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Abstract Topic:- Clinical Genetics

Abstract Title:- Medically actionable incidental findings in healthy exomes

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Aims:-Classifying incidental or secondary findings in diagnostic testing is well reported. In the current study we determine the prevalence, phenotype and variant details of the incidental findings from deemed healthy individuals by whole exome sequencing.

Methods:- DNA was extracted using the Qiagen DNA extraction kit from EDTA-WB (2ml), from deemed healthy individuals who had consented for the predictive genomics test as well as to receive information regarding incidental findings (IF). The DNA libraries were prepared using Twist Exome 2.0 Library Preparation kit (Twist Biosciences USA) and sequenced on the Illumina Nova Seq platform using the 150 X 2 paired end chemistry. The sequencing data was processed with a GATK-based genome analysis pipeline developed in-house. The performance of the bioinformatic workflows for detecting single nucleotide variants (SNVs) and small insertion and deletion (indels) in human samples was assessed by using the gold standard dataset. Variants were annotated for the list of genes indicated in the American College of Medical Genetics (ACMG) SF v3.1. published guidance and coded for pathogenicity.

Results:- The current study identifies a high proportion of incidental findings in our population as compared to global data. Fifteen individuals out of 200 (7.5%) were identified with IF, of which the predominant phenotype was cardiac 8/200 (4%), followed by cancer phenotype (4/200, 2%), 3/200 (1.5%) had pathogenic, likely pathogenic variants in the remaining phenotypes. Variants were identified in LDLR, PCSK9, LMNA, SCN5A and TTN gene related to the cardiovascular phenotype, RET, BRCA2, PALB2 related to the cancer phenotype, as well as variants were identified in the RYR1 gene associated with malignant hyperthermia and GLA with Fabry disease. A high frequency of carrier status was seen for Hereditary hemochromatosis (35/200, 17.5%) and biotinidase deficiency (17/200, 8.5%). In addition, 14/200 (7%) individuals had a variant of unknown significance (VUS).

Conclusions:- This study provides important information on the frequency of IF in healthy Indians, which is critical if we are to reap the benefits of genomic medicine. This is important both at an individual level as recommendation, surveillance and management strategies can be initiated but also at the population level for the underrepresented population.

Keywords:- Incidental findings, whole exome sequencing, next generation sequencing, healthy individuals, Indians