Analysis of *MED13L*, a neurodevelopmental morbid gene, in the 100k Genomes Project data

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Introduction

Pathogenic variants in *MED13L*, which is among the most frequently mutated neurodevelopmental morbid genes,[1] cause *MED13L* syndrome (Asadollahi-Rauch syndrome), leading to intellectual disability, speech impairment, hypotonia, distinctive facial gestalt and variable other anomalies such as congenital heart defects and epilepsy.[2] The objective of the current study has been to assess the spectrum of *MED13L* missense variants and linked phenotypes in 100k Genomes project data.

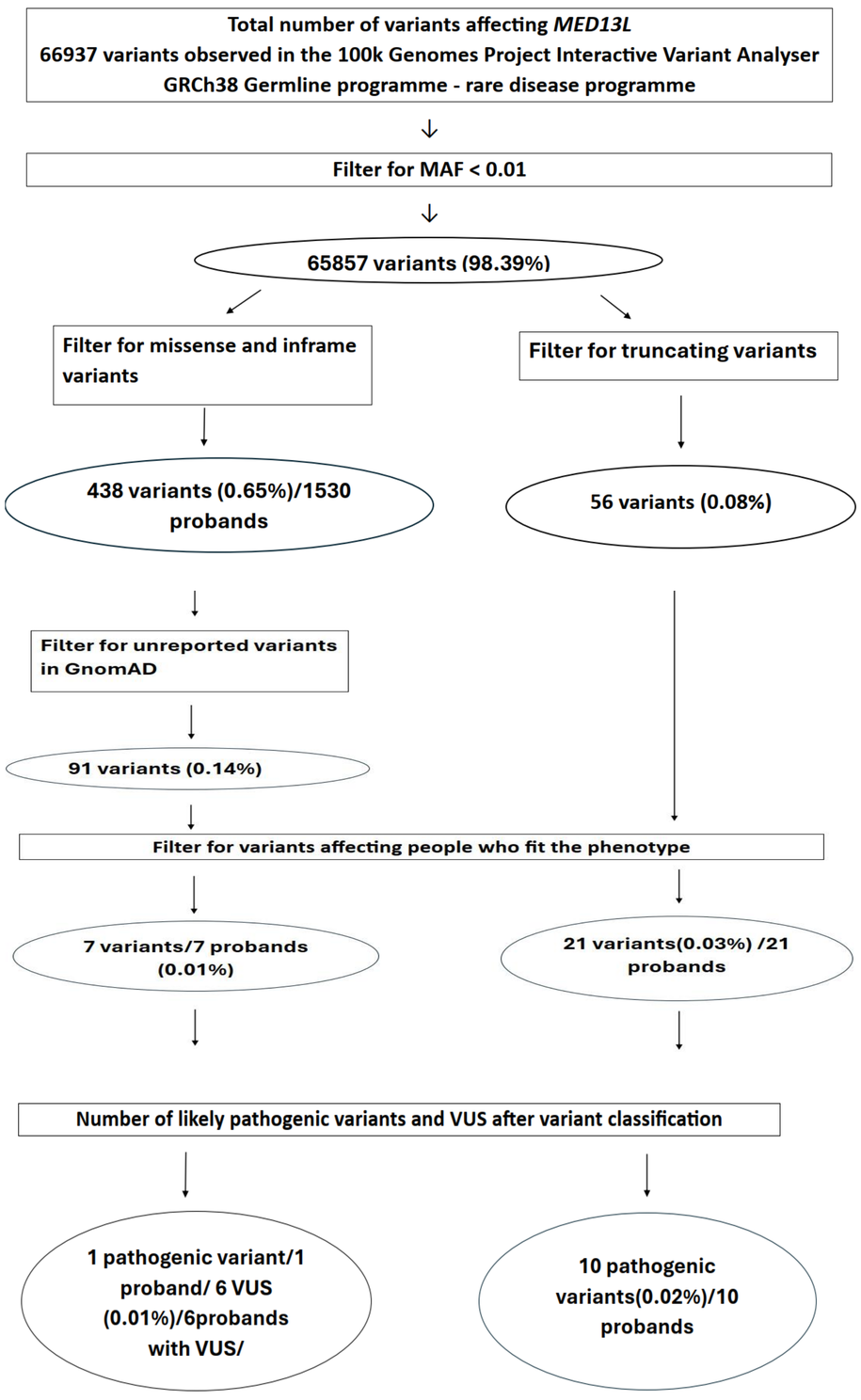

Table 1: Overview of *MED13L* missense and intronic variants for seven patients left after filtering and their classification

Patient	c.Nomen-clature& p.nomen-clature	Reported in GnomAD /ClinVar/ published in the literature	Denovo list from GEL	NGS analysis carried out	CADD	SIFT	Polyphen	Alpha-missense	Variant classification	Pheno-type	Additional comments / evidence from Richards *et al.* [3]
Patient 1	c.250T>C\p.TRP84ARG	No	No	Duo (absent in mother or father)	29.8	0 (dele-terious)	0.9988 (likely patho-genic)	0 (un-known)	VUS in MED13L, no other variant	ND	Absent from controls (PM2), multiple lines of computational evidence (PP3)
Patient 2	c.2432A>G\p.ASP811GLY	No	No	Duo (absent in mother or father)	29.2	0	0.42527 (ambi-guous)	0	VUS in *MED13L*, no other variant	ND	PM2
Patient 3	c.4745C>A\p.SER1582TYR	No	No	Duo (absent in mother or father)	23.4	0	0.1857 (likely benign)	0	VUS in *MED13L* and *ASXL3*	ND	PM2
Patient 4	*c.182C>T\p.PRO62SER*	*No*	*No*	*Duo (absent in mother or father)*	*0.038*	*0.41 (tolerated low confi-dence)*	*--*	*-0 (benign)*	*VUS in MED13L, no other variant*	*ND and con-genital heart defect*	*PM2*
Patient 5	c.1466A>G\p.HIS489ARG	No	No	Trio	22.2	0	0.4852 (ambi-guous)	0	VUS in *MED13L*, also variants in *RPSAP62*, *IQSEQ2*	ND	PM2, assumed de novo (PM6)
Patient 6	p.1688C>A\p.GLU872LYS	No	No	Trio	26.5	0	0.4309 (ambi-guous)	0	Primary coenzyme q10 deficiency, in *COQ4* / VUS in *MED13L*	ND	PM2, PM6
Patient 7	p.2614G>A\p.GLN1730ARG	No	Yes	Trio	27.6	0	0.9851 (likely patho-genic)	0	Likely pathogenic in MED13L (classified by GEL)	ND	PM2, PP3, de novo (PS2)

ND neurodevelopmental, PM2 Absent from controls, PM6 Assumed denovo, PP3 Multiple lines of computational evidence. Duo: sequencing absent in mother or father trio: both mother and father were sequenced

Method and Results

Based on 100k Genomes Project GRCh38 Rare Disease Programme, we looked at both truncating and missense variants affecting the *MED13L* gene. Clinical phenotypes were manually reviewed using the Participant Explorer, and variants were classified following ACMG guidelines. The following filtering steps were carried out:

Figure 1: Flowchart for Filtering *MED13L* Variants: Number of variants and probands after filtering

Conclusions

Through our investigation of 63,349 participants, six probands with clinically relevant *MED13L* variants were identified: three probands with variants of uncertain significance (VUS) and three probands with likely pathogenic variants. Both VUS and likely pathogenic variants were associated with consistent neurodevelopmental phenotypes. One individual carried an intronic variant with predicted spliceogenic potential and a congenital heart defect, suggesting a regulatory impact and highlighting the possible genotype-phenotype correlations that can emerge from comprehensive genomic analyses. Four probands also harboured additional pathogenic or likely pathogenic variants in other neurodevelopmental genes, indicating genetic heterogeneity.

This study underscores the critical value of large-scale genomic projects, such as the IVA 100k Genomes Project CRCh38 Germline Programme - Rare Disease Programme, in our understanding of the frequency of pathogenic variants and variants of uncertain significance (VUS) in *MED13L*.[2] It emphasizes the importance of considering genetic heterogeneity, improving diversity in reference databases, and using trio sequencing and functional studies to aid reclassification of VUS in *MED13L*-associated syndromes.

References

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