PREVENTION GENETICS

Testing Outcomes of an Exome-Based Panel for Ehlers-Danlos Syndrome

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ABSTRACT

Ehlers-Danlos Syndrome (EDS) is a clinically and genetically heterogeneous group of heritable connective tissue disorders that affects the skin, joints, ligaments, blood vessels, and internal organs. The classification of EDS was recently revised to include 13 subtypes caused by 19 different genes (Malfait et al. 2017. PubMed ID: 28306229). We have developed an EDS panel that includes all 19 genes recommended by The International EDS Consortium in a single next generation sequencing test (Malfait et al. 2017. PubMed ID: 28306229). This study summarizes the phenotypic and demographic makeup of the patients referred for diagnostic EDS testing and reports the sequencing results from the 19 genes analyzed. Next generation sequencing (NGS) was performed with copy number variation (CNV) analysis on exome-based library preparations. We received clinical samples from 171 unrelated individuals suspected of having EDS. Of these 171 individuals, 35 (~21%) were male and 136 (79%) were female. The average age at testing was 27 years of age. Phenotypic information was provided for 72 of 171 patients (~42%). Key phenotypic features included joint hypermobility, joint pain, and joint dislocation. At least one heterozygous likely pathogenic or pathogenic variant in *COL1A1*, *COL5A1*, *COL5A2*, *FLNB*, or *TNXB* was identified in 11 of 171 (~6%) probands. Variants of uncertain significance were identified in an additional 59% of probands. Only one clinically-relevant CNV event was detected. In summary, sequencing of the 19 known EDS genes yielded a molecular diagnosis in a small proportion of patients with clinical symptoms consistent with EDS. Our data suggests that the etiology of a large majority of EDS remains to be elucidated. New EDS gene discovery and further studies of the mechanisms underlining EDS-related conditions are warranted.

RESULTS

- 171 unrelated probands (136 females, 35 males) were tested for the EDS panel from November 2017 to June 2019 at PreventionGenetics (Figure 1).
- Ages of all probands at time of testing ranged from 11 days to 70 years of age. The average age of testing was 27 years of age (Figure 2).
- 6% of probands had a pathogenic (P)/likely pathogenic (LP) variant, 59% had a variant of uncertain significance, and 35% were negative (Figure 3).
- A large copy number variation (CNV) was detected by NGS sequencing and confirmed by gene centric aCGH (Figure 4).
- Approximately 70% of the likely pathogenic and pathogenic variants found in these patients were novel at the time of reporting. Novel variants are listed in Table 1.

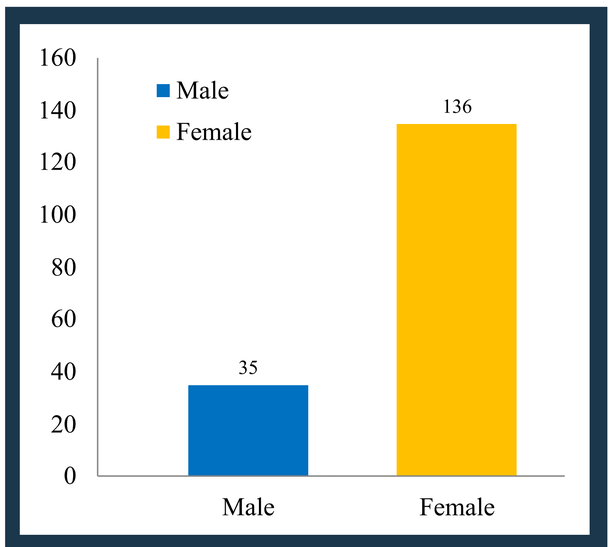

Figure 1: *Of 171 individuals, 35 (~21%) were male and 136 (79%) were female.*

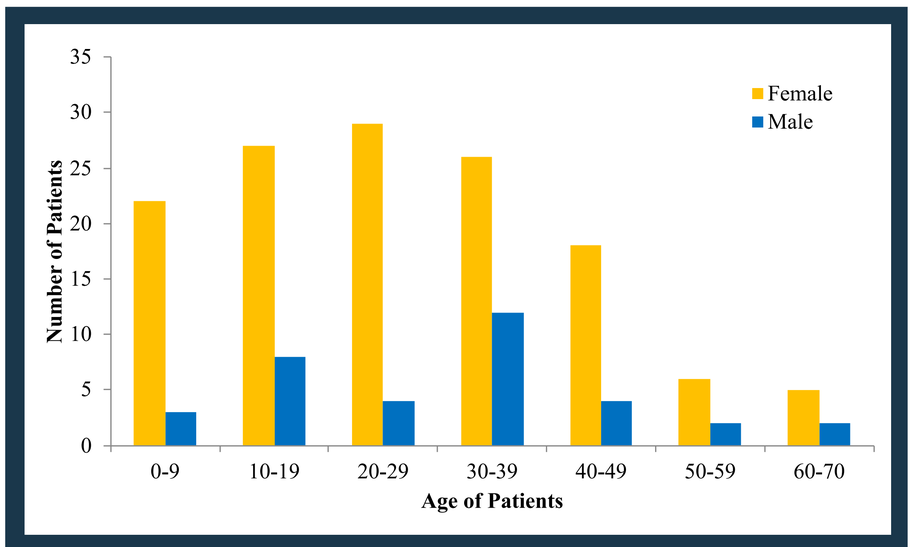

Figure 2: *At the time of testing, the ages of all probands ranged from 11 days to 70 years of age. The average age of testing was 27 years of age.*

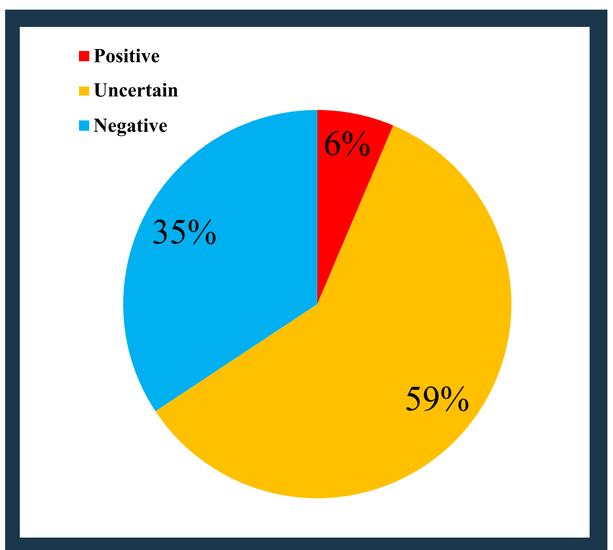

Figure 3: *Summary of Testing Results*

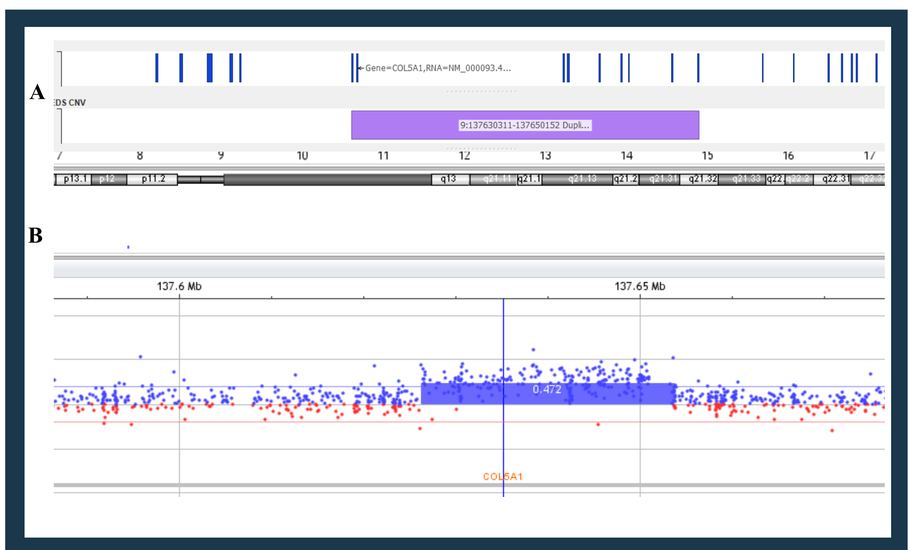

Figure 4: *A large duplication involving exons 10 to 18 of COL5A1 was initially detected through analysis of the sequence data (A) and then confirmed by gene targeted aCGH (B).*

Table 1: Novel Pathogenic and Likely Pathogenic Variants Identified in Probands

Patient	Phenotype Information	Gene	cDNA	Protein	Zygosity	Interpretation
PG03	• Joint laxity • External rotation of feet bilaterally • Blue sclera	*COL1A1*	c.644G>T	p.Gly215Val	HET	LP
PG05	N/A	*COL5A1*	Exon 10-18 duplication	N/A	HET	LP
PG06	N/A	*COL5A2*	c.3572G>A	p.Gly1191Glu	HET	LP
PG07	• Generalized hypermobility • Delayed walking • Club foot (right)	*COL5A2*	c.457-2A>G	Splicing	HET	LP
PG13	N/A	*TNXB*	c.10489C>T	p.Gln3497*	HET	LP
PG14	• Joint hypermobility • Inguinal hernia	*TNXB*	c.4334delA	p.Glu1445Glyfs*13	HET	LP

CONCLUSIONS

- NGS sequencing of the 19 known EDS genes yielded a molecular diagnosis in a ~6% of patients with suspected clinical EDS.
- Our data suggests that the etiology of a large majority of EDS remains to be elucidated. New EDS gene discovery and further studies of mechanisms underlining EDS-related conditions are warranted.
- Exome based panel testing is cost effective and adds the value of CNV detection.

ACKNOWLEDGMENTS

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REFERENCES

Malfait et al. 2017. PubMed ID: 28306229