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Abstract Topic: - Molecular effects of genetic variation

Abstract Title: - Candidate germline alterations in familial cancer: Our case reports.

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Aims: - AIM1:

Collection of data regarding incidences of familial cancers:

Objective 1: Identification of families with history of multiple cancers in blood relatives across generations.

Objective 2: Contacting the families for their medical history, consent for genetic analysis

AIM2:

Genotyping for identification of constitutional genetic variants, data mining and interpretation:

Objective 1: Blood collection of cancer patients and unaffected blood relatives and DNA isolation for NGS-WES

Objective 2: Bioinformatic analysis and in-silico functional studies for genetic variants

Objective 3: Evaluation and interpretation of results by data mining and standard guidelines

Methods: - Identification of families with a history of more than two same or different types of cancers across generations, followed by peripheral blood collection in EDTA vials from the patient and their blood relatives with their informed consent.

NGS-WES is performed on the Illumina platform, with a sequencing depth of approximately >80X. The germline alterations are identified with GATK tool and Ensembl VEP. The pathogenicity and allelic frequency of the variants are determined using MutationTaster and GnomAD respectively. The functional analysis of the genetic variants is assessed by HOPE and Imutant2.0.

The genotyping results will be validated by cross-referencing data obtained from various open-source databases such as NCBI, OMIM, HapMap, GenomAD, the 1000 Genome Project etc. These databases provide information on the reported variants for the gene of interest, including their clinical significance

as per the ACMG classification, and their potential role in different types of cancers due to the constitutional genetic alterations affecting protein structures and functions.

Results: - We report the following constitutional genetic variants with the following classifications:

1. 2 pathogenic variants; BRCA2c.5240dup and CHEK2c.58C>T
2. 2 variants of uncertain significance NOS3c. 1246_1255del, NTHL1c.374dup
3. 1 likely pathogenic variant; BRCA2c.8954-3C>G

In silico functional analysis indicates changes in protein stability, length, and loss of possible external and internal interactions. These can potentially lead to altered endonuclease and catalytic activity, Nitric Oxide Synthetase activity, DNA repair interference due to BRCA2/RAD51D. These alterations suggest pathogenicity of these genetic variants.

Conclusions: - In-silico analysis of these genetic variants revealed differences in protein interactions which could be interfering with their normal DNA repair and angiogenesis mechanism.

We propose to study more families with familial cancer cases to identify constitutional genetic variants from local population. Identification of germline variants via in-depth studies will help in unravelling the distribution of the genetic variants, relative risk assessment of a population and mitigation of genetic predisposition risk via improved disease risk management and genetic counseling.

Keywords: - We report the following constitutional genetic variants with the following classifications:

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