Detection of Single-Gene Copy-Number Variations Through High-Resolution Exon-Targeted Chromosomal Microarray Analysis

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INTRODUCTION

Disease-causing copy-number variants (CNVs) often encompass large genomic regions affecting multiple contiguous genes. However, they may also affect single protein-coding and disease-associated genes, causing Mendelian disorders. Genic CNVs are usually challenging to detect due to their small size. Herein, clinically relevant CNVs affecting single protein-coding genes captured by high-resolution exon-targeted chromosomal microarray analysis (CMA) are investigated.

METHODS

High-resolution CMA results from over 13,000 individuals referred to Baylor Genetics for the investigation of suspected genetic etiologies were reviewed. This custom comprehensive array contains 400k probes with exon-targeted probe coverage for >4,200 genes associated with autosomal and X-linked conditions, as well as candidate disease genes. This array also contains 60K SNP probes which enable the detection of copy-number neutral regions of absence of heterozygosity, and 670 probes covering the mitochondrial genome.

RESULTS

Monogenic CNVs were detected in 3,770 cases; of which 190 monogenic CNVs from 188 individuals were classified as pathogenic/likely pathogenic (P/LP). The majority of P/LP monogenic CNVs affected genes associated with autosomal dominant conditions, followed by X-linked conditions. The median sizes of losses and gains were 28.0 kb and 53.5 kb, respectively. Monogenic CNVs also resulted in autosomal recessive conditions (AR) in 15 cases (Table 1) and multiple diagnostic findings in 13 cases (Table 2). Other monoallelic CNVs predicted to affect genes associated with AR conditions were detected in 1,828 (13.4%), likely conferring carrier statuses.

FIGURE 1

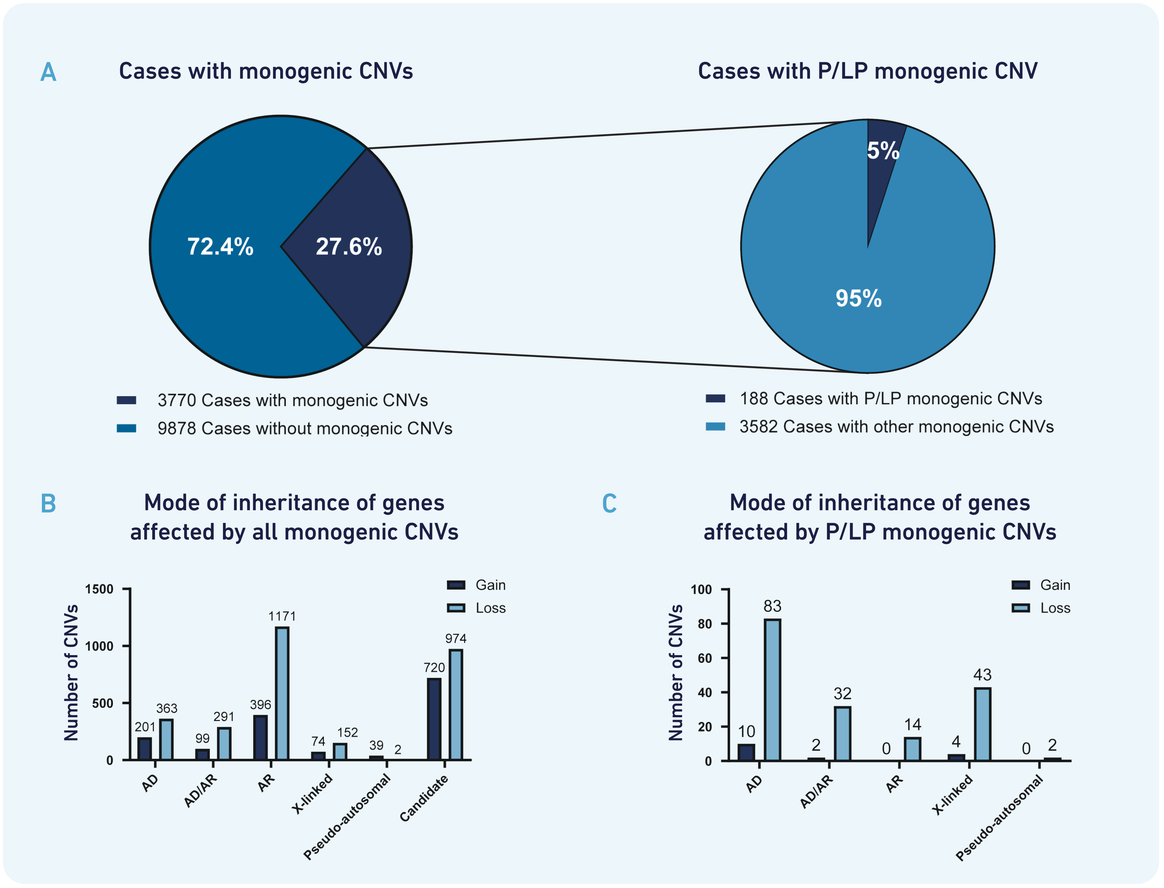

Figure 1. A. The proportion of cases harboring CNVs that affect single protein-coding genes. **B.** Mode of inheritance of genes affected by all monogenic CNVs. **C.** Mode of inheritance of genes affected by pathogenic/likely pathogenic monogenic CNVs.

FIGURE 2

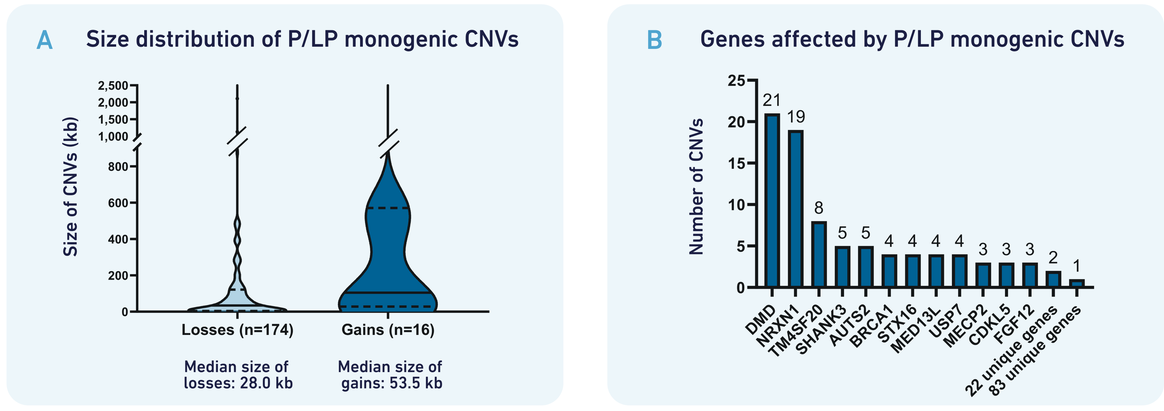

Figure 2. A. The size distribution of the P/LP monogenic CNVs. The solid horizontal line represents the median size, and the dotted horizontal lines mark the first and third quartiles. **B.** The genes that are frequently affected by P/LP monogenic CNVs.

FIGURE 3

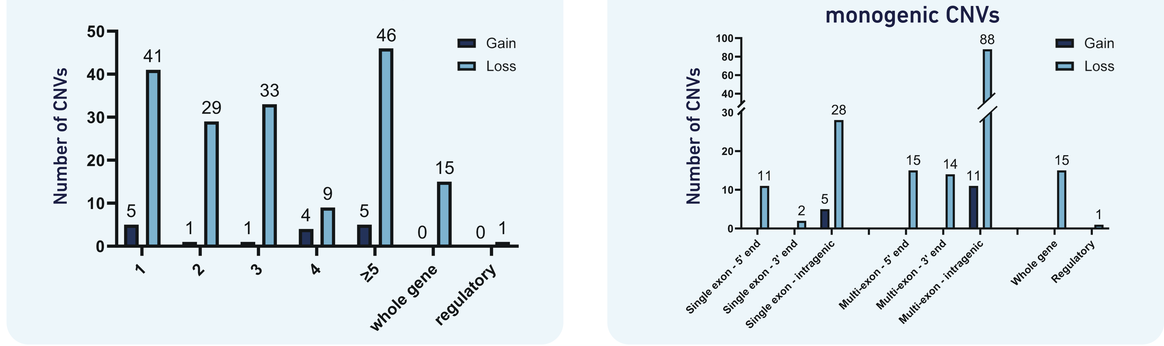

Figure 3. A. The number of exons or gene elements affected by P/LP monogenic CNVs. **B.** The gene content affected by P/LP monogenic CNVs

Table 1. Monogenic CNVs contributing to single or biallelic variants in autosomal recessive conditions

Case ID	Gene	Allele 1	Allele 2
1	*ERCC8*	Exon 4 del	Exon 4 del
2-1*	*HINT1*	Exon 3 del	Exon 3 del
2-2*	*HINT1*	Exon 3 del	Exon 3 del
3	*ITGB4*	Exons 19-25 del	Exons 19-25 del
4	*PTPRQ*	Exons 9-10 del	Exons 9-10 del
5	*CD36*	Exons 1-3 del	Exons 1-3 del
6	*DIAPH1*	Exons 2-16 del	Exons 2-16 del
7	*OTOA*	Exons 2-20 del	Exons 2-20 del
8	*VPS13B*	Exons 18-23 del	Exons 18-23 del
9	*WDR19*	Exons 10-13 del	c.3703G>A (p.E1235K)
10	*TANGO2*	Exons 3-9 del	22q11.2 del (2.5 Mb)
11	*GALC*	Exons 11-17 del	c.673G>A (p.A225T)
12	*LRBA*	Exon 36 del	Del of exons 35-41 with other genes
13	*MCPH1*	Exons 1-8 del	Del of the entire gene with other genes
14	*EYS*	Exons 13 del	Exons 13-16

* Cases 2-1 and 2-2 are affected siblings. Del: deletion

Table 2. Monogenic CNVs contributing to one or more diagnostic variants in individuals with multiple diagnostic findings

Case ID	CMA findings	
10	*TANGO2,* exons 3-9 hemi del (22.6 kb)	22q11.2 del (2.5 Mb)
15	*DMD,* exons 49-51 hemi del (110.3 kb)	22q11.2 del (2.5 Mb)
16	*TM4SF20,* exon 3 het del (0.2 kb)	2q24.2 del (2.6 Mb)
17	*DMD,* exons 49-51 het del (110.3 kb)	22q11.2 del (2.0 Mb)
18	*SHOX,* whole gene del (197.8 kb)	15q11.2q13.1 del (4.7 Mb)
19	*SHOX,* whole gene del (484.7 kb)	11q22.2q22.3 del (1.7 Mb)
20-1*	*SHANK2,* exons 9-13 het del (105.9 kb)	1q21.1q21.2 del (1.2 Mb)
20-2*	*SHANK2,* exons 9-13 het del (105.9 kb)	1q21.1q21.2 del (1.2 Mb)
21	*DMD,* exons 3-34 hemi del (504.7 kb)	16p12.2 del (443 kb)
22	*MED13L,* exons 3-4 het del (120.2 kb)	16p13.11 dup (1.2 Mb)
23	*RAD51C,* exons 8-9 het del (2.5kb)	Trisomy 21
24	*DMD,* exons 18-23 het del (49.7 kb)	*BMPR2,* exon 1 het del (33.9 kb)
25	*NSD2*, exons 2-3 het del (22.4 kb)	12p terminal del (22.7 Mb)
		17p13.3 del (5.1 Mb)

* Cases 20-1 and 20-2 are affected siblings. Del: deletion; Dup: duplication; Hemi: hemizygous; Het: heterozygous.

CONCLUSIONS

High-resolution CMA with exon-targeted coverage of disease-associated genes facilitated the detection of small-sized CNVs affecting single protein-coding genes. This approach resolved single-gene CNVs associated with both autosomal and X-linked monogenic etiologies and yielded multiple findings in addition to the detection of genomic disorders. Small CNVs affecting single protein-coding genes still represent an under-recognized yet clinically significant subset of disease-causing alleles for Mendelian disorders.

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