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DEVELOPMENTS IN BIOLOGICAL ADVANCEMENTS OF DISORDER OF AUTISM SPECTRUM

AMJAD HUSSAIN[*1], DR. JOICEY P. MANICKAM[2] AND RAYEES ZAHOOR SHAH[3]

1: Ph.D. Research scholar at PG and Research Department of Rehabilitation Science, Holy Cross College (Autonomous) Tiruchirappalli, Affiliated to Bharathidasan University, Tiruchirappalli

2: Associate Professor, PG and Research Department of Rehabilitation Science, Holy Cross College (Autonomous) Tiruchirappalli

3: Ph.D. Research scholar at PG and Research Department of Rehabilitation Science, Holy Cross College (Autonomous) Tiruchirappalli, Affiliated to Bharathidasan University, Tiruchirappalli

***Corresponding Author: Mr. Amjad Hussain: E Mail: amjed.wani@yahoo.com**

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ABSTRACT

The field of autism inheritance has seen tremendous growth in the past four and a half decades with an ever-increasing array of findings. As of right now, we are aware of the fact that disorder of autism spectrum is amongst one of the most strongly inheritable conditions with very little influence from the environment. The current literature also indicates that typical gene variations with minor implications and rare variants with substantial effect sizes all increase the likelihood of autism. These findings expose the enormous variation in disorder of autism spectrum and question established diagnostic parameters. In the current review, we take a look at a handful of major developments that are influencing our comprehension of disorder of autism spectrum today and discuss the implications for medical professionals.

Keywords: Autism, Genes, Inheritance, Environment, Diagnostic Parameters, advancements

INTRODUCTION:

The past forty-five years have seen a significant evolution in our comprehension of disorder of autism spectrum. When the research on twins and families revealed disorder of autism spectrum autism to be one amongst the greatly inheritable conditions, we have evolved from an era in which the influence of genetics was unclear.

These family-centred research served as the impetus for molecular investigation on genes, which in recent times have produced a expanding body of dossier on possible biological insights along with an rising amount of reported gene advances related to disorder of autism spectrum. In the present review study, we want to examine how new research is influencing our comprehension of disorder of autism spectrum and how new results could help doctors. These conditions are regarded by certain individuals as high penetrance or syndromal types of disorder of autism spectrum. Nevertheless, which we shall cover subsequently, recent discoveries in genetics and biology have shown that it is impossible to distinguish amongst widespread multifaceted disorder of autism spectrum and uncommon monogenic in nature autism.

Autism Heritability: An Overview of Earlier and Contemporary Twin and Family Studies:

Tick and colleagues' most current meta-analyses **[1]** of all documented twin-study investigations of autism/autism spectrum disorder also produced an elevated hereditary figure ranging from 64–91% with no discernible associated environmental influence. These authors demonstrated that if the estimated prevalence rate of autism is incorrectly specified for the study population (1% instead of 5% which is the appropriate figure for a broader autism phenotype), this essentially results in an increased non identical (dizygotic DZ) twin correlation but does not affect identical (monozygotic MZ) twin correlations, thereby resulting in a reduced heritability estimate and a stronger shared environmental contribution. The researchers do note that distinct kinds of designs are needed to thoroughly evaluate the impact of initial exposures, as the proposed approach was limited to looking at genetic markers shared between sisters. When combined, these research on twins offer compelling proof that autism is mostly a hereditary disorder with minimal environmental influence.

What the Autism Phenotype Tells Us Regarding Families and Twin Investigations:

According to an investigation **[2]**, research on families have indicated that the greater occurrence of pragmatic linguistic impairments, social deviations, and unique personality traits including nervousness and isolation in relatives of probands with autism may be explained by familial vulnerability to disorder of autism spectrum **[3]**. According to the majority of studies **[4,5]**, there is a high genetic association between autistic phenotype and diagnoses, and estimations of heritability remain consistent throughout the usual population ranges and extreme autism scores. The greatest current and extensive population-centred analysis **[1]** looked at the results of 2,256 MZ twin pairs and 4157 DZ pairs at the ages of 8 using the Childhood Autism Spectrum Test (CAST). In this case, estimations of heritability for individuals who had high autism scores were not significantly different when compared to those who had lower scores. The results obtained demonstrate that there exists no precise line that separates an autism diagnosis from the broader autism phenotype, as do data from family studies.

The overlapping between autism and other neurodevelopmental disorders in early years:

The significant degree of comorbidity that autism exhibits has become well acknowledged, and population-centred research on twins have repeatedly found an extensive genetic association between autistic features and other neurodevelopmental traits and disorders.

For instance, a twin research investigation conducted in Sweden revealed that tic disorders, learning difficulties, and motor coordination issues are all associated with disorder of autism spectrum. It was also found that autism is highly inheritable, with more than three quarters of its genetic variability shared with ADHD **[6]**. According to the research, relatives of people with autism are not solely more likely to experience ADHD and other neurodevelopmental disorders than people without autism, but they additionally have a higher chance of developing autism plus the wider autism phenotype. Nonetheless, data from research on twins and families support the positions adopted by the DSM-5 and ICD-11 in classifying neurodevelopmental disorders in children and allowing co-diagnosing ADHD and autism.

Gene-Environment Interaction:

Despite the significant heritability of autism, environmental factors also play a role in its explanation. There have been a lot of review writing done on the connection between autism risk and environment **[7]**. Given the current understanding of the linkage between various environmental risks and genetic

vulnerabilities, several of the prenatal and initial life factors linked to autism may have their origin s in the gene-environment relationship. Numerous prenatal exposures, like as smoking during pregnancies, have been linked to mother's genetic susceptibility to ADHD. But as of now, maternal autism genetic vulnerability has not shown comparable results **[8]**. Youngsters having disorder of autism spectrum are more likely to experience abuse and become victims of bullies **[9, 10]**. According to genetic research, these exposures may be linked to hereditary risk and background family history **[11, 12]**. A distinct notion known as "gene-environment interplay" describes the phenomena whereby genetic susceptibility or the background genotype influences how environmental exposures affect phenotypic.

Despite being demonstrated to demonstrate an impact in animal research, strong evidence linking the interaction of genes and environments to an elevated likelihood of autism has not yet been obtained.

Molecular Genetic Methods in the Study of Disorder of Autism Spectrum:

The amount of available molecular genetic research on autism has increased dramatically during the past ten years. In medical, psychiatric, and social science genome-wide investigations, genomic variation has been examined to look for connections amongst particular variants and characteristics or disorders. According to an inquiry, genomic variation might be classified based on its population's frequencies plus the extent to which it affects the sequence of DNA or structure. Single nucleotide polymorphisms (SNPS; frequency > 5%) are tens of thousands of frequent gene variants that are compared between subjects and controls in genome-wide association studies (GWAS) **[13]**. Employing case-control cohorts and familial in nature layouts, several genome-wide research studies have investigated the role of uncommon structural and sequence variations with greater impact sizes. In the literature, uncommon DNA variants can also be referred to as mutations, despite suggestions that the word "variant" nought to be used instead **[14]**. Within the community, autism genetic susceptibility might be thought of as a risk continuum, with individuals who have a clinical disorder at one end of the susceptibility curves. The majority of risk among individuals appears to be caused by prevalent gene variants; stochastic and environmental factors are also likely to contribute to the conversation and as we will discover, rare variants function in concert with these other factors to shift a person's

vulnerability along the risk continuum towards disorder.

The Influence of Typical Gene Variants to Autism:

Notwithstanding the strong heritability of autism and the long-standing belief that prevalent gene variants significantly increase individuals risk, individual gene variants are only now being identified. Five genome-wide significant loci were found in the most recently genome-wide meta-analysis, which included 27, 969 controls and 18,381 autistic individuals **[15]**.

In several fields of medical care, polygenic risk scores in conjunction with clinical factors are seen to be possibly beneficial prognosticators and indicators of illness onset, for instance among those with elevated risk **[16]**. Additional examination of the Danish database ICD-10 diagnosis records for the Danish iPsych cohort—which consisted of 22,664 controls and 13,076 cases—was conducted by the investigators of the biggest GWAS on autism. SNP inheritance was shown to be threefold greater in individuals with autism who did not also have an intellectual handicap in contrast to individuals who did. Before the release of the GWAS results, it became well-known that approximately one-third of people with autism were also described as "savants" due to their exceptional cognitive abilities **[17]**. Observations such as preliminary language deterioration in some autistic individuals and the typical teenage start of concomitant seizures are among several other remarkable clinical findings. It is unclear the way these clinical data relate to the most contemporary genetic discoveries on autism and IQ.

A further conclusion from GWAS reveals that prevalent variants that capture genetic accountability for disorder of autism spectrum diagnoses (using polygenic risk scores and disequilibrium in linkage (LD) score regression) in order to indicate overlap with attributes associated with disorder of autism spectrum and population social-communication **[18-21]**. Hence, the results of research on twins and molecular genetic research agree that autism is situated on the extremity of a continuum.

Uncommon Genetic Variants:

Compared to the results of GWAS, studies on uncommon genetic variations (<1% frequency) related to autism have so far produced considerably more conclusions. In broad terms, uncommon variations typically exhibit greater impact sizes in contrast with typical variations. Initially, copy number variation (CNVs) was the primary emphasis of the entire genome uncommon variant searches. Such DNA areas with thousands to

millions of base pair variances—the fundamental constituents of DNA—that have been replicated or removed in comparison to a benchmark genome are known as copy number variants. Despite being big, these deletions and duplications, which can affect numerous genes, are way too minimal to be visible under a light microscope. Contemporary sequencing investigations have concentrated on uncommon variations involving insertions or deletions of base pairs (indels) plus modifications to a single base pair referred to as single nucleotide variants (SNVs). Uncommon variants may appear de novo, during which the variant emerges in the parental germline (oocytye or spermatozoa), or subsequently, after fertilisation, when they are recognised as post zygotic somatic variants **[22]**. Infrequent variants may additionally be propagated from parent to descendants (inherited). Such variations generally seem to increase the chance of autism.

Variations in Copy Numbers:

A researcher **[23]** undertook a preliminary research study with 264 families: 118 "simplex" households having only one autistic kid, 47 "multiplex" families that included multiple autistic brothers and sisters and 99 control families without diagnoses of disorder of autism spectrum. In contrast to typical controls (1% rate), the researchers found that people with autism had a higher burden of uncommon de novo chromosomal structural variants, or copy number variants (CNVs), which are deletions and duplications. In simplex cases, the de novo CNV rate was 10%, while in multiplex cases, it was 3%. The identical findings were seen in later research, particularly in simplex families, where there was a higher incidence of uncommon de novo CNVs in autism **[24, 25]**. Nonetheless, several documented cases of recurring autism linked to de novo CNVs exist **[26]**. 1q21.1, 3q29, 7q11.23, 16p11.2, 15q11.2–13, alongside 22q11.2 are among the replicated CNV areas **[26]**. Furthermore, CNVs linked to autism are substantially pleiotropic; plenty of these identical CNVs have also been linked to an increased likelihood of schizophrenia, ADHD, and intellectual disability **[27-29]**.

Research on Sequencing:

71 autism risk loci were found in the work by Sanders and co. **[30]**, which integrated analysis of exome sequencing variations, such as single nucleotide variants (SNVs) alongside indels (small insertions and deletions), with de novo CNVs. The most extensive exome sequencing investigation of autism ever conducted yielded insights after assessing 11,986 cases of autism, including 6, 430 proband-parent trios and 5556 cases with

8809 controls. 102 autism risk genes have been implicated as a result of the integration and analysis of these data **[31]**. The quantity of genes implicated is expected to expand considerably, possibly to hundreds at minimum, with the advent of whole genome sequencing **[32-34]**. Preliminary results point to potential roles for tandem repeat sequences (repeated nucleotide sequences, like those found in fragile X syndrome) and non-coding variations **[35]**. Nevertheless, considerably bigger proportions of samples will be needed to produce highly trustworthy breakthroughs in genetics because sequencing the whole genome entails probing a far greater number of variations than whole exome sequencing **[36]**.

These research on uncommon variants of autism provide a number of findings. Firstly, compared to common variants, uncommon variants for autism have been discovered at a far higher rate. The second problem is that, despite penetration for numerous mutations seems to be widely variable, the observed uncommon variants, in contrast to prevalent variations, have bigger impact sizes (e.g., odds ratio of > 20 **[37]**. Thirdly, de novo uncommon mutations related to autism are found throughout the spectrum of intellectual aptitude, despite being over-represented in individuals with concomitant intellectual disability. There is a fourth aspect regarding the prevalence of autism in men. According to earlier family and twin investigations, siblings of female autistic individuals are more likely to develop autism than siblings of male autistic individuals **[38]**. Lastly, it is abundantly evident from molecular genetic research that autism is not only exceedingly variable in terms of its clinical presentation, but also extremely diverse in respects of its molecular genetic aetiology, with uncommon variations related to autism pleiotropic similar typical variants.

Genomics to Physiology and Therapy:

Genetic testing and counselling are gaining importance among clinicians and families impacted to be an outcome of scientific advancements that have brought about a general understanding that genetic contributions play a significant role in the aetiology of autism **[39, 40]**. Siblings of probands normally had autism rates ranging from 10% to 15% **[41]**. According to the female protective impact, there is a larger chance of autism in male siblings compared to female siblings, and this risk increases whenever the proband is a woman **[42-44]**. Furthermore, if a pair of siblings have been previously impacted, the chance of recurring increases significantly and has been estimated to reach 30–50% **[45, 46]**.

But there are undoubtedly a lot of difficulties with genetic testing for autism. Firstly, clinical interpretation of the results is challenging. Variable penetrance, expressiveness, and strong pleiotropy are characteristics of rare variations linked to autism risk **[47-50]**. Secondly, while detected mutations might be linked to an increased likelihood of autism, it is not often evident if these variations are causative for a particular person. Thirdly, it's critical to take into account any possible drawbacks to genetic tests. In general, we are of the opinion when autism is combined with ID or presents in a complicated manner (comorbid dysmorphic features, a medical situation), being referred to clinical genetics services for examination and counselling is worthwhile. However, we also think that decisions about referrals will be made quickly, and they may vary depending on the particular circumstances and case mix of the clinic. Upcoming referral guidelines and national decisions will be based on results from studies related to technologically advanced genetic advances along with the clinical utility of genetic testing, health services and social resource availability, and more. This is because there presently exists no proof that genetic testing for autism is economically viable **[51]**.

CONCLUSION:

Over the past forty years, a great deal of advancement has already been achieved regarding our comprehension of the genomics of autism. Knowing that we understand, it happens to be one of among the most inheritable disorders and usually has a multifactorial in nature aetiology. Vulnerability is influenced via both typical and uncommon genetic variations, as well as there is a lot of curiosity in applying gene findings to learn more about the biological mechanisms behind autism. Nonetheless, there is a great deal of clinical and genetic variability in autism. Even if the genetic breakthroughs are a significant advancement, clinical investigation must be connected to this effort. An additional urgent clinical concern, considering the general population's curiosity regarding genetics, is the appropriate approach for communicating genetic data with families and to employ it in a manner that is both morally just and practically helpful.

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