Detection of sequence variant and copy number mosaicism in genetic testing and its impact on clinical practice

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1 Introduction

Mosaicism is defined as presence of two or more cell populations with unique genotypes despite originating from the same zygote. Based on the timing of variant acquisition, mosaicism is further divided as gonadal mosaicism and somatic mosaicism. Mosaic variants have been very well studied in hereditary cancer syndromes and overgrowth syndromes. However, mosaic variants in genes related to inherited disorders are under-recognized, due to challenges associated with traditional sequencing methods to detect mosaic variants that are present in limited population of cells. More studies are needed to identify mosaic variants in inherited disorders to further understand how these variants arise, transmit and cause varied clinical features depending on the alternate allele percentages. These studies ultimately help in better understanding the genotype phenotype correlations of mosaic variants especially for the possible mild late onset clinical features in these families.

2 Methods

A comprehensive analysis of mosaic sequence and copy number variants was conducted in different NGS based clinical cases including whole genome, exome, CNGnome and targeted gene panel sequencing cases. Sequencing was performed on genomic DNA isolated from various sample types by 2x150 bp reads on an Illumina NGS platform at a mean coverage of 80X for panels and exome sequencing, 40X for genome sequencing and 8X for CNGnome. Sequence variants (SNVs) were assessed by our proprietary analysis and interpretation pipeline, Ordered Data Interpretation Network (ODIN). CNV analysis was completed using Bionano NxClinical™ software. All variants were classified according to ACMG guidelines.

3 Results

Rare reportable mosaic sequence and copy number variants were identified in 107 cases including whole genome (8.4%), exome (16.8%), CNGnome (13%) and targeted gene panel sequencing cases (61.8%) reported in our laboratory from the year 2019 to 2025.

Total of 69 mosaic sequence variants were identified in 42 different genes including *ABCD1*, *LDLR*, *MSH2*, *BRCA1*, *DMD*, *MLH1*, *RYR1*, *AR*, *BRCA2*, *OTC*, *RB1*, *SCN1A*, *SPTB*, *ALAS2*, *ARX*, *COL4A1*, *COL4A2*, *COL6A1*, *COL6A3*, *DSCAM*, *EHMT1*, *F9*, *FLNC*, *FLT3*, *GATA1*, *IDS*, *KIF23*, *MSH6*, *MYH2*, *NEB*, *NF2*, *PHIP*, *PIEZO1*, *PMS2*, *PURA*, *RHAG*, *SETD2*, *SLC4A1*, *TERT*, *TPM2*, *TSC2*, and *TTN*.

Total 41 mosaic copy number variants were identified including mosaic sex chromosomes (29%), mosaic autosomal aneuploidy (12%), mosaic intragenic gene deletions (12%), mosaic tetrasomy 12p (12%), mosaic whole chromosome arm gains (5%), ring chromosomes (5%), possible supernumerary marker chromosome (5%), mosaic terminal CNVs (5%), and isodicentric chromosome (2.4%). Out of 41 cases 6 (14.6%) prenatal cases identified with mosaic copy number variants.

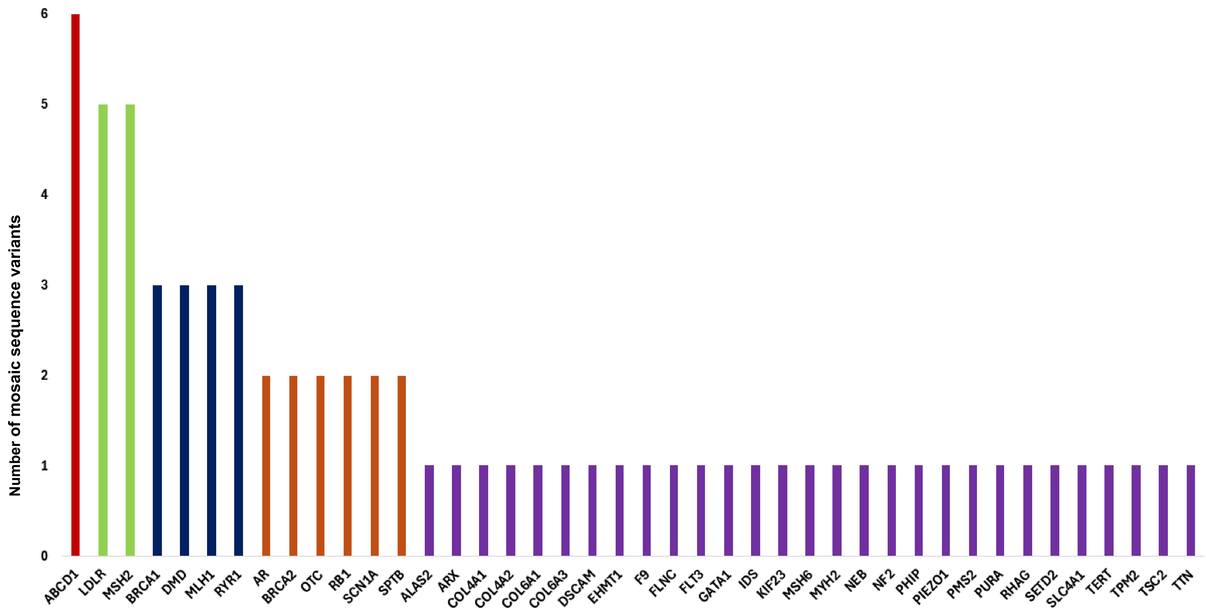

Figure 1. Number of mosaic sequence variants identified in different genes

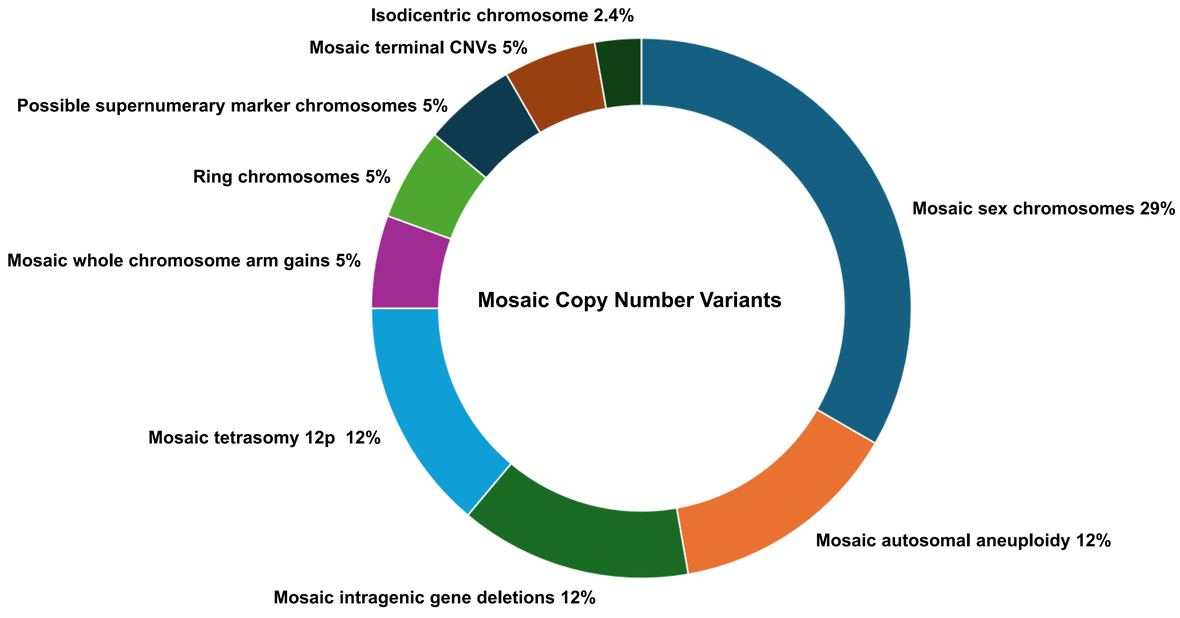

Figure 2. Different types of Mosaic copy number variants identified in this study

4 Conclusions

This study greatly helped in understanding the role of mosaic variants in different inherited genetic disorders including adrenoleukodystrophy, familial hypercholesterolemia, DMD and other muscular dystrophies, Dravet syndrome and epileptic encephalopathy, ornithine transcarbamylase deficiency, mucopolysaccharidosis, retinoblastoma, breast, ovarian cancer and other inherited cancer syndromes. Our NGS based copy number analysis using Bionano NxClinical™ software helped to detect mosaic chromosome abnormalities down to 20% mosaicism, however further manual review and correlation with the clinical presentation, mosaicism as low as 13% identified in certain cases. The detected mosaic copy number variants encompassed a spectrum from whole chromosome mosaicism to structural abnormalities, including intragenic deletions. This comprehensive approach enhances diagnostic accuracy and enables appropriate genetic counseling for patients with mosaic chromosomal abnormalities and possible mild or late onset clinical presentations.