Abstract ID: - 96

Abstract Topic: - Molecular and cytogenetic diagnostics

Abstract Title: - Diagnostic yield of exome sequencing in a cohort of 1134 individuals for rare genetic disorders.

Presenting author name: - Shreya

Presenting author institute: - CSIR- Centre for Cellular and Molecular Biology

Co-authors name: - Dr Aneek Das Bhowmik, Dr Karthik Bharadwaj

Co-authors institute: - CSIR- Centre for Cellular and Molecular Biology, CSIR- Centre for Cellular and Molecular Biology

Aims: - To study the diagnostic yield & clinical utility of exome sequencing in a cohort for rare Mendelian disorders & its effectiveness.

Methods: - Genomic DNA extracted from blood or umbilical cord fluid was used to sequence to mean ~100X coverage on Illumina Novaseq 6000 / MGIseq 2000 sequencing platform following the manufacturer's protocol. Library prep kits included Twist Comprehensive Exome enrichment kit, TruSeq Exome Library Prep kit, MGIEasy Exome V5 Library Prep Set, Illumina exome V8 & Agilent SureSelect CRE V2. The raw sequences were aligned to the human reference genome GRCh37/hg19 & variants were called using DRAGEN software (Illumina). Variant annotation was performed using ANNOVAR & ANNOTSV for location & predicted function. Common variants were filtered based on allele frequency in 1000 Genomes, EVS, ExAC, gnomAD, dbSNP, Indian Exome Database & our in-house exome database. Clinically relevant mutations were annotated using published variants in literature & databases like OMIM, ClinVar & HGMD. In-silico prediction software like SIFT, Polyphen-2, MutationTaster2, CADD & HSF3.1 were also used. ACMG guidelines were followed in reporting the variants.

Results: - Our cohort included a total of 1134 symptomatic patients ranging from prenatal samples to adults who had undergone exome sequencing. Primary findings were reported in 685 patients that harbored 824 variants of which 290 variants (22.69%) were categorized as pathogenic, 256 variants (20.03%) as likely pathogenic & 274 variants (21.43%) as VUS. About 401 variants were identified as novel findings & 380 variants have been submitted to ClinVar (Access ID: 507246). The cohort predominantly included variants with clinical features of neurodevelopmental disorder (N=143) followed by neuromuscular disorder (N=117). Of the 54 carrier screening & 28 trio-based screening samples in the cohort, variants were reported in 31 & 10 samples respectively. 11 variants in 8 genes were reported as secondary findings in 11 patients. Overall, 3 patients presented pathogenic variants, 5 patients presented likely pathogenic variants & 3 patients presented variants with variants of uncertain significance for genes in the ACMG gene list.

Conclusions: - The overall diagnostic yield of 60.93% (including variants of uncertain significance) is proof of how reliable exome sequencing is for the diagnosis & deciphering pathogenesis of monogenic

disorders. In a nutshell, it can be concluded that NGS-based tests for rare genetic conditions can be a potential tool to redirect the treatment specific to the condition.

Keywords: - Our cohort included a total of 1134 symptomatic patients ranging from prenatal samples to adults who had undergone exome sequencing. Primary findings were reported in 685 patients that harbored 824 variants of which 290 variants (22.69%) were categorized as pathogenic, 256 variants (20.03%) as likely pathogenic & 274 variants (21.43%) as VUS. About 401 variants were identified as novel findings & 380 variants have been submitted to ClinVar (Access ID: 507246). The cohort predominantly included variants with clinical features of neurodevelopmental disorder (N=143) followed by neuromuscular disorder (N=117). Of the 54 carrier screening & 28 trio-based screening samples in the cohort, variants were reported in 31 & 10 samples respectively. 11 variants in 8 genes were reported as secondary findings in 11 patients. Overall, 3 patients presented pathogenic variants, 5 patients presented likely pathogenic variants & 3 patients presented variants with variants of uncertain significance for genes in the ACMG gene list.