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Chromosomal Microarray Analysis as a first-tier test in autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a brain-based, developmental condition. Children with ASD have communication difficulties, narrow interests and repetitive behaviour. ASD is defined by a certain set of behaviours and is a "spectrum condition" that affects individuals differently and to varying degrees. The role of copy number variations with specific gene regulation and human diseases is already well documented. Chromosomal microarray analysis should be considered as a first-tier genetic diagnostic test for autism spectrum disorders because of its strong ability to detect chromosomal abnormalities. The Chromosomal microarray analysis (CMA) plays an important role to rule out the CNVs that can cause the Autism. The reported yield of the array is approx. 10-15 %. Whereas the diagnostic yield of G banded karyotyping is only 3%.The diagnostic yield is found to be significantly higher when more complex abnormalities such as ID, Dysmorphism are also present along with ASD. In this study, it was explained about CMA for 100 postnatal cases of autism, as a first-tier test followed by G banded karyotyping.

Keywords— *ASD, Microaaray, CMA*

1. INTRODUCTION

In recent years there have been many improvements in our knowledge and understanding of autism spectrum disorder (ASD). Autism Spectrum Disorder (ASD) is a pervasive developmental disorder affecting many areas of functioning. The core symptoms are deficits in social communication and social interaction and restricted, repetitive patterns of behaviour, interests or activities. Many individuals with ASD also experience sensory difficulties, such as hypo- or hypersensitivity to light, sound, colour, smell, taste or touch.

Autism spectrum disorders (ASD)[1] are multifactorial neurological disorders in which social and verbal communication skills get affected. Repetitive or stereotyped behaviour such as rocking, hand-flapping, or repetition of words or noises (echolalia) and restricted interest are the main identification of this disorder. It is a heterogeneous developmental disorder, having a strong genetic component which transfers generation to generation and has a rather complex etiology. It is essential to understand the pathogenesis of ASD. It appears in very early stages of development of life, varies in degree of severity, the spectrum of ADS is not defined properly. There are many cases which fall outside of the category but still have ASD. Many ASD children may have mild to severe intellectual disability (ID) and some have average or above average intellectual abilities. It is noted that some individual with ASD showed excellent output in their work such as musician, mathematics, with a sharp memory. Some do not speak at all; some can speak fluently but with defects like a monotone, on the same topic for a long time. The ability to community changes over time. The prevalence of ASD increasing tremendously. It is usually diagnosed between ages 2 and 4, when a child started to learn communication and social skills, such as learning to play with others. Hence very common amongst the school going children, and they referred to Geneticist to find out the genomic cause. It affects the social, academic, and employment stages, which increases the possibility of having psychiatric problems such as anxiety, depression, obsessive-compulsive disorder, and eating disorders.

The number of ASD individuals has been increasing rapidly over the past few decades.
According to the CDC (centre for disease control and prevention) 27 March 2014, United state study[3], the prevalence of ASD is 1:68 (1 in 42 boys, 1 in 189 girls)[4].

There are more than 1,000 genes have been reported to be associated with ASD, but a large number of genes are still in study[8]. Environmental risk factors such as advanced maternal age, birth complications also contribute up to 40 % of the risk, but the risk increases tremendously when there is some gene variation happened along with this. ASD have a tendency to pass on generation

to generations but the mode of inheritance is still unclear. There are many genes which are responsible for protein synthesis required for brain mechanism, causes the ASD. The protein produces by them responsible for multiple functions of the brain with a variable degree of effects.

CNVs (pathogenic, benign, VOUS) - copy number variations are the gain or loss of genetic material. The size of CNVs is ≥ 1Kb. CNVs can be categorized as pathogenic, VOUS(variation of unknown significance) or benign based on region involved, gene content, and inheritance. Genes involved in the CNVs and adjacent to the CNVs are subjected to examination. CNVs that involved disease-causing autosomal dominant genes are called pathogenic.

2. AIM OF CURRENT STUDY

In our retrospective-prospective study, our aim was to find out the role of microarray analysis as a first tier test as compared to G banded karyotyping in patients with Autism with dysmorphism, and developmental delay.

3. MATERIAL AND METHODS

3.1 Subject selection criteria

We have enrolled 100 patients of autism, speech delay along with variable Developmental delay, referred by clinical geneticists and Paediatricians in New Delhi. The average age of children was 5 yrs which are ranging from 1year to 10 yrs.
Children were categorised on the basis of the following criteria:

- Isolated Autism,
- Autism with ADHD, speech delay, hyperactivity
- Autism with variable Developmental delay and Dysmorphism[2]

3.2 Technique used

Microarray-based comparative genomic hybridization – first line test

Whole genome microarray-based hybridisation was performed as a first tier test on AGILENT[13] catalogue 4x180K (CGH+SNP) array slide. The software utilized for analysis is also based on UCSC build 37(hg19).

Chromosome banding analysis (GTG-banding)

Standard GTG banding analyses were performed on the heparinized peripheral blood samples at approximately the 500-800 band level using standard techniques. The chromosomes[6] were analysed on **Metafer Slide Scanning Platform | MetaSystems** and the karyotype described according to the International System for Cytogenetic Nomenclature [ISCN, 2013].

4. RESULT AND DISCUSSION

No chromosomal abnormality was detected in 100 patients by karyotyping technique due to its limitations of resolutions which are 5-10 Megabase pairs(Mb) but simultaneously on the parallel side of the testing procedure it resulted in a yield of 29% chromosomal abnormalities by Chromosomal microarray analysis technique where the resolution (≥1 kilo Base pair) is much higher than Karyotyping technique.

Out of first randomly enrolled 100 patients there were only 20 females as compared to 80 males, which also concordant with the ratio(Female: Male) of 1:4 which is already been established in various other researches at different places in the world[11].

5. CONCLUSION

CNVs[9] are segments of DNA ranging from 1 Kb to several Mb. More and more CNVs can identify with the availability of new technology for higher resolution analysis of the entire genome. The chief characteristics and features of aCGH which makes it useful in the diagnostic field of genetics are to identified subtle deletion/ duplication which cannot be picked by routine karyotyping technique. Although the resolution of FISH is below 5Mb, it cannot be used for a whole genome, as it is a targeted approach. The probe used in this technique is of the known region. Many times it is used as a confirmatory test for known syndromes and microdeletion duplications.
The frequent use of aCGH in research and diagnostic field of genetics has increased the identification of known /unknown CNVs, that could be pathogenic non-pathogenic and variations of uncertain clinical significance (VOUS)[12]. The identification of CNVs depends on the resolution, target size, and the data extraction method.

The diagnostic yield of aCGH in our study was 29%. The chromosomal reports of all cases were normal, All the CNVs picked by aCGH were below microscopic resolution and missed by chromosomal study at 400-600 resolution level. It is proven that only karyotyping is not a complete diagnostic test for autism cases .aCGH should be preferred as a first line test to detect the CNVs causing the ASD.

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