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RESEARCH ARTICLE

A COMPLEX HETEROGENEITY OF AUTISM SPECTRUM DISORDER – PROMISE OF GENETICS

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ABSTRACT

Autism is a neuro developmental disorder of clinical and genetic heterogeneity affecting males three times more than female children. Autism is characterized by a deficit in social interaction and communication, restricted repetitive, aggressive, and stereotyped behavior, motor function deficits, disturbed sleep patterns, abnormality in gastrointestinal functions, epilepsy, and intellectual disability. It is also known as an autism spectrum disorder (ASD) due to diverse risk factors that might be inheritable genetic factors (40-80%) or *de novo* gene mutations causing multiple phenotypic expressions such as neurocognitive impairment and physical abnormalities. The interplay of genetic (monogenic and multiple gene variants), nongenetic and environmental factors contributes to the predisposition of ASD. A clinical genetic investigation is important to rule out the underlying cause and manage the disease accordingly with the best possible clinical interventions. This review is a step toward understanding the orchestra of genomic and epigenomic interactions, their mechanisms, and pathways influencing the phenotypic expressions which are crucial for both diagnosis, as well as the management of ASD and for novel interventions.

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INTRODUCTION

Autism is a neurodevelopmental disorder that affects physical, social, and communication skills before the onset of the age of 3 years. The term early infantile autism was given by Leo Kanner as a specific syndrome found in children between the age of 18-24 months, with certain features, symptoms, and abnormal social and emotional behavioral deficits (Kanner, 1968). Since then autism is considered autism spectrum disorder (ASD) as recommended by the DSM-5 (Diagnosis and Statistical Manual of Mental Disorders, 5th edition), by American Psychiatric Association (APA 2013), the ICD-10 (International Classification of Diseases, 10th Revision) and world Health organization(Regier *et al*., 2013). However, ASD ranges from mild to severe, prior to the age of 3 years, with symptoms of cognitive impairment (Genovese and Butler, 2020). The hallmark of autism disorder is heterogeneity in the symptoms of the patient and the presence of co-morbid conditions in autism are motor abnormalities (79%), gastrointestinal problems (70%), epilepsy (30%), intellectual disability (45%), and sleep disorders (50–80%) (Khan *et al*., 2012; Lord *et al.,* 2018; Rylaarsdam and Guemez-Gamboa, 2019; Lecavalier *et al*., 2019; Vargason *et al*., 2019). ASD significantly affects the life of individuals across several aspects. The disease represents a substantial heavy economic and social burden (Lord *et al.,* 2018).

Prevalence: Approximately 1 in 100 children has ASD globally, the number of cases may vary as per reported literature based on socioeconomic and ethnic groups. As per World Health Organization (WHO) cases in some well-controlled studies are higher, however, reports in many low and middle-income countries are not known (WHO ICD-10, 2004). Studies across Asia, Europe, and North America have documented individuals with ASD with an average prevalence of between 1% and 2% (Jin *et al*., 2018). According to an estimate in India, 1 in 100 children have ASD and 1 in 8 showed abnormal neurodevelopmental conditions. In a large study including children, (465 to ~50 million samples) the prevalence range was found from 1.09/10,000 to 436/10,000 (Kočovská *et al*., 2012; Amr *et al*., 2012; Blumberg *et al*., 2013; Poovathinal *et al*., 2016; Raina *et al*., 2017)with males outnumbering females with a male/female ratio of 0.8 to 6.

Mechanism underlying multidimensional ASD Phenotype: The intricate interplay of genetics, epigenetics, and other factors is the cornerstone of the pathophysiological development of ASD (Bollati and Baccarelli, 2010; Perera and Herbstman, 2011). Hypoconnectivity

among brain structures has been correlated with ASD. Neuroanatomic features can also influence brain and behavior patterns in ASD. Most remarkably the neuronal activity regulating the function of many ASD-related genes is impaired, which code for chromatin remodeling, protein synthesis, degradation, and synaptic functions (Bourgeron, 2016). Therefore, synaptic plasticity becomes abnormal causing failure of synaptic/neuronal homeostasis, and the altered concentration of GABAergic receptors and enhanced inhibitory synaptic function are related to ASD (Sacai *et al*., 2020).

Autism: **Heterogeneous Risk Factors:** There is no single known cause of the complex disease ASD, variation in severity, symptoms, causes, risk factors and interplay of genetics and environmental factors are responsible for ASD (Figure 1). Autism disorder runs in families. Several genes have been reported from familial aggregation studies in association with autism. In some cases, the children develop autism due to the presence of a single gene disorder in Mendelian forms such as Rett Syndrome or fragile X syndrome, for others multi genetic mutations might contribute to ASD. The genetic alterations result in impairment in functions in brain development and synaptic dysfunction also known as synaptopathy. Epigenetics and its complex mechanisms significantly affect gene expression via epigenetics including the methylation, acetylation, and expression of non-coding RNA. These modifications are transferred to harmful environmental factors can cause alterations in the expression of the key developmental gene at a very early age in the critical period of embryogenesis accelerating the risk of ASD (Bollati and Baccarelli, 2010; Perera and Herbstman, 2011; Bourgeron, 2016; Sacai *et al*., 2020).

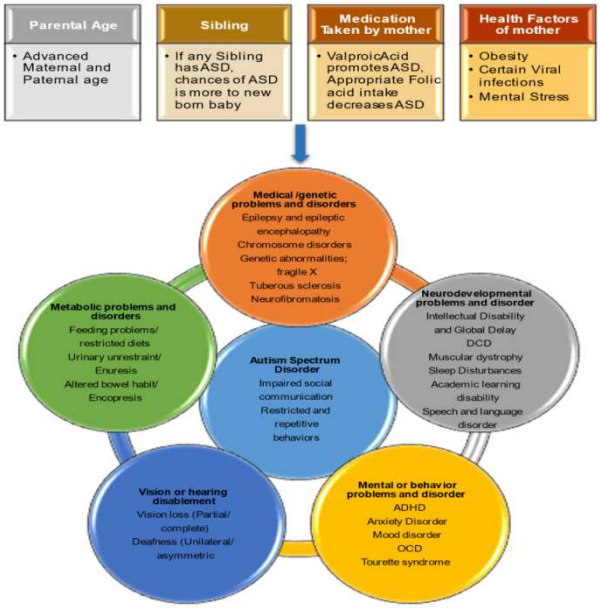

Figure 1. Autism Spectrum Disorder its risk factors and Associated abnormalities

Genetic Epidemiology of ASD: Studies involving twins, siblings, and family pedigrees have reported significant evidence for the heritability of ASD. Therefore, understanding the complex pattern of genes involved in the pathogenesis of autism is crucial. The genetic architecture of ASD is very complex and diverse in frequency (either the variation is common or rare, inherited or de novo), type of variation (single nucleotide polymorphism, indel, or copy number variation), and pattern of inheritance (dominant, recessive, or additive) (Study Corgi, 2021). Approximately up to 20% of all autism cases occur due to known genetic causes, explaining the transmission pattern of recurrence of autism in families e.g., de novo chromosomal rearrangements have been found in certain 10% of autistic children when compared with substantially lower rates in the general population (Constantino *et al*., 2021). There has been 3-18% recurrence risk of ASD among siblings.

Twin and Family Studies of ASD: Twin studies conducted between 1977 and 2015 and further in the year 2017, have established the genetic and environmental contribution to ASD. The very first twin study of autism reported a cohort of 11 monozygotic twins (MZ) and 10 dizygotic twins (DZ) have found a higher concordance rate of autism in monozygotic twins (77-95%) as compared with DZ twins (31%), with a significant contribution shared by neurodevelopmental disorders such as ADHD (Attention deficit hyperactivity disorder) (> 50%) and learning disability (>40%) (Folstein and Rutter, 1977; Bourgeron, 2016]. A careful assessment of the family history of autism with pedigree analysis is used as a potential calculation of risk stratification. Familial aggregation of neurological disorders has been often observed in ASD among first- to fourth-degree relatives in a largest population-based cohort study including 567,436 index persons from Stockholm, Sweden (Xie *et al*., 2019).

Potential Candidate Genes: The mutations in genes have been found to play a crucial role in various neurodevelopmental diseases/disorders including autism (Table 1) (D'Gama and Walsh, 2018; Rylaarsdam and Guemez-Gamboa, 2019). During the process of neuron formation, each progenitor produces roughly five single nucleotide variants (SNV) per day in the rapid development of the brain (D'Gama and Walsh, 2018). The ASD susceptibility genes are interconnected at the level of transcriptional and functional protein networks, and influence as regulators of synaptic function and neuronal activity (Iakoucheva *et al*., 2019).

Mendelian forms or Monogenic Disorders in ASD: The monogenic conditions linked with ASD have been summarized in Table 1. Fragile-X syndrome is one of the most common conditions due to the duplication of maternal alleles in chromosome 15(15q11–q13) and affects synaptic plasticity. The available transient gene therapies include antisense oligonucleotides (ASO), noncoding RNA (ncRNA), RNA editing, and gene delivery for monogenic cases of ASD(Krupp *et al*., 2017; Weuring *et al*., 2021). Permanent gene therapies include the ones which edit the host cell genome such as gene replacement (aimed at integration in the genome), CRISPR-KO (gene editing knockout kit for targeted genomic disruptions), and Gene editing (for targeted repair of disease-causing mutations)(Krupp *et al*., 2017).

Chromosomal aberrations: Chromosomal aberrations play a substantial role in the development of ASD. The rearrangements in regions of chromosome 1, 1q21, chromosome 7 (7q11.23) chromosome 15 (15q13 and 15q11-13), chromosome16 (16p11.2), chromosome 17 (17p11.2) chromosome 22 (22q13.3 and 22q11.21) have been well established with autism phenotype. The serotonin neurotransmitter transporter gene SLC6A4 HTT (solute carrier family 6 member 4) in 17q11-12, has been found to be linked to autistic phenotype in many GWAS (Genome-wide association studies) (Auranen *et al*., 2002; Strobel *et al*., 2007). Several studies have reported around 19 % contribution of Down syndrome, sex chromosome aneuploidies, and segmental aneuploidies (microdeletion or microduplication) of chromosomes 2q37, 15q11–13 duplications, 22q11.2, 22q13.3 and 16p11.2, in particular, leading to ASD(Bishop *et al*., 2011; Leroy *et al*., 2013; Simons VIP Consortium, 2012). In a study, the particular CNV region of chromosome 15(15q11.2) was linked to autistic controls in two brain areas with dose-dependent structural and functional effects (Stefansson *et al*., 2014; Rylaarsdam and Guemez-Gamboa, 2019). Duplication of chromosome 7 is characterized by delayed motor signs, and neurological abnormalities and is a significant pathogenic risk factor for ASD development. Chromosome 7(7q11.23) consists of many genes including the (elastin gene) ELN is related to WS (Pinelli *et al*., 2020). There is a recurrent 1.5-1.8-Mb heterozygous duplication of the Williams-Beuren syndrome (WS) which is a cardiovascular disease characterized by pulmonary stenosis. Deletions of more than 1.84 Mb including the HIP1 gene have been found to be related to severe intellectual disability (Pinelli *et al*., 2020).The structural variants of chromosome 16, 16p11.2 duplications including the 25 genes in this region have been found to be highly active during nervous system development and for the proper formation of neurons (Blaker-Lee *et al*., 2012; Golzio *et al*., 2012).

Table 1. Monogenic disorder leading to syndromic ASD

Monogenic Condition	Associated Gene and its function	Mutation & Mechanism	References
Rett Syndrome (leads to X-linked ASD)	MECP2 on Xq28 chromosome (methyl-CpG-binding protein 2) Global translation repressor	Missense, truncating Impaired neuronal excitation and inhibition at the circuit leveland alters neurotransmitter metabolism	(Zappella *et al*., 2003)
Fragile X	FMR1 CGG repeat (> 200 repeats) in the 5' untranslated portion Translation repressor	Repeat expansion Alteration in Synaptic function and plasticity	(Hagerman *et al*., 2010)
Tuberculosis	TSC1 (TSC Complex Subunit 1&2) (chromosome 9q34), TSC2 (16p13.3) mTOR inhibitor	Missense, truncating Alteration in an imbalance between excitatory and inhibitory neurotransmitters	(Vignoli *et al*., 2015)
Angle man	(UBE3A) E3 ubiquitin ligase 15q11-13 Duplication of 15q	Structural variant Altered synaptic plasticity and memory impairment	(Kalsner and , Chamberlain, 2015)
Familial ASD	NLGN3/4 (Neuroligin 3) and NRXN1(Neurexin 1)	Synaptic adhesion	(Porokhovnik, 2019)

The recurrent microdeletion in 17q12 which encompasses the HNF1B gene (hepatocyte nuclear factor 1 homeobox B, the gene responsible for renal cysts and diabetes syndrome maturity-onset diabetes of the young (MODY)has been found to be strongly related to both ASD and schizophrenia. Therefore, a shared genetic etiology in a subset of cases and pointing to one or more of the 15 genes in the deleted interval as strong candidates for neurodevelopmental and psychiatric disorder among 24 patients out of more than 23,000 patients with ASD, developmental delay, intellectual disability, or schizophrenia has been reported previously (Moreno-De-Luca *et al*., 2010). The deletion of 22q11.2 in chromosome 22 occurs due to an interstitial chromosomal microdeletion in a length of 1.5 to 3 Mb of DNA and includes 40 genes. The microdeletion in this region results in Di-George syndrome. Both types of Copy Number Variations (CNVs) deletion and duplication in this region predispose an individual toward the risk of developing ASD (Lin *et al*., 2020). Almost 25 genes in this region have been found to be related to ASD in a report including 46 cases showing deletion and duplication of the 22q11.2 region (Clements *et al*., 2017). The genotype-phenotype complexity of ASD and several gene deletions, duplications, and gene mutations linked with associated abnormalities in ASD have been reviewed extensively with gene mutations, and chromosomal location in relation to clinical manifestation with symptoms (Vorstman *et al*., 2015). The hyposensitive syndromes such as Phelan–McDermid Syndrome due to deletion of 22q13 with a prevalence ranging in between 1:8000–15,000. The encoded protein of deleted 22q13 locus encoding for gene SHANK3 (SH3 and multiple ankyrin repeat domains 3), is a scaffolding protein in postsynaptic glutamate receptors NMDA (N-methyl-D-aspartate), mGluRs (metabotropic glutamate receptor), and AMPA (α-amino-3-hydroxy-5-methyl-4-isox) might lead to ASD (Moessner *et al*., 2007).

***de novo* Variants:** Studies estimated that of de novo pathogenic variations, roughly 5–7% are postzygotic, though estimates of up to 22% have been reported (Rylaarsdam and Guemez-Gamboa, 2019).

Immunogenetics of Autism: Autoimmune disorders increase the susceptibility risk of ASD e.g., rheumatoid arthritis, hypothyroidism, and type I diabetes. The mutation in human leukocyte antigen (HLA) genes located in class I, class II, and class III certain regions causing immune dysregulation, has been linked with alterations in functions of the developing brain leading to autism (Figure 2). HLA genes are located on the short arm of chromosome 6, many studies have found the major histocompatibility gene as the susceptibility gene for ASD among different ethnic groups (Warren *et al*., 1992; Sadeharju *et al*., 2003; Mostafa *et al*., 2014). Maternal HLA-DR4 can interact with environmental factors and maternal infections during pregnancy and may act as risk factor for ASD development by hampering the brain development of the fetus(Al-Hakbany *et al*., 2014). The familial studies have reported the maternal contribution of certain HLA-DR4 alleles to autism susceptibility, which might cause abnormal fetal brain development due to the triggered immune response.

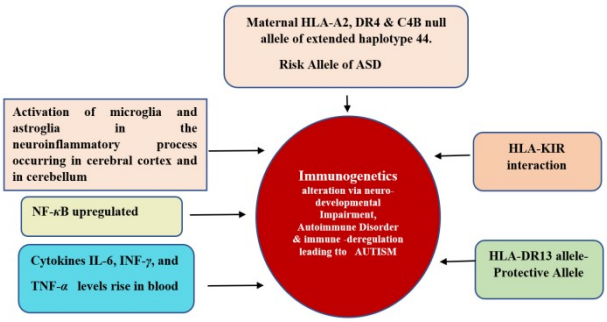

Figure 2: Immunogenetics mechanism of ASD

The shared epitope binding pocket (DRβ1*0401, *0404, and *0101) in the third hypervariable region of DRβ1 had a strong association with ASD (Warren *et al*., 1992). Other positively associated HLA alleles are the class I A*01, A*02, and B*07, while DRβ1*03 and some DQB1 alleles were found to be negatively associated with rates of autism (Mostafa *et al*., 2014; Al-Hakbany *et al*.,2014). The HLA-DRβ1 alleles including DR4 were reported in association with autism in Han Chinese population (DR4, DR11, and DR14). These had proven effects on deficits in intelligence and neuropsychological conditions among autistic children (Guerini *et al*., 2014). Torres *et al*., reported a protective association of DR13 in Caucasians (Torres *et al*., 2002). Another study claimed that the HLA-B*07 allele and linked haplotype A*01 B*07 DRB1*0701 DQB1*0602 might serve as a marker for genetic susceptibility to autism in the Saudi population (Torres *et al*., 2002). The HLA non-classical gene, HLA-G is responsible for protecting against the destruction of the fetal tissues by the maternal immune system. Guerini *et al* (2014) reported a 14-basepair insertion in the HLA-G gene more often in individuals with ASD and their mothers (Guerini *et al*., 2014). HLA-G interacts with natural killer cells as it is involved in innate immunity and is primarily expressed in placental tissues as a part of immune tolerance during pregnancy (Guerini *et al*., 2015). The activated HLA/KIR complexes lead to neurodevelopmental impairment and were found in autistic children and in their mothers (Torres *et al*., 2002; Guerini *et al*., 2015).

Diagnosis and Management: The diagnosis of ASD involves a comprehensive evaluation including clinical evaluation, medical history, and family history to rule out inheritance using three generation pedigree study, and physical examination, biochemical and molecular laboratory investigations. The available tests include autism-specific and metabolic panels for screening, diagnosis, and prognosis, myosin16 gene-related, targeted variant analysis including monogenic conditions e.g., fragile X syndrome, Robertsonian translocation, methylation analysis, whole exome, SNP-based microarray, neuro developmental disorder panel, and many more being added to this list, and these are commercially available (Figure 3). Given the multifaceted nature of ASD, molecular diagnosis and

testing provide the information to determine the underlying risk factors predisposing an individual towards ASD risk (Kreiman and Boles, 2020). The variation of heterochromatin region is linked with abnormalities in autistic children e.g., regions 1phqh, 9qh+, and 16qh- were found significantly more frequently in children with autism (Vorsanova *et al*., 2006). The high-resolution microarray or targeted panels are recommended by clinical and professional societies to use in specific conditions of testing the atypical phenotypic characteristics associated with ASD. Whole exome sequencing is in use for ASD and is considered investigational, whereas chromosomal microarray analysis (CMA) is the first-line recommended test for confirmation for indications like ASD, intellectual disability, and gross structural or functional anomalies (Chang *et al*., 2019). Trio (Child and parents) sequencing is used to find the de novo variants, not present in parents, especially in severe cases of ASD. CMA is mainly used for the indication of suspected chromosomal duplications or micro-duplications and deletions or micro-deletions conditions. Clinical interpretation is based on phenotypic expression, the CNV size, the gene content within the CNV region, de novo status, and the relative frequencies of similar CNVs in available clinical databases of ASD. The clinical significance of CNVs remains a challenging task and requires extensive searches of databases from the literature. Examples of databases used for reference and interpretation include the Database of Genomic Variants UCSC Genome Browser, Simons Foundation Autism Research Initiative (collated more than 900 genes associated with autism) and Autism Chromosome Rearrangement Database, and many others added to the list (http://dgv.tcag.ca/dgv/app/home; http://genome.ucsc.edu; https:// sfari.org http:// projects.tcag. ca/autism). The identification and interpretation of genetic variants by using Next generation sequencing (NGS) has been in use for the diagnosis of ASD. NGS-based targeted gene panels and exome sequencing are other high-throughput tests used to detect small DNA sequence variations but not structural ones. Several NGS-based uses of whole genome analysis and gene panels targeting known ASD genes are commercially available. In addition to the clinician, family, caregivers, school and college teachers, and social workers, everyone makes a significant difference in improving the life of ASD patients in many ways.

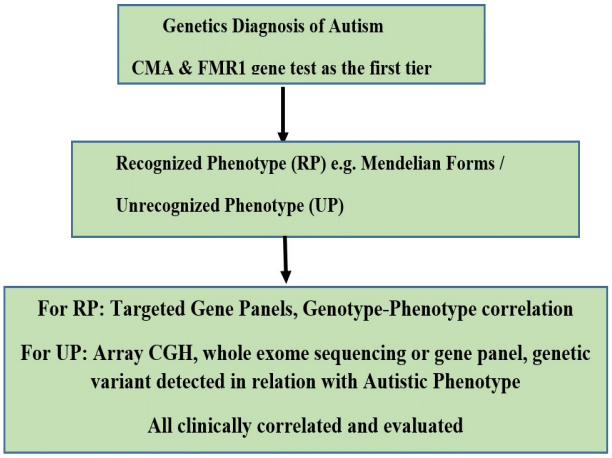

Figure 3. Diagnostic algorithm in ASD

Future Directions: Autism is not a single entity but a continuum of genetically and epigenetically diverse risk factors. The strong interplay of multiple genetic and epigenetic interactions makes it a complex and challenging disease to be treated accurately. Tackling the ASD pathophysiology which varies from individual to individual is possible via evaluating the overall risk factors (ASD risk genes patterns and epigenetic causes). The 360^0 management of ASD requires proper diagnosis, care, and family support, with therapeutic measures with drugs prescribed by clinicians in its treatment and neurobehavioral therapies. However, the interventions are added as per the case requirement. The use of advanced molecular techniques e.g., CMA and NGS have made it possible to confirm the accurate diagnosis of ASD and to plan further therapeutic management.

Conflict of Interest: None declared.

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