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Abstract Topic:- Genetic, genome and epigenome databases and resources

Abstract Title:- Familial cancer genomics and lessons learnt from Whole Exome Sequencing

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Aims:-Cancer etiology is multifactorial with an interplay between genetic and environmental factors contributing to cancer risk. The major role of genetic factors is known to be in case of familial cancers that account for approximately 10% of global cancer incidences. The genetic component of cancer onset can be germline genetic variant expression due to mutations. These genetic variants have different degrees of penetrance and expressivity that results in varying association with the phenotype.

Methods:- Our research focus is constitutional genetic analysis in familial cancer cases to understand the role of known and novel genetic variants in predisposition to cancer risk. Our study indicates the need for a dedicated database of familial cancer to know the incidence and population-specific variants. This can help the study of the association of the genetic variants with the phenotype by performing an in-silico functional analysis followed by in vivo study.

Results:- We have enrolled 32 families with a strong history of cancer, and have identified variants of RAD51D, NTHL1, NOS3, BRCA2, and PPM1D using whole exome sequencing in various individuals. The lessons learned till now are summarized below;

India is a country with ethnic and cultural diversity. Studies have reported that variants associated with familial cancers show different expressivity with varying ethnicities. The BRCA genes that are responsible for almost 90% of the breast cancer occurrences in Ashkenazi Jews are found to be normal in cases from South India, with later reported mutations in CHEK2 and MRE11. A registry dedicated to familial cancers would prove to be beneficial in mapping such variants differing in ethnicities, and would further contribute to existing hereditary cancer gene panels for better clinical management. The database would also give an account of the incidences of familial cancer in the country that are not available now.

Conclusions:- Variants obtained in familial cancer cases are usually missense variants that are classified as VUS. Such findings put the patient and the family in a difficult spot, especially with their impending diagnosis and future decisions. A national registry would leverage the reclassification of such variants and better sub-classification of the tumor. The intervention by genetic counselors based on personalized genetic data helps the family in cancer risk assessment.

While many research institutes and diagnostic laboratories have their own databases, none of these are accessible on a public level. It is essential that data should be integrated and made available on a public forum for researchers to compare and contribute their data globally.

Keywords:- Familial cancers, Whole Exome Sequencing, national registry, variant classification