# Direct Effects of Inbreeding: Increased Burden of Rare Genetic Disorders in Indian Sub-continent

Akanchha Kesari, Ph.D[1], Shruti Sureshkumar[1], Rajiv Rose[1], Babi Nallamilli[2], Yang Wang[3], Jing Xie[4], Alice Tanner[5], Christin Collins[6], Megan Landsverk[7], Alka Chaubey[8], Madhuri Hegde[9].

[1]PerkinElmer Genomics, Duluth, GA, USA, [2]PerkinElmer Genomics, Duluth, GA, [3]PerkinElmer Genomics, Johns Creek, GA, [4]PerkinElmer Genomics, Johns Creek, GA, [5]PerkinElmer Inc., Waltham, MA, [6]PerkinElmer, Atlanta, GA, [7]PerkinElmer, Duluth, GA, [8]PerkinElmer Genomics, Duluth, GA, [9]PerkinElmer, Waltham, MA.

## BACKGROUND

Consanguineous marriages, though considered prejudicial in the western world, are still practiced in some of the communities in the Middle-East and India. Social and cultural beliefs are the driving factors for consanguineous marriages. This practice increases the incidences and prevalence of rare genetic disorders in these communities. The mutation spectrum or the consequences of consanguinity for rare genetic condition is yet to be established in Indians. The recent IndiGen Genome Initiative supported by the Government of India highlights the need to utilize whole genome sequencing of different ethnic populations endemic in India for the identification and characterization of variants contributing towards rare genetic disorders. With this same aim, here we present an integrative approach utilizing data derived from a singular NGS assay for clinical exome analysis in a cohort of Indian patients.

## METHODS

The clinical exome strategy used in this project allows rapid sequencing and copy number analysis of multiple disease related genes and mitochondrial genome in a single test. The test has been validated in our laboratory for detection of single nucleotide and copy number variation using a custom SureSelect capture library and short base pair read sequencing on Illumina. Primary data analysis is performed using Illumina DRAGEN Bio-IT Platform v.2.03. In this framework, secondary and tertiary data analysis is performed using PerkinElmer's in-house proprietary program ODIN (Ordered Data Interpretation Network) software for SNVs and Biodiscovery's NxClinical v.4.3 or Illumina DRAGEN Bio-IT Platform v.2.03 for CNV and absence of heterozygosity (AOH).

## RESULTS

- Over all homozygous variants were observed in ~40% cases of families with proven consanguinity. Interestingly, ~60% of families with undisclosed familial relationships, also had homozygous variants.
- Of the cases reported, 12% had homozygous pathogenic and/or likely pathogenic variants and another 9% cases has homozygous variants of uncertain significance reported.

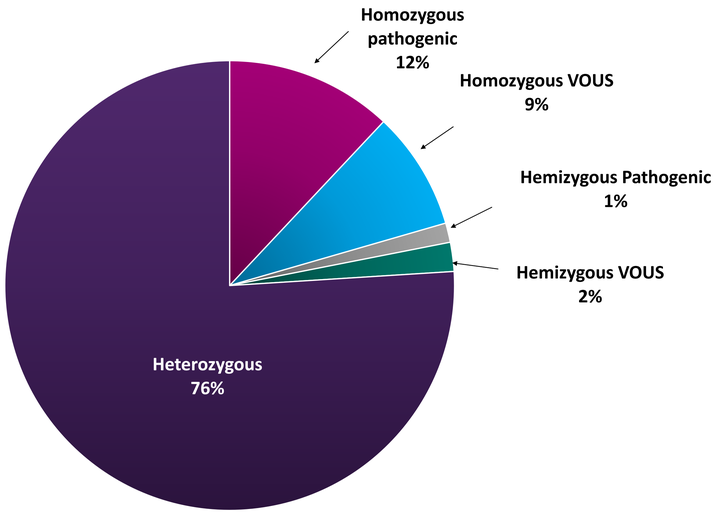


**Figure 1: Diagnostic data from Clinical Exome Analysis**

## CASE 1

**Clinical presentation**:

- Family history of fetal loss due to hydrocephalus and bilateral echogenic kidney.
- Fetal sample unavailable, hence mother's sample referred for whole exome analysis.
- *CRB2* c.3385T>A (p.Cys1129Ser) VOUS- Heterozygous in mother and father.
- Couple recent pregnancy had similar USG features as their other fetus, the sample was tested and fetus was homozygous c.3385T>A p.Cys1129Ser *CRB2* variant.
- *CRB2* c.3385T>A (p.Cys1129Ser) VOUS was upgraded to Pathogenic, based on the USG finding and segregation in the family.
- Subsequently Prenatal diagnosis was performed for their next pregnancy.

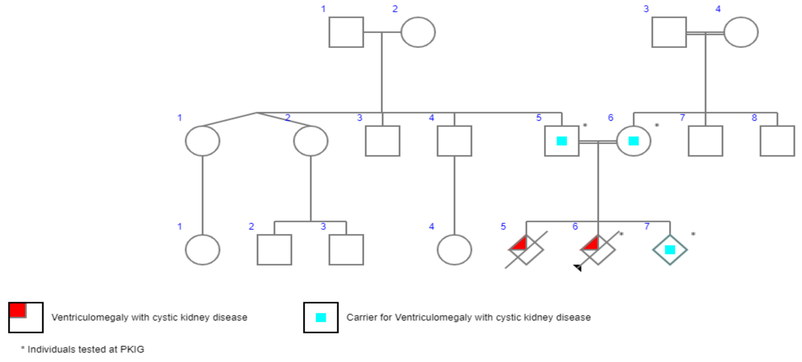


**Figure 2: Pedigree chart indicating $3^0$ consanguinity in a family with a pathogenic finding in the *CRB2* gene**

## CASE 2

**Clinical presentation:**

- 33 year old female from consanguineous family.
- Hypoplasia of deltoid muscle, walking disability, hyperCKemia, shoulder girdle muscle weakness.
- Clinical suspicion of limb girdle muscular dystrophy and dysferlinopathy.

**No Reportable Single Nucleotide Variant Detected**

**Copy Number Variants Analysis: Showing homozygous deletion in *DYSF* gene**

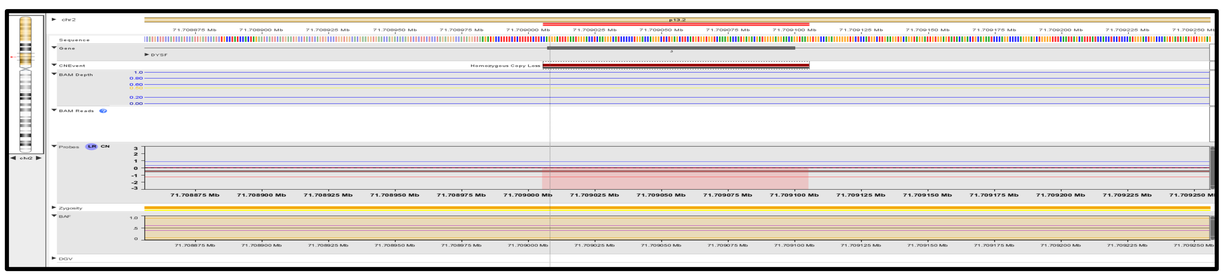

**Figure 3: CNV analysis indicating exon 3 deletion in the *DYSF* gene**

AOH regions analysis: AOH regions ~ 3 Mb or larger were observed across the genome of this individual, encompassing ~ 14.0% of the genome.

## CONCLUSIONS

- Homozygous variants are frequently reported in the Indian population even when consanguinity is not evident.
- Though the impact of consanguinity is not fully recognized in India, it is a common indication for genetic counseling, which however, is rarely offered in the hospitals.
- Our data provides further evidence that genomic screening for genetic diseases before planning a baby or at least in the first trimester of pregnancy, helps the families to reduce the chance of giving birth to a child with rare genetic conditions, and also reduce the burden on health system of the country.
- Increased homozygosity in the Indian sub-continent clearly demonstrates the immediate need for carrier testing in Indian sub-continent.