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Abstract Topic:- Clinical Genetics

Abstract Title:- Secondary findings in the research exome cohort: Spectrum and Clinical translation.

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Aims:-

- Study the prevalence of the secondary finding variants in our cohort.
- Compilation of clinical data of patients and their families and define the spectrum of presentation
- Study of the selected cohort of families with positive secondary findings to delineate the disease phenotype
- Study clinical impact in terms of treatment, preventive measures, and reproductive options.

Methods:- Study type: Observational cohort study

Sample size: 400 cases.

These cases were enrolled under the following research projects:

Indian Undiagnosed Disease Program (I-UDP) (IEC-2020-13-EMP-114).

The Indian Movement Disorder Registry and Biobank: Clinical and Genetics (IEC-2017-164-EMP99(A)).

Centre for molecular medicine at SGPGIMS-exploring genomic disorders-detection of copy number variations in cases with idiopathic mental retardation and autism (IEC-2011-07(I)-EMP-58).

Genomic Studies into limb malformations and related syndromes (IEC-2014-158-EMP-80).

Inclusion Criteria:

- Previous patients with exome sequencing/genome sequencing report having at least 1 variant in the secondary finding gene.

Exclusion Criteria:

- Patients who opt out of secondary finding analysis.
- Patients in whom these 73 variants are the primary findings.
- Trio analysis.

Study design:

Phase I:

Step 1: The internal data repository was used to obtain the genomic data of all the enrolled patients for further analysis. Collection of raw data of samples in FASTQ format.

Step 2: The gender check and family sample relatedness (kinship relationship coefficient range) were performed using Qualimap (version 2.2.1) and VCFtools (version 0.1.15), respectively.

Step 3: Realignment and reannotation of the SNVs: Sequenced reads were aligned to the Human Genome Reference GRCh38 (GCF 000001405.40 GRCh38.p14) using the BWA-MEM-2 algorithm (version 0.7.17). Annotation was done using the Annovar tool.

Step 4: Variant filtration was done for Pathogenic and likely pathogenic variants along with less than 1% population frequency variant in different categories of nonsense/stop gain, frameshift, canonical splice site, and stop-loss.

Step 6: After summing all this information, manual curation and review for the quality parameter was done with a table of 78 genes in ACMG secondary finding V3.1(2022).

Step 7: Subjects with Pathogenic/Likely pathogenic variants in the SF genes were listed.

Phase II:

Step 1: These selected subjects were called.

Step 2: Re-evaluation of the patient personal medical history, family history, and physical examination associated with the secondary finding.

Step 3: Confirmation of the variant by the Sanger sequencing in the index case as well as the family members.

Step 4: Genetic counseling was done after familial segregation.

Step 5: On the basis of the physical examination and the history a management plan was made. Framework of the patient management was tailored to an individual's specific needs. The management plan included the surveillance plan and symptomatic treatment plan when applicable. The patients and their family members with the positive findings are under follow-up.

Results:- After QC, 400 exomes were available. The average coverage was 92%. We calculated the coverage for the genes considered in this analysis and the average percentage of the bases with coverage of 20x was greater than 95%. We did manual curation for all the 78 secondary finding genes.

In the 400 exomes in our cohort, 30600 non-synonymous variants in the 78 SF genes had a MAF of less than 1%. The number of the secondary finding gene variants ranged from 52-98 in an individual. Out of 400 subjects of the cohort, eight of them had a predicted pathogenic deleterious variant(2.0%). One subject had two variants in two different secondary finding genes. The pathogenic secondary finding gene variants were not repeated in any of the subjects included in the cohort.

Sanger segregation was done in a total of 22 family members and Sanger validation was done in all 8 index patients.

4/9 Secondary findings were related to cardiovascular diseases, among them:

SCNA5 associated Brugada Syndrome, LMNA: Dilated cardiomyopathy 1A, MYH7: Dilated Cardiomyopathy, 1S, PKP2: Familial arrhythmogenic Right Ventricular Dysplasia.

2/9 were cancer-predisposing secondary finding genes which included PMS2 and RET gene. A pathogenic variant in RYR1 related to malignant hyperthermia was detected in one patient. . A pathogenic variant was found in the ACVRL1 gene associated with Hereditary Hemorrhagic telangiectasia type 2 in one patient.

Conclusions:- In a diagnostic context, secondary discoveries are crucial and should be viewed differently than sequencing data. In the autosomal-dominant state, secondary findings can be particularly significant because the autosomal-dominant pattern can be influenced by special characteristics like incomplete penetrance or variable expression, which is controversial and may account for the lack of clinical manifestations during the experiment. Ultimately, aside from the advantages of recognizing secondary results, the following are some crucial things to think about: They may have three possible causes: (1) they require family consent; (2) some may be connected to the underlying illness; and (3) they may be psychologically stressful.

The management strategy is to be tailored to an individual's specific needs. The approach is based on the current clinical knowledge to optimize the opportunity to mitigate the disease. Ultimately, predictive genomic medicine has the potential to greatly improve health and healthcare.

Keywords:- Secondary findings,RYR1, PMS2, PKP2, SCN5A.