Abstract ID:- 140

Abstract Topic:- Clinical Genetics

Abstract Title:- Exome Sequencing as first line of investigation in a cohort of 50 families with Syndromic Global Developmental Delay

Presenting author name & Institute :- Anjana Kar, Centre for DNA Fingerprinting and Diagnostics

Co-authors name:- Pragna Lakshmi, S J Patil, Shagun Aggarwal, Prajnya Ranganath, Mahesh Kamate, Ashwin Dalal

Co-authors institute:-Centre for DNA Fingerprinting and Diagnostics, Hyderabad, Mazumdar Shaw Medical centre, Narayana Hrudayalaya, Bengaluru, Department of Medical Genetics, Nizam Institute of Medical Sciences, Hyderabad, KLE Hospital, Belgavi, Karnataka, Diagnostics Division, Centre for DNA Fingerprinting and Diagnostics, Hyderabad

Aims:-Globally 3% of children are affected with Global developmental delay (GDD) with and without syndromic features. 40% of them are caused due to Genetic aberrations.Cases of GDD exhibit diverse symptoms where it is difficult to establish a specific diagnosis. Many patients undergo a long diagnostic journey at various other medical departments before necessary genetic testing to identify the cause of GDD. Use of exome sequencing as first line of investigation can provide an early diagnosis and improve the clinical management of disease. The aim of this study was to evaluate diagnostics and clinical utility of exome sequencing in patients with syndromic GDD.

Methods:- 50 patients (age range 1 Year to 23 Years) were recruited based on clinical evaluation by geneticist. Blood samples from proband, affected and unaffected siblings and parents were collected after taking informed consent. Solo exome sequencing (n=2 sib-ship, n=2 trio) was done using TWIST human exome capture kit. Sequencing data was analyzed using in-house GATK adopted pipeline. Variants were screened for MAF<0.01, protein coding or splicing, CADD> 20, and clinical correlation of phenotype. Variants were classified according to ACMG parameters. Sanger validation was performed to establish segregation pattern in family. For functional validation of variants mini-gene spicing assay, GAP-PCR, RT-PCR, q-PCR were used.

Results:- In year 2022 – 2023, a total of 50 cases with GDD with syndromic features were sequenced [Proband (n=50) and affected sibling (n=6)]. Exome sequencing analysis as first line of investigation led to identification of total of 28 variants in 26 cases (Homozygous n = 16, Heterozygous n=8 and compound heterozygous n=2) leading to diagnostic yield of 52%. Variants were classified as Pathogenic n= 13, Likely pathogenic n = 4 and VOUS n = 7. A total of 20 novel and 8 known variants were identified in the study.Proportion of homozygous n=16) variants were significantly higher (61.54%) in the study group due to practice of consanguineous marriage in families. In this study we identified variants for Fucosidosis, Alagille Syndrome 1, MOPD2, Bardet Biedl Syndrome, Cockayne Syndrome 2 etc. In 24 cases, we could not identify any disease-causing variants. The reasons for lack of diagnosis in some case may be due limitations of exome sequencing such as large deletion or duplications, gene inversions etc or due to lack of our understanding on variants at promoter, UTR or intronic regions.

Conclusions:- Our study indicates that, practice of exome sequencing as first line of investigation in cases with GDD with syndromic features for identification of genetic cause has a good diagnostic yield.

Keywords:- Exome sequencing, Global Developmental Delay, Variant identification, Bioinformatics pipeline, Diagnostics yield