. 2011). Mutations in X-linked genes are coincidence but it has been reported that these events increase with advanced parental age. Mutation is not inherited but copy errors in germ cells of older fathers during childbirth causes de novo mutations in offspring with ASDs. Multiple studies of whole genome or exome sequencing have identified the presence of de novo loss- of -function single nucleotide variants in older fathers contributing to ASDs in offspring (Jiang, Yuen, Jin, Wang, Chen, Wu, Ju, Mei, Shi, and He 2013, Kong, Frigge, Masson, Besenbacher, Sulem, Magnusson, Gudjonsson, Sigurdsson, Jonasdottir, and Jonasdottir 2012, O'Roak et al. 2012, Sanders et al. 2012, Dong et al. 2014). Numerous effective down-regulated genes were noted in the blood of autistic children as well as children of older fathers than up-regulated genes (Alter et al. 2011). The occurrence of autism spectrum disorders are higher in male offspring as X-linked mutations are inherited by them from their unaffected mothers (Jiang, Yuen, Jin, Wang, Chen, Wu, Ju, Mei, Shi, He, et al. 2013).

However, X-linked copy number variants are significant candidates for the risk of ASDs although the association of advanced parental age and CNVs has not been well established. Advancing maternal age increase chromosomal abnormalities of

both structural and numerical (Nielsen and Wohlert 1991), leading to several congenital disorders. However, further studies on mechanisms of de novo mutations linked advanced parental age and the risk of ASDs become worth mentioning.

4. CONCLUSION:

Offspring inherit X-chromospome duplication from their healthy 'carrier' mother. X-chromosome deletions or duplications may remain phenotypically silent in female offspring but can be expressed easily in male offspring. The role of mutation in X-linked genes is complex and heterogeneous. Twenty X-linked genes out of sixty-nine X-linked genes have been reported to be associated with ASD in this study. Individual genes contribute to ASD when they suffer heterozygous inactivation by coding mutation, copy number variations and chromosomal abnormalities. Available information should be in the National Birth Registry, Bangladesh about date of birth of children, parent's age, health condition of parents, name of mother and father etc which can provide the actual facts of disorders in progenies.

REFERENCES

1 Abrahams, Brett S., and Daniel H. Geschwind. 2008. "Advances in autism genetics: on the threshold of a new neurobiology." *Nature Reviews Genetics* no. 9:341. doi: 10.1038/nrg2346 https://www.nature.com/articles/nrg2346#supplementary-information.

2 Alter, Mark D., Rutwik Kharkar, Keri E. Ramsey, David W. Craig, Raun D. Melmed, Theresa A. Grebe, R. Curtis Bay, Sharman Ober-Reynolds, Janet Kirwan, Josh J. Jones, J. Blake Turner, Rene Hen, and Dietrich A. Stephan. 2011.

"Autism and Increased Paternal Age Related Changes in Global Levels of Gene Expression Regulation." *PLOS ONE* no. 6 (2):e16715. doi: 10.1371/journal.pone.0016715.

3 Aso, Teijiro, Ali Shilatifard, Joan Weliky Conaway, and Ronald C Conaway. 1996. "Transcription syndromes and the role of RNA polymerase II general transcription factors in human disease." *Journal of Clinical Investigation* no. 97 (7):1561.

4 Bain, Jennifer M, Megan T Cho, Aida Telegrafi, Ashley Wilson, Susan Brooks, Christina Botti, Gordon Gowans, Leigh Anne Autullo, Vidya Krishnamurthy, and Marcia C Willing. 2016. "Variants in HNRNPH2 on the X chromosome are associated with a neurodevelopmental disorder in females." *The American Journal of Human Genetics* no. 99 (3):728-734.

5 Beaudet, Arthur L. 2007. "Autism: highly heritable but not inherited." *Nature Medicine* no. 13:534. doi: 10.1038/nm0507-534.

6 Bhat, Gifty, Danielle LaGrave, Alison Millson, John Herriges, Allen N. Lamb, and Reuben Matalon. 2016. "Xq11.1-11.2 deletion involving ARHGEF9 in a girl with autism spectrum disorder." *European Journal of Medical Genetics* no. 59 (9):470-473. doi: https://doi.org/10.1016/j.ejmg.2016.05.014.

7 Bhat, S. S., S. Ladd, F. Grass, J. E. Spence, C. K. Brasington, R. J. Simensen, C. E. Schwartz, B. R. Dupont, R. E. Stevenson, and A. K. Srivastava. 2008. "Disruption of the IL1RAPL1 gene associated with a pericentromeric inversion of the X chromosome in a patient with mental retardation and autism." *Clin Genet* no. 73 (1):94-6. doi: 10.1111/j.1399-0004.2007.00920.x.

8 Brandt, T., K. Desai, D. Grodberg, L. Mehta, N. Cohen, A. Tryfon, A. Kolevzon, L. Soorya, J. D. Buxbaum, and L. Edelmann. 2012. "Complex autism spectrum disorder in a

patient with a 17q12 microduplication." *Am J Med Genet A* no. 158a (5):1170-7. doi: 10.1002/ajmg.a.35267.

9 Carney, Regina M., Chantelle M. Wolpert, Sarah A. Ravan, Mona Shahbazian, Allison Ashley-Koch, Michael L. Cuccaro, Jeffery M. Vance, and Margaret A. Pericak-Vance. "Identification of MeCP2 mutations in a series of females with autistic disorder." *Pediatric Neurology* no. 28 (3):205-211. doi: 10.1016/S0887-8994(02)00624-0.

10 Celestino-Soper, P. B., S. Violante, E. L. Crawford, R. Luo, A. C. Lionel, E. Delaby, G. Cai, B. Sadikovic, K. Lee, C. Lo, K. Gao, R. E. Person, T. J. Moss, J. R. German, N. Huang, M. Shinawi, D. Treadwell-Deering, P. Szatmari, W. Roberts, B. Fernandez, R. J. Schroer, R. E. Stevenson, J. D. Buxbaum, C. Betancur, S. W. Scherer, S. J. Sanders, D. H. Geschwind, J. S. Sutcliffe, M. E. Hurles, R. J. Wanders, C. A. Shaw, S. M. Leal, E. H. Cook, Jr., R. P. Goin-Kochel, F. M. Vaz, and A. L. Beaudet. 2012. "A common X-linked inborn error of carnitine biosynthesis may be a risk factor for nondysmorphic autism." *Proc Natl Acad Sci U S A* no. 109 (21):7974-81. doi: 10.1073/pnas.1120210109.

11 Ching, Michael SL, Yiping Shen, Wen-Hann Tan, Shafali S Jeste, Eric M Morrow, Xiaoli Chen, Nahit M Mukaddes, Seung-Yun Yoo, Ellen Hanson, and Rachel Hundley. 2010. "Deletions of NRXN1 (neurexin-1) predispose to a wide spectrum of developmental disorders." *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* no. 153 (4):937-947.

12 Chung, R. H., D. Ma, K. Wang, D. J. Hedges, J. M. Jaworski, J. R. Gilbert, M. L. Cuccaro, H. H. Wright, R. K. Abramson, I. Konidari, P. L. Whitehead, G. D. Schellenberg, H. Hakonarson, J. L. Haines, M. A. Pericak-Vance, and E. R. Martin. 2011a. "An X chromosome-wide association study in autism families identifies TBL1X as a novel autism spectrum disorder candidate gene in males." *Mol Autism* no. 2 (1):18. doi: 10.1186/2040-2392-2-18.

13 Chung, Ren-Hua, Deqiong Ma, Kai Wang, Dale J. Hedges, James M. Jaworski, John R. Gilbert, Michael L. Cuccaro, Harry H. Wright, Ruth K. Abramson, Ioanna Konidari, Patrice L. Whitehead, Gerard D. Schellenberg, Hakon Hakonarson, Jonathan L. Haines, Margaret A. Pericak-Vance, and Eden R. Martin. 2011b. "An X chromosome-wide association study in autism families identifies TBL1X as a novel autism spectrum disorder candidate gene in males." *Molecular Autism* no. 2 (1):18. doi: 10.1186/2040-2392-2-18.

14 Cook Jr, Edwin H, and Stephen W Scherer. 2008. "Copy-number variations associated with neuropsychiatric conditions." *Nature* no. 455 (7215):919-923.

15 Croen, L. A., D. V. Najjar, B. Fireman, and J. K. Grether. 2007. "Maternal and paternal age and risk of autism spectrum disorders." *Arch Pediatr Adolesc Med* no. 161 (4):334-40. doi: 10.1001/archpedi.161.4.334.

16 Crow, James F. 2000. "The origins, patterns and implications of human spontaneous mutation." *Nature Reviews Genetics* no. 1:40. doi: 10.1038/35049558.

17 De Wolf, V., A. Crepel, F. Schuit, L. van Lommel, B. Ceulemans, J. Steyaert, E. Seuntjens, H. Peeters, and K. Devriendt. 2014. "A complex Xp11.22 deletion in a patient with syndromic autism: exploration of FAM120C as a positional candidate gene for autism." *Am J Med Genet A* no. 164a (12):3035-41. doi: 10.1002/ajmg.a.36752.

18 Devlin, Bernie, and Stephen W. Scherer. 2012. "Genetic architecture in autism spectrum disorder." *Current Opinion in Genetics & Development* no. 22 (3):229-237. doi: https://doi.org/10.1016/j.gde.2012.03.002.

19 Dong, Shan, Michael F Walker, Nicholas J Carriero, Michael DiCola, A Jeremy Willsey, Y Ye Adam, Zainulabedin Waqar, Luis E Gonzalez, John D Overton, and Stephanie Frahm. 2014. "De novo insertions and deletions of predominantly paternal origin are associated with autism spectrum disorder." *Cell reports* no. 9 (1):16-23.

20 Fassio, Anna, Lysanne Patry, Sonia Congia, Franco Onofri, Amelie Piton, Julie Gauthier, Davide Pozzi, Mirko Messa, Enrico Defranchi, Manuela Fadda, Anna Corradi, Pietro Baldelli, Line Lapointe, Judith St-Onge, Caroline Meloche, Laurent Mottron, Flavia Valtorta, Dang Khoa Nguyen, Guy A. Rouleau, Fabio Benfenati, and Patrick Cossette. 2011. "SYN1 loss-of-function mutations in autism and partial epilepsy cause impaired synaptic function." *Human Molecular Genetics* no. 20 (12):2297-2307. doi: 10.1093/hmg/ddr122.

21 Folstein, Susan E, and Michael L Rutter. 1988. "Autism: familial aggregation and genetic implications." *Journal of autism and developmental disorders* no. 18 (1):3-30.

22 Giannandrea, Maila, Veronica Bianchi, Maria Lidia Mignogna, Alessandra Sirri, Salvatore Carrabino, Errico D'Elia, Matteo Vecellio, Silvia Russo, Francesca Cogliati, Lidia Larizza, Hans-Hilger Ropers, Andreas Tzschach, Vera Kalscheuer, Barbara Oehl-Jaschkowitz, Cindy Skinner, Charles E. Schwartz, Jozef Gecz, Hilde Van Esch, Martine Raynaud, Jamel Chelly, Arjan P. M. de Brouwer, Daniela Toniolo, and Patrizia D'Adamo. 2010. "Mutations in the Small GTPase Gene RAB39B Are Responsible for X-linked Mental Retardation Associated with Autism, Epilepsy, and Macrocephaly." *The American Journal of Human Genetics* no. 86 (2):185-195. doi: https://doi.org/10.1016/j.ajhg.2010.01.011.

23 Gilman, Sarah R, Ivan Iossifov, Dan Levy, Michael Ronemus, Michael Wigler, and Dennis Vitkup. 2011. "Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses." *Neuron* no. 70 (5):898-907.

24 Griswold, A. J., N. D. Dueker, D. Van Booven, J. A. Rantus, J. M. Jaworski, S. H. Slifer, M. A. Schmidt, W. Hulme, I. Konidari, P. L. Whitehead, M. L. Cuccaro, E. R. Martin, J. L. Haines, J. R. Gilbert, J. P. Hussman, and M. A. Pericak-

Vance. 2015. "Targeted massively parallel sequencing of autism spectrum disorder-associated genes in a case control cohort reveals rare loss-of-function risk variants." *Mol Autism* no. 6:43. doi: 10.1186/s13229-015-0034-z.

25 Hall, Layla, and Elizabeth Kelley. 2014. "The contribution of epigenetics to understanding genetic factors in autism." *Autism* no. 18 (8):872-881. doi: 10.1177/1362361313503501.

26 Henningsson, Susanne, Lina Jonsson, Elin Ljunggren, Lars Westberg, Carina Gillberg, Maria Råstam, Henrik Anckarsäter, Gudrun Nygren, Mikael Landén, Kent Thuresson, Catalina Betancur, Marion Leboyer, Christopher Gillberg, Elias Eriksson, and Jonas Melke. 2009. "Possible association between the androgen receptor gene and autism spectrum disorder." *Psychoneuroendocrinology* no. 34 (5):752-761. doi: https://doi.org/10.1016/j.psyneuen.2008.12.007.

27 Ho, A. C., A. P. Liu, K. S. Lun, W. F. Tang, K. Y. Chan, E. Y. Lau, M. H. Tang, T. Y. Tan, and B. H. Chung. 2012. "A newborn with a 790 kb chromosome 17p13.3 microduplication presenting with aortic stenosis, microcephaly and dysmorphic facial features - is cardiac assessment necessary for all patients with 17p13.3 microduplication?" *Eur J Med Genet* no. 55 (12):758-62. doi: 10.1016/j.ejmg.2012.09.011.

28 Hultman, C. M., S. Sandin, S. Z. Levine, P. Lichtenstein, and A. Reichenberg. 2010. "Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies." *Molecular Psychiatry* no. 16:1203. doi: 10.1038/mp.2010.121

29 https://www.nature.com/articles/mp2010121#supplementary-information.

30 Jiang, Y. H., Y. Wang, X. Xiu, K. W. Choy, A. N. Pursley, and S. W. Cheung. 2014. "Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the

genomics era." *Crit Rev Clin Lab Sci* no. 51 (5):249-62. doi: 10.3109/10408363.2014.910747.

31 Jiang, Yong-hui, Ryan KC Yuen, Xin Jin, Mingbang Wang, Nong Chen, Xueli Wu, Jia Ju, Junpu Mei, Yujian Shi, and Mingze He. 2013. "Detection of clinically relevant genetic variants in autism spectrum disorder by whole-genome sequencing." *The American Journal of Human Genetics* no. 93 (2):249-263.

32 Jiang, Yong-hui, Ryan K C. Yuen, Xin Jin, Mingbang Wang, Nong Chen, Xueli Wu, Jia Ju, Junpu Mei, Yujian Shi, Mingze He, Guangbiao Wang, Jieqin Liang, Zhe Wang, Dandan Cao, Melissa T Carter, Christina Chrysler, Irene E Drmic, Jennifer L Howe, Lynette Lau, Christian R Marshall, Daniele Merico, Thomas Nalpathamkalam, Bhooma Thiruvahindrapuram, Ann Thompson, Mohammed Uddin, Susan Walker, Jun Luo, Evdokia Anagnostou, Lonnie Zwaigenbaum, Robert H Ring, Jian Wang, Clara Lajonchere, Jun Wang, Andy Shih, Peter Szatmari, Huanming Yang, Geraldine Dawson, Yingrui Li, and Stephen W Scherer. 2013. "Detection of Clinically Relevant Genetic Variants in Autism Spectrum Disorder by Whole-Genome Sequencing." *The American Journal of Human Genetics* no. 93 (2):249-263. doi: https://doi.org/10.1016/j.ajhg.2013.06.012.

33 Jonsson, L., H. Anckarsater, A. Zettergren, L. Westberg, H. Walum, S. Lundstrom, H. Larsson, P. Lichtenstein, and J. Melke. 2014. "Association between ASMT and autistic-like traits in children from a Swedish nationwide cohort." *Psychiatr Genet* no. 24 (1):21-7. doi: 10.1097/ypg.0000000000000010.

34 Kim-Cohen, J., A. Caspi, A. Taylor, B. Williams, R. Newcombe, I. W. Craig, and T. E. Moffitt. 2006. "MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-

analysis." *Mol Psychiatry* no. 11 (10):903-13. doi: 10.1038/sj.mp.4001851.

35 Kim, Hyung-Goo, Shotaro Kishikawa, Anne W Higgins, Ihn-Sik Seong, Diana J Donovan, Yiping Shen, Eric Lally, Lauren A Weiss, Juliane Najm, and Kerstin Kutsche. 2008. "Disruption of neurexin 1 associated with autism spectrum disorder." *The American Journal of Human Genetics* no. 82 (1):199-207.

36 Kolevzon, A., R. Gross, and A. Reichenberg. 2007. "Prenatal and perinatal risk factors for autism: a review and integration of findings." *Arch Pediatr Adolesc Med* no. 161 (4):326-33. doi: 10.1001/archpedi.161.4.326.

37 Kong, Augustine, Michael L Frigge, Gisli Masson, Soren Besenbacher, Patrick Sulem, Gisli Magnusson, Sigurjon A Gudjonsson, Asgeir Sigurdsson, Aslaug Jonasdottir, and Adalbjorg Jonasdottir. 2012. "Rate of de novo mutations and the importance of father/'s age to disease risk." *Nature* no. 488 (7412):471-475.

38 Kong, Augustine, Michael L. Frigge, Gisli Masson, Soren Besenbacher, Patrick Sulem, Gisli Magnusson, Sigurjon A. Gudjonsson, Asgeir Sigurdsson, Aslaug Jonasdottir, Adalbjorg Jonasdottir, Wendy S. W. Wong, Gunnar Sigurdsson, G. Bragi Walters, Stacy Steinberg, Hannes Helgason, Gudmar Thorleifsson, Daniel F. Gudbjartsson, Agnar Helgason, Olafur Th Magnusson, Unnur Thorsteinsdottir, and Kari Stefansson. 2012. "Rate of de novo mutations and the importance of father's age to disease risk." *Nature* no. 488:471. doi: 10.1038/nature11396 https://www.nature.com/articles/nature11396#supplementary-information.

39 Koochek, M., C. Harvard, M. J. Hildebrand, M. Van Allen, H. Wingert, E. Mickelson, J. J. Holden, E. Rajcan-Separovic, and M. E. Lewis. 2006. "15q duplication associated with autism in a multiplex family with a familial cryptic translocation t(14;15)(q11.2;q13.3) detected using array-

CGH." *Clin Genet* no. 69 (2):124-34. doi: 10.1111/j.1399-0004.2005.00560.x.

40 Krumm, N., T. N. Turner, C. Baker, L. Vives, K. Mohajeri, K. Witherspoon, A. Raja, B. P. Coe, H. A. Stessman, Z. X. He, S. M. Leal, R. Bernier, and E. E. Eichler. 2015. "Excess of rare, inherited truncating mutations in autism." *Nat Genet* no. 47 (6):582-8. doi: 10.1038/ng.3303.

41 Laumonnier, F., C. Shoubridge, C. Antar, L. S. Nguyen, H. Van Esch, T. Kleefstra, S. Briault, J. P. Fryns, B. Hamel, J. Chelly, H. H. Ropers, N. Ronce, S. Blesson, C. Moraine, J. Gecz, and M. Raynaud. 2010. "Mutations of the UPF3B gene, which encodes a protein widely expressed in neurons, are associated with nonspecific mental retardation with or without autism." *Mol Psychiatry* no. 15 (7):767-76. doi: 10.1038/mp.2009.14.

42 Lauritsen, M, and H Ewald. 2001. "The genetics of autism." *Acta Psychiatrica Scandinavica* no. 103 (6):411-427.

43 Lee, A. Y., W. Chen, S. Stippec, J. Self, F. Yang, X. Ding, S. Chen, Y. C. Juang, and M. H. Cobb. 2012. "Protein kinase WNK3 regulates the neuronal splicing factor Fox-1." *Proc Natl Acad Sci U S A* no. 109 (42):16841-6. doi: 10.1073/pnas.1215406109.

44 Lee, Brian K, and John J McGrath. 2015. "Advancing parental age and autism: multifactorial pathways." *Trends in molecular medicine* no. 21 (2):118-125.

45 Levy, Dan, Michael Ronemus, Boris Yamrom, Yoon-ha Lee, Anthony Leotta, Jude Kendall, Steven Marks, B. Lakshmi, Deepa Pai, Kenny Ye, Andreas Buja, Abba Krieger, Seungtai Yoon, Jennifer Troge, Linda Rodgers, Ivan Iossifov, and Michael Wigler. 2011. "Rare De Novo and Transmitted Copy-Number Variation in Autistic Spectrum Disorders." *Neuron* no. 70 (5):886-897. doi: https://doi.org/10.1016/j.neuron.2011.05.015.

46 Lopez-Rangel, E, and MES Lewis. 2006. "Loud and clear evidence for gene silencing by epigenetic mechanisms in

autism spectrum and related neurodevelopmental disorders." *Clinical genetics* no. 69 (1):21-22.

47 Marshall, Christian R, Abdul Noor, John B Vincent, Anath C Lionel, Lars Feuk, Jennifer Skaug, Mary Shago, Rainald Moessner, Dalila Pinto, and Yan Ren. 2008. "Structural variation of chromosomes in autism spectrum disorder." *The American Journal of Human Genetics* no. 82 (2):477-488.

48 Miles, Judith H. 2011. "Autism spectrum disorders—A genetics review." *Genetics In Medicine* no. 13:278. doi: 10.1097/GIM.0b013e3181ff67ba.

49 Moessner, R., C. R. Marshall, J. S. Sutcliffe, J. Skaug, D. Pinto, J. Vincent, L. Zwaigenbaum, B. Fernandez, W. Roberts, P. Szatmari, and S. W. Scherer. 2007. "Contribution of SHANK3 mutations to autism spectrum disorder." *Am J Hum Genet* no. 81 (6):1289-97. doi: 10.1086/522590.

50 Nava, C., F. Lamari, D. Heron, C. Mignot, A. Rastetter, B. Keren, D. Cohen, A. Faudet, D. Bouteiller, M. Gilleron, A. Jacquette, S. Whalen, A. Afenjar, D. Perisse, C. Laurent, C. Dupuits, C. Gautier, M. Gerard, G. Huguet, S. Caillet, B. Leheup, M. Leboyer, C. Gillberg, R. Delorme, T. Bourgeron, A. Brice, and C. Depienne. 2012. "Analysis of the chromosome X exome in patients with autism spectrum disorders identified novel candidate genes, including TMLHE." *Transl Psychiatry* no. 2:e179. doi: 10.1038/tp.2012.102.

51 Nava, C., J. Rupp, J. P. Boissel, C. Mignot, A. Rastetter, C. Amiet, A. Jacquette, C. Dupuits, D. Bouteiller, B. Keren, M. Ruberg, A. Faudet, D. Doummar, A. Philippe, D. Perisse, C. Laurent, N. Lebrun, V. Guillemot, J. Chelly, D. Cohen, D. Heron, A. Brice, E. I. Closs, and C. Depienne. 2015. "Hypomorphic variants of cationic amino acid transporter 3 in males with autism spectrum disorders." *Amino Acids* no. 47 (12):2647-58. doi: 10.1007/s00726-015-2057-3.

52 Newschaffer, Craig J, Lisa A Croen, Julie Daniels, Ellen Giarelli, Judith K Grether, Susan E Levy, David S Mandell, Lisa A Miller, Jennifer Pinto-Martin, and Judy Reaven. 2007. "The epidemiology of autism spectrum disorders." *Annu. Rev. Public Health* no. 28:235-258.

53 Nielsen, Johannes, and Mogens Wohlert. 1991. "Chromosome abnormalities found among 34910 newborn children: results from a 13-year incidence study in Århus, Denmark." *Human genetics* no. 87 (1):81-83.

54 Noor, A., P. J. Gianakopoulos, B. Fernandez, C. R. Marshall, P. Szatmari, W. Roberts, S. W. Scherer, and J. B. Vincent. 2009. "Copy number variation analysis and sequencing of the X-linked mental retardation gene TSPAN7/TM4SF2 in patients with autism spectrum disorder." *Psychiatr Genet* no. 19 (3):154-5. doi: 10.1097/YPG.0b013e32832a4fe5.

55 Noor, Abdul, Annabel Whibley, Christian R. Marshall, Peter J. Gianakopoulos, Amelie Piton, Andrew R. Carson, Marija Orlic-Milacic, Anath Lionel, Daisuke Sato, Dalila Pinto, Irene Drmic, Carolyn Noakes, Lili Senman, Xiaoyun Zhang, Rong Mo, Julie Gauthier, Jennifer Crosbie, Alistair T. Pagnamenta, Jeffrey Munson, Annette M. Estes, Andreas Fiebig, Andre Franke, Stefan Schreiber, Alexandre F. R. Stewart, Robert Roberts, Ruth McPherson, Stephen J. Guter, Edwin H. Cook, Geraldine Dawson, Gerard D. Schellenberg, Agatino Battaglia, Elena Maestrini, Consortium Autism Genome Project, Linda Jeng, Terry Hutchison, Evica Rajcan-Separovic, Albert E. Chudley, Suzanne M. E. Lewis, Xudong Liu, Jeanette Holden, Bridget Fernandez, Lonnie Zwaigenbaum, Susan E. Bryson, Wendy Roberts, Peter Szatmari, Louise Gallagher, Michael R. Stratton, Jozef Gecz, Angela F. Brady, Charles E. Schwartz, Russell J. Schachar, Anthony P. Monaco, Guy A. Rouleau, Chi-chung Hui, F. Lucy Raymond, Stephen W. Scherer, and John B. Vincent. 2010. "Disruption at the

PTCHD1 locus on Xp22.11 in autism spectrum disorder and intellectual disability." *Science translational medicine* no. 2 (49):49ra68-49ra68. doi: 10.1126/scitranslmed.3001267.

56 O'Roak, Brian J, Laura Vives, Santhosh Girirajan, Emre Karakoc, Niklas Krumm, Bradley P Coe, Roie Levy, Arthur Ko, Choli Lee, and Joshua D Smith. 2012. "Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations." *Nature* no. 485 (7397):246.

57 Pagnamenta, Alistair T., Richard Holt, Mohammed Yusuf, Dalila Pinto, Kirsty Wing, Catalina Betancur, Stephen W. Scherer, Emanuela V. Volpi, and Anthony P. Monaco. 2011. "A family with autism and rare copy number variants disrupting the Duchenne/Becker muscular dystrophy gene DMD and TRPM3." *Journal of Neurodevelopmental Disorders* no. 3 (2):124-131. doi: 10.1007/s11689-011-9076-5.

58 Philibert, R. A., and A. Madan. 2007. "Role of MED12 in transcription and human behavior." *Pharmacogenomics* no. 8 (8):909-16. doi: 10.2217/14622416.8.8.909.

59 Pinto, Dalila, Alistair T Pagnamenta, Lambertus Klei, Richard Anney, Daniele Merico, Regina Regan, Judith Conroy, Tiago R Magalhaes, Catarina Correia, and Brett S Abrahams. 2010. "Functional impact of global rare copy number variation in autism spectrum disorders." *Nature* no. 466 (7304):368.

60 Pinto, Dalila, Alistair T. Pagnamenta, Lambertus Klei, Richard Anney, Daniele Merico, Regina Regan, Judith Conroy, Tiago R. Magalhaes, Catarina Correia, Brett S. Abrahams, Joana Almeida, Elena Bacchelli, Gary D. Bader, Anthony J. Bailey, Gillian Baird, Agatino Battaglia, Tom Berney, Nadia Bolshakova, Sven Bölte, Patrick F. Bolton, Thomas Bourgeron, Sean Brennan, Jessica Brian, Susan E. Bryson, Andrew R. Carson, Guillermo Casallo, Jillian Casey, Lynne Cochrane, Christina Corsello, Emily L. Crawford, Andrew Crossett, Geraldine Dawson, Maretha de Jonge, Richard Delorme, Irene Drmic, Eftichia Duketis,

Frederico Duque, Annette Estes, Penny Farrar, Bridget A. Fernandez, Ana Filipa, Susan E. Folstein, Eric Fombonne, Christine M. Freitag, John Gilbert, Christopher Gillberg, Joseph T. Glessner, Jeremy Goldberg, Andrew Green, Jonathan Green, Stephen J. Guter, Hakon Hakonarson, Elizabeth A. Heron, Matthew Hill, Richard Holt, Jennifer L. Howe, Gillian Hughes, Vanessa Hus, Roberta Igliozzi, Cecilia Kim, Sabine M. Klauck, Alexander Kolevzon, Olena Korvatska, Vlad Kustanovich, Clara M. Lajonchere, Janine A. Lamb, Magdalena Laskawiec, Marion Leboyer, Ann Le Couteur, Bennett L. Leventhal, Anath C. Lionel, Xiao-Qing Liu, Catherine Lord, Linda Lotspeich, Sabata C. Lund, Elena Maestrini, William Mahoney, Carine Mantoulan, Christian R. Marshall, Helen McConachie, Christopher J. McDougle, Jane McGrath, William M. McMahon, Alison Merikangas, Ohsuke Migita, Nancy J. Minshew, Ghazala K. Mirza, Jeff Munson, Stanley F. Nelson, Carolyn Noakes, Abdul Noor, Gudrun Nygren, Guiomar Oliveira, Katerina Papanikolaou, Jeremy R. Parr, Barbara Parrini, Tara Paton, Andrew Pickles, Marion Pilorge, Joseph Piven, Chris P. Ponting, David J. Posey, Annemarie Poustka, Fritz Poustka, Aparna Prasad, Jiannis Ragoussis, Katy Renshaw, Jessica Rickaby, Wendy Roberts, Kathryn Roeder, Bernadette Roge, Michael L. Rutter, Laura J. Bierut, John P. Rice, Sage Consortium, Jeff Salt, Katherine Sansom, Daisuke Sato, Ricardo Segurado, Lili Senman, Naisha Shah, Val C. Sheffield, Latha Soorya, Inês Sousa, Olaf Stein, Vera Stoppioni, Christina Strawbridge, Raffaella Tancredi, Katherine Tansey, Bhooma Thiruvahindrapduram, Ann P. Thompson, Susanne Thomson, Ana Tryfon, John Tsiantis, Herman Van Engeland, John B. Vincent, Fred Volkmar, Simon Wallace, Kai Wang, Zhouzhi Wang, Thomas H. Wassink, Caleb Webber, Kirsty Wing, Kerstin Wittemeyer, Shawn Wood, Jing Wu, Brian L. Yaspan, Danielle Zurawiecki, Lonnie

Zwaigenbaum, Joseph D. Buxbaum, Rita M. Cantor, Edwin H. Cook, Hilary Coon, Michael L. Cuccaro, Bernie Devlin, Sean Ennis, Louise Gallagher, Daniel H. Geschwind, Michael Gill, Jonathan L. Haines, Joachim Hallmayer, Judith Miller, Anthony P. Monaco, John I. Nurnberger, Andrew D. Paterson, Margaret A. Pericak-Vance, Gerard D. Schellenberg, Peter Szatmari, Astrid M. Vicente, Veronica J. Vieland, Ellen M. Wijsman, Stephen W. Scherer, James S. Sutcliffe, and Catalina Betancur. 2010. "Functional Impact of Global Rare Copy Number Variation in Autism Spectrum Disorder." *Nature* no. 466 (7304):368-372. doi: 10.1038/nature09146.

61 Piton, Amélie, Loubna Jouan, Daniel Rochefort, Sylvia Dobrzeniecka, Karine Lachapelle, Patrick A Dion, Julie Gauthier, and Guy A Rouleau. 2013. "Analysis of the effects of rare variants on splicing identifies alterations in GABAA receptor genes in autism spectrum disorder individuals." *European Journal of Human Genetics* no. 21 (7):749-756.

62 Ramos, P. S., S. Sajuthi, C. D. Langefeld, and S. J. Walker. 2012. "Immune function genes CD99L2, JARID2 and TPO show association with autism spectrum disorder." *Mol Autism* no. 3 (1):4. doi: 10.1186/2040-2392-3-4.

63 Reichenberg, Abraham, Raz Gross, Mark Weiser, Michealine Bresnahan, Jeremy Silverman, Susan Harlap, Jonathan Rabinowitz, Cory Shulman, Dolores Malaspina, and Gad Lubin. 2006. "Advancing paternal age and autism." *Archives of general psychiatry* no. 63 (9):1026-1032.

64 Richler, Jennifer, Marisela Huerta, Somer L Bishop, and Catherine Lord. 2010. "Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders." *Development and psychopathology* no. 22 (1):55-69.

65 Ross, Mark T., Darren V. Grafham, Alison J. Coffey, Steven Scherer, Kirsten McLay, Donna Muzny, Matthias Platzer, Gareth R. Howell, Christine Burrows, Christine P. Bird,

Adam Frankish, Frances L. Lovell, Kevin L. Howe, Jennifer L. Ashurst, Robert S. Fulton, Ralf Sudbrak, Gaiping Wen, Matthew C. Jones, Matthew E. Hurles, T. Daniel Andrews, Carol E. Scott, Stephen Searle, Juliane Ramser, Adam Whittaker, Rebecca Deadman, Nigel P. Carter, Sarah E. Hunt, Rui Chen, Andrew Cree, Preethi Gunaratne, Paul Havlak, Anne Hodgson, Michael L. Metzker, Stephen Richards, Graham Scott, David Steffen, Erica Sodergren, David A. Wheeler, Kim C. Worley, Rachael Ainscough, Kerrie D. Ambrose, M. Ali Ansari-Lari, Swaroop Aradhya, Robert I. S. Ashwell, Anne K. Babbage, Claire L. Bagguley, Andrea Ballabio, Ruby Banerjee, Gary E. Barker, Karen F. Barlow, Ian P. Barrett, Karen N. Bates, David M. Beare, Helen Beasley, Oliver Beasley, Alfred Beck, Graeme Bethel, Karin Blechschmidt, Nicola Brady, Sarah Bray-Allen, Anne M. Bridgeman, Andrew J. Brown, Mary J. Brown, David Bonnin, Elspeth A. Bruford, Christian Buhay, Paula Burch, Deborah Burford, Joanne Burgess, Wayne Burrill, John Burton, Jackie M. Bye, Carol Carder, Laura Carrel, Joseph Chako, Joanne C. Chapman, Dean Chavez, Ellson Chen, Guan Chen, Yuan Chen, Zhijian Chen, Craig Chinault, Alfredo Ciccodicola, Sue Y. Clark, Graham Clarke, Chris M. Clee, Sheila Clegg, Kerstin Clerc-Blankenburg, Karen Clifford, Vicky Cobley, Charlotte G. Cole, Jen S. Conquer, Nicole Corby, Richard E. Connor, Robert David, Joy Davies, Clay Davis, John Davis, Oliver Delgado, Denise DeShazo, Pawandeep Dhami, Yan Ding, Huyen Dinh, Steve Dodsworth, Heather Draper, Shannon Dugan-Rocha, Andrew Dunham, Matthew Dunn, K. James Durbin, Ireena Dutta, Tamsin Eades, Matthew Ellwood, Alexandra Emery-Cohen, Helen Errington, Kathryn L. Evans, Louisa Faulkner, Fiona Francis, John Frankland, Audrey E. Fraser, Petra Galgoczy, James Gilbert, Rachel Gill, Gernot Glöckner, Simon G. Gregory, Susan Gribble, Coline Griffiths, Russell Grocock, Yanghong Gu, Rhian Gwilliam,

Cerissa Hamilton, Elizabeth A. Hart, Alicia Hawes, Paul D. Heath, Katja Heitmann, Steffen Hennig, Judith Hernandez, Bernd Hinzmann, Sarah Ho, Michael Hoffs, Phillip J. Howden, Elizabeth J. Huckle, Jennifer Hume, Paul J. Hunt, Adrienne R. Hunt, Judith Isherwood, Leni Jacob, David Johnson, Sally Jones, Pieter J. de Jong, Shirin S. Joseph, Stephen Keenan, Susan Kelly, Joanne K. Kershaw, Ziad Khan, Petra Kioschis, Sven Klages, Andrew J. Knights, Anna Kosiura, Christie Kovar-Smith, Gavin K. Laird, Cordelia Langford, Stephanie Lawlor, Margaret Leversha, Lora Lewis, Wen Liu, Christine Lloyd, David M. Lloyd, Hermela Loulseged, Jane E. Loveland, Jamieson D. Lovell, Ryan Lozado, Jing Lu, Rachael Lyne, Jie Ma, Manjula Maheshwari, Lucy H. Matthews, Jennifer McDowall, Stuart McLaren, Amanda McMurray, Patrick Meidl, Thomas Meitinger, Sarah Milne, George Miner, Shailesh L. Mistry, Margaret Morgan, Sidney Morris, Ines Müller, James C. Mullikin, Ngoc Nguyen, Gabriele Nordsiek, Gerald Nyakatura, Christopher N. O'Dell, Geoffery Okwuonu, Sophie Palmer, Richard Pandian, David Parker, Julia Parrish, Shiran Pasternak, Dina Patel, Alex V. Pearce, Danita M. Pearson, Sarah E. Pelan, Lesette Perez, Keith M. Porter, Yvonne Ramsey, Kathrin Reichwald, Susan Rhodes, Kerry A. Ridler, David Schlessinger, Mary G. Schueler, Harminder K. Sehra, Charles Shaw-Smith, Hua Shen, Elizabeth M. Sheridan, Ratna Shownkeen, Carl D. Skuce, Michelle L. Smith, Elizabeth C. Sotheran, Helen E. Steingruber, Charles A. Steward, Roy Storey, R. Mark Swann, David Swarbreck, Paul E. Tabor, Stefan Taudien, Tineace Taylor, Brian Teague, Karen Thomas, Andrea Thorpe, Kirsten Timms, Alan Tracey, Steve Trevanion, Anthony C. Tromans, Michele d'Urso, Daniel Verduzco, Donna Villasana, Lenee Waldron, Melanie Wall, Qiaoyan Wang, James Warren, Georgina L. Warry, Xuehong Wei, Anthony West, Siobhan L. Whitehead, Mathew N. Whiteley,

Jane E. Wilkinson, David L. Willey, Gabrielle Williams, Leanne Williams, Angela Williamson, Helen Williamson, Laurens Wilming, Rebecca L. Woodmansey, Paul W. Wray, Jennifer Yen, Jingkun Zhang, Jianling Zhou, Huda Zoghbi, Sara Zorilla, David Buck, Richard Reinhardt, Annemarie Poustka, André Rosenthal, Hans Lehrach, Alfons Meindl, Patrick J. Minx, LaDeana W. Hillier, Huntington F. Willard, Richard K. Wilson, Robert H. Waterston, Catherine M. Rice, Mark Vaudin, Alan Coulson, David L. Nelson, George Weinstock, John E. Sulston, Richard Durbin, Tim Hubbard, Richard A. Gibbs, Stephan Beck, Jane Rogers, and David R. Bentley. 2005. "The DNA sequence of the human X chromosome." *Nature* no. 434:325. doi: 10.1038/nature03440 https://www.nature.com/articles/nature03440#supplementary-information.

66 Roze, Elise, Lisethe Meijer, Koenraad NJA Van Braeckel, Selma AJ Ruiter, Janneke LM Bruggink, and Arend F Bos. 2010. "Developmental trajectories from birth to school age in healthy term-born children." *Pediatrics* no. 126 (5):e1134-e1142.

67 Sanders, Stephan J, Michael T Murtha, Abha R Gupta, John D Murdoch, Melanie J Raubeson, A Jeremy Willsey, A Gulhan Ercan-Sencicek, Nicholas M DiLullo, Neelroop N Parikshak, and Jason L Stein. 2012. "De novo mutations revealed by whole-exome sequencing are strongly associated with autism." *Nature* no. 485 (7397):237.

68 Sebat, Jonathan, B. Lakshmi, Dheeraj Malhotra, Jennifer Troge, Christa Lese-Martin, Tom Walsh, Boris Yamrom, Seungtai Yoon, Alex Krasnitz, Jude Kendall, Anthony Leotta, Deepa Pai, Ray Zhang, Yoon-Ha Lee, James Hicks, Sarah J. Spence, Annette T. Lee, Kaija Puura, Terho Lehtimäki, David Ledbetter, Peter K. Gregersen, Joel Bregman, James S. Sutcliffe, Vaidehi Jobanputra, Wendy Chung, Dorothy Warburton, Mary-Claire King, David

Skuse, Daniel H. Geschwind, T. Conrad Gilliam, Kenny Ye, and Michael Wigler. 2007. "Strong Association of De Novo Copy Number Mutations with Autism." *Science* no. 316 (5823):445-449. doi: 10.1126/science.1138659.

69 Shoubridge, Cheryl, Patrick S. Tarpey, Fatima Abidi, Sarah L. Ramsden, Sinitdhorn Rujirabanjerd, Jessica A. Murphy, Jackie Boyle, Marie Shaw, Alison Gardner, Anne Proos, Helen Puusepp, F. Lucy Raymond, Charles E. Schwartz, Roger E. Stevenson, Gill Turner, Michael Field, Randall S. Walikonis, Robert J. Harvey, Anna Hackett, P. Andrew Futreal, Michael R. Stratton, and Jozef Gécz. 2010. "Mutations in the guanine nucleotide exchange factor gene IQSEC2 cause nonsyndromic intellectual disability." *Nature Genetics* no. 42:486. doi: 10.1038/ng.588 https://www.nature.com/articles/ng.588#supplementary-information.

70 Simic, M., and J. Turk. 2004. "Autistic spectrum disorder associated with partial duplication of chromosome 15; three case reports." *Eur Child Adolesc Psychiatry* no. 13 (6):389-93. doi: 10.1007/s00787-004-0414-y.

71 Stephan, Dietrich A. 2008. "Unraveling autism." *The American Journal of Human Genetics* no. 82 (1):7-9.

72 Sugathan, A., M. Biagioli, C. Golzio, S. Erdin, I. Blumenthal, P. Manavalan, A. Ragavendran, H. Brand, D. Lucente, J. Miles, S. D. Sheridan, A. Stortchevoi, M. Kellis, S. J. Haggarty, N. Katsanis, J. F. Gusella, and M. E. Talkowski. 2014. "CHD8 regulates neurodevelopmental pathways associated with autism spectrum disorder in neural progenitors." *Proc Natl Acad Sci U S A* no. 111 (42):E4468-77. doi: 10.1073/pnas.1405266111.

73 Sykes, Nuala H, and Janine A Lamb. 2007. "Autism: the quest for the genes." *Expert Reviews in Molecular Medicine* no. 9 (24):1-15.

74 Tran Mau-Them, F., M. Willems, B. Albrecht, E. Sanchez, J. Puechberty, S. Endele, A. Schneider, N. Ruiz Pallares, C.

Missirian, F. Rivier, M. Girard, M. Holder, S. Manouvrier, I. Touitou, G. Lefort, P. Sarda, A. Moncla, S. Drunat, D. Wieczorek, and D. Genevieve. 2014. "Expanding the phenotype of IQSEC2 mutations: truncating mutations in severe intellectual disability." *Eur J Hum Genet* no. 22 (2):289-92. doi: 10.1038/ejhg.2013.113.

75 Van Maldergem, Lionel, Qingming Hou, Vera M Kalscheuer, Marlène Rio, Martine Doco-Fenzy, Ana Medeira, Arjan PM de Brouwer, Christelle Cabrol, Stefan A Haas, and Pierre Cacciagli. 2013. "Loss of function of KIAA2022 causes mild to severe intellectual disability with an autism spectrum disorder and impairs neurite outgrowth." *Human molecular genetics* no. 22 (16):3306-3314.

76 Vervoort, V. S., M. A. Beachem, P. S. Edwards, S. Ladd, K. E. Miller, X. de Mollerat, K. Clarkson, B. DuPont, C. E. Schwartz, R. E. Stevenson, E. Boyd, and A. K. Srivastava. 2002. "AGTR2 mutations in X-linked mental retardation." *Science* no. 296 (5577):2401-3. doi: 10.1126/science.1072191.

77 Wang, Kai, Haitao Zhang, Deqiong Ma, Maja Bucan, Joseph T Glessner, Brett S Abrahams, Daria Salyakina, Marcin Imielinski, Jonathan P Bradfield, and Patrick MA Sleiman. 2009. "Common genetic variants on 5p14. 1 associate with autism spectrum disorders." *Nature* no. 459 (7246):528-533.

78 Wilkinson, B., N. Grepo, B. L. Thompson, J. Kim, K. Wang, O. V. Evgrafov, W. Lu, J. A. Knowles, and D. B. Campbell. 2015. "The autism-associated gene chromodomain helicase DNA-binding protein 8 (CHD8) regulates noncoding RNAs and autism-related genes." *Transl Psychiatry* no. 5:e568. doi: 10.1038/tp.2015.62.

79 Wong, Wendy S. W., Benjamin D. Solomon, Dale L. Bodian, Prachi Kothiyal, Greg Eley, Kathi C. Huddleston, Robin Baker, Dzung C. Thach, Ramaswamy K. Iyer, Joseph G. Vockley, and John E. Niederhuber. 2016. "New observations on maternal age effect on germline de novo mutations."

Nature Communications no. 7:10486. doi: 10.1038/ncomms10486 https://www.nature.com/articles/ncomms10486#supplementary-information.

80 Zhao, Xiaoyue, Anthony Leotta, Vlad Kustanovich, Clara Lajonchere, Daniel H Geschwind, Kiely Law, Paul Law, Shanping Qiu, Catherine Lord, and Jonathan Sebat. 2007. "A unified genetic theory for sporadic and inherited autism." *Proceedings of the National Academy of Sciences* no. 104 (31):12831-12836.

81 Zoghbi, Huda Y. 2005. "MeCP2 dysfunction in humans and mice." *Journal of child neurology* no. 20 (9):736-740.