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A REVIEW ON MOLECULAR IDENTIFICATION OF COMMON AUTISM GENE IN AUTISTIC SPECTRUM DISORDER, INTELLECTUAL DIABILITY& AUTISTIC LIKE BEHAVIOUR

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ABSTRACT

Among several developmental disabilities Autism is a complex lifelong brain development disorder collectively known as Autism spectrum disorder (ASD).Characterized by significant impairment in reciprocal, social interaction & communication skills. The genetic basis of ASD has been pursued aggressively over the past few decades.ASD is highly heritable disorder of complex &heterogeneous nature. However owing to its polygenic nature & clinical heterogeneity majority of the identified genes through whole genome screening are those known to function in brain development. The present studies review methods to identify common candidate autism gene in several intellectual disabilities including autism & also in autistic like abnormalities seen affecting individuals with normal intelligence.

Autism spectrum disorder (ASD) is an developmental disability characterized by a complex neurodevelopmental disorder that appears during the first three years of infancy and lasts throughout a person's life. The Centers for Disease Control and Prevention (CDC) reported in 2012 that approximately 1 per 88 children in the United States has a diagnosis of ASD.Muhle ,Ret al.,(2014)reviewed on Autism as a syndrome but not a disease with multiple nongenetic and genetic causes. In one of the review Talkowski et al., (2014) stated that genetic basis of ASD is highly heterogeneous, with hundreds of genes capable of conferring varying degrees of risk. Moreover, many genes that have been implicated in ASD also appear to be risk factors for

related neurodevelopment disorders, as well as for a spectrum of psychiatric phenotypes . Thus scarcity of specific genetic causes has sustained persistent skeptics about role of definite gene in ASD or other intellectual disabilities or in autistic like behavior. Currently molecular approaches for identifying genetic loci depends on whole genome screen, searching for linkage of autism to shared genetic markers in population of multiplex family(Muhle ,R et al ., 2014). Investigators apply genome wide screening technology to uncover specific chromosomal regions that affected individuals inherit more often than predicted by chance. These studies entail multiplex family screening using microsatellite markers, where submicroscopic deletion or duplication are analyzed for copy number variation(CNV)through methods like comparative genomic hybridization & single nucleotide polymorphism arrays.

Molecular studies using a 1Mb genome-wide array, Jacquemont et al.,(2006) identified clinically relevant CNVs in 27.5% of individuals with autism and dysmorphology, who previously had a normal karyotype as determined by routine cytogenetic studies. Sebat et al.,(2007) analyzed a denovo copy number mutation in autism , using an oligonucleotide array,& found denovo copy number changes in 10% of children from simplex families (i.e., autism in a single family member) and 2% from multiplex families (i.e., autism in multiple family members) compared with 1% in controls. Using a dense genome-wide single nucleotide polymorphism array, Marshall et al.,(2008)found unbalanced CNVs in 44% of unrelated families with autism that were not present in control families. Christian marshal et al., (2008) combined cytogenic study & microarray based method to identity copy number variation among structural variation chromosome reported that copy number variation at 16p 11.2 at 1% frequency leads to ASD. Glessner et al.,(2009) adopted a whole genome CNV study in ubiquitin & neuronal genes using 550,000 single nucleotide polymorphism markers on a cohort of 859 individuals with ASD and 1,409 healthy children of European ancestry revealed several pathogenic genomic changes in genes encoding neuronal cell adhesion molecules(NRXN1, CNTN4, NLGN1, and ASTN2) and in genes involved in the ubiquitin pathways (UBE3A, PARK2,RFWD2, and FBXO40). Kai wang&Haitaozhang, (2009),whole genome studies, where six single nucleotide polymorphism between cadherin 10(CDH 10) & Cadherin 9(CDH 9) gene encoding for neuronal cell adhesion molecule revealed neuronal pathogenesis in ASD. Salyakina,D et al.,(2011) genotyped ASD families for polymorphism in SNPs to detect CNVs that may contribute to ASD susceptibility & found that CNVs overlap with regions on 7p21.3 and 15q24.1 that have been previously reported in ASD individuals and two additional CNVs on 3p26.3 and 12q24.32 occur near

regions associated with schizophrenia. Lesch K,P et al.,(2013)Using high-resolution array comparative genomic hybridization (CGH)detected CNV comprise 4 deletions and 13 duplications with approximate sizes ranging from 110 kb to 3 Mb. Two CNVs occurred de novo and nine were inherited from a parent with Attention-deficit/hyperactivity disorder (ADHD).Williams N,M,et al.,(2013) used several Single nucleotide polymorphisms (SNPs)to detect CNV common to both Comparative Genomic Hybridization & Whole Genome screen found excess of chromosomal duplication in chromosome 16p13.11 were genotyped in the ADHD, Autism & Schizophrenia. Gazzellone M,J, et al.,(2014)carried out whole genome screening method to identify CNV in Han Chinese individual with ASD & reported rare inherited CNVs showing duplication of 24kb was identified at YWHAE a gene previously implicated in ASD & other neurological disorder .other inherited l candidate genes including GRID2, LINGO2, and SLC39A12 to chromosomal loci 16p13.3, 16p11.2, 17p13.3-17p13.2 were also reported .Although CGH array & SNP array are successful tool used for identification of over 10 genes, till to date many genes are identified some with known & others with unknown function may be because such huge identified sequences positive findings in one study often fail to replicate in other studies, and a consistent picture of susceptibility loci in autism is still lacking.

Cytogenetic studies that may guide molecular studies by pointing to relevant inherited or denovo chromosomal abnormalities in affected individuals & their families. These cytogenetic assays have long been used to uncover chromosomal defects in patients with autism on the basis of visible break points, duplication ,deletion & translocation through high resolution staining methods Based on a recent systematic review, cytogenetically detectable chromosome abnormalities are found in 7.4% of ASD cases(Xu et al. ,2004;vorstman et al.,2006). The highest occurrence of events is observed in syndromic forms of ASD(vorstman et al.,2006).Balanced translocations and inversions accounted for 17% of rearrangements. Whereas the most frequent anomaly observed is maternally derived duplication of chromosome 15q11–q13 in 1%–3% of cases.Veenstra-Vanderweele, J, et al.,(2004)little is known about the proportion of inherited compared to spontaneous karyotypic changes at other sites. With chromosome abnormalities as the initial step to identify ASD candidate loci, mutations have most convincingly been reported in SHANK3on chromosome22q13.Durand etal.,(2007);Moessner, R,et al., (2007),two neuroligin

(NLGN3 and NLGN4) genes on the X chromosome .Jamain, S, et al., (2003),identified the neurexin 1 gene on chromosome 2p16.4,11,12 (Jamain, S et al 2003; Chubykin et al 2007)

Evaluation of candidate genes known to affect brain development is also significantly linked to autism many of the earliest known genes associated with ASD were identified based on the fact that they also caused broader, multi-organ syndromes, and several such syndromes have ASD as a frequent manifestation. Tuberous sclerosis syndrome (TSC) is an autosomal dominant disorder, associated with a high spontaneous mutation rate that manifests with cardiac tumors, skin lesions, lesion in other organs, including the brain. Up to 50% of affected children show autistic symptoms, most in the setting of intellectual disability (Wiznitzer, 2004). So far, there is no clear understanding of the determinants of ASD symptoms in patients with TSC. Recently, animal models have shown that there are widespread abnormalities in myelination (Meikle et al., 2007), axonal connectivity, and other developmental events in mice heterozygous for TSC mutations, suggesting that humans with TSC mutations may also have widespread neuronal abnormalities beyond the focal lesions that are only evident with newer, sophisticated magnetic resonance imaging (MRI) methods (Choi et al., 2008).

Fragile X syndrome, associated often with mild dysmorphic features of the ears and head, is associated with ASD in about 50% of children and can rarely present with ASD in the absence of severe intellectual disability. Fragile X is probably the most common single-gene disorder causing ASD (Belmonte and Bourgeron, 2006; Bolton, 2009; McLennan et al., 2011).The progressive neurodevelopment disorder Retts syndrome is caused by mutations in the X-linked gene MECP2(Amir et al., 1999). RTT is characterized by normal development in the first 6–18 months of life, followed by loss of any acquired speech and the replacement of purposeful hand use with stereotypic movements. MECP2mutations, as well as increased gene dosage, can result in a range of neurobehavioral abnormalities, including autism, mild learning disabilities, X-linked mental retardation, and infantile encephalopathy (ChahrourandZoghbi, 2007). RTT phenotypes overlap with nonsyndromic autism, and RTT is included in DSM-IV. MECP2mutations have been reported in ~1% of children diagnosed with autism (Moretti and Zoghbi, 2006), and males with MECP2duplications often present with autism (Ramocki and Zoghbi, 2008; Ramocki et al., 2009). The MECP2 protein regulates the expression of its target genes, and a better understanding of its role in maintaining neuronal function will have implications for autism.

A plethora of other Mendelian syndromes are associated with autistic symptoms as well, but less commonly or universally studied pertaining to ASD. As many as 300 different genetic syndromes have been reported at some level to be associated with ASD, although the proportion of patients with the genetic syndrome that manifest ASD is highly variable, so that the strength of these associations is variable. It is important to note that, given that up to 1% of all children suffer from ASD, ASD will of course at some point be reported in children with any possible condition as a coincidence, and larger series will eventually be needed to prioritize which genetic syndromes are truly most commonly associated with ASD

Conclusion

The current scenario of diagnosis in ASD is limited largely to clinical profiles, rating scales, neurobiological assessments such as nueroimaging, neuropsychological profile ,eye movement recording. Few attempts are made to study genetic condition through chromosomal anomalies in autistic disorder showing 50.6% cases with fragile X syndrome , 30.5% cases with other autosomal anomalies and with some of the single-gene disorders, like tuberous sclerosis and phenylketonuria. On the basis of study reports of ASD candidate genes are linked to chromosome 22,16,7,15 & X in different loci. .Though whole genome screening research has nearly identified 18 over candidate genes no gene identified to date exclusive known to cause ASD and nothing else; rather, the genes found to be altered in ASD are also found to be altered in other development brain disorder that do not have any ASD clinical symptoms. Perhaps designing a new protocol for Autism gene identification could enable molecular diagnosis, as well as testing gene carriers among parents will speed up diagnosis.

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