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P11.052.C

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Novel bi-allelic missense SVBP variant causes neurodevelopmental disorder with microcephaly

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INTRODUCTION

Small vasohibin-binding protein (SVBP) functions as a chaperone and a co-factor for vasohibin 1 and 2 (VASH1 and 2). VASH1-SVBP and VASH2-SVBP complexes exhibit specific Tyr/Phe carboxypeptidase activity on microtubules. Recent literature has associated biallelic truncating variants in SVBP gene with neurodevelopmental disorders in five unrelated families[a,b]. Here we report four patients from two unrelated families with similar neurodevelopmental disorders.

METHOD

Patient recruitment: Biological samples from two unrelated families were collected after obtaining informed consent from the patients or their parents. Index patients were analysed by Whole Genome Sequencing (WGS) (family 1; encompassing 6 family members) or Whole Exome Sequencing (WES) (family 2; encompassing 5 family members). Sanger sequencing was used for segregation analyses in all available family members.

WGS: DNA was extracted, and libraries were prepared using TruSeq Nano DNA High Throughput Library Prep Kit (Illumina®). Libraries were 150nt paired-end sequenced on an Illumina platform to yield a mean coverage depth of 30x for the nuclear genome and at least 1000x for the mitochondrial genome.

WES: Whole exome libraries were generated using Twist Human Core Exome kit with RefSeq and Mitochondrial Panel enrichment. The libraries were 100nt paired end sequenced on an Illumina platform to obtain 20x depth of coverage for >98% of the autosome target region and at least 1000x coverage of the mitochondrial genome.

Read alignment to reference genome GRCh38 and variant calling, including single nucleotide substitutions (SNVs), small insertions/deletions (Indels) and copy number variants (CNVs) with default parameters were performed using DRAGEN (version 4.2.4, Illumina). SNV and indel annotation was performed by geneyx® (https://geneyx.com). CNVs were annotated with ANNOTSV3.1 and an in-house CNV database to obtain allele frequencies. Genetic variants are described following the Human Genome Variation Society (HGVS) recommendations.

Sanger sequencing: The relevant region of the SVBP was amplified via the PCR method and sequenced bidirectionally using the internal primer pairs. FinchTV version 1.4.0 was used for viewing and for analyzing trace data from Sanger DNA Sequencing (scf or ab1 file formats).

RESULTS

Clinical assessment

We studied two unrelated families with four patients originating from Pakistan and sharing global developmental delay (GDD), developmental regression, ataxia, speech problem, imbalance and movement disorder.

Table 1. Clinical features of patients

	F1, II3	F1, II4	F2, II3	F2, II4
Gender	Male	Female	Female	Male
Age at diagnosis (Years)	11	9	5	2
GDD	Yes	Yes	Yes	Yes
Microcephaly	Yes	Yes	Yes	Yes
Developmental regression	Yes	Yes	Yes	Yes
Ataxia	Yes	Yes	Yes	Yes
Short stature	Yes	Yes	No	Growth delay
Cerebellar signs	Ataxia and Speech problems, Imbalance	Ataxia and Speech problems, Imbalance	Ataxia and Speech problems, Imbalance	NA
Movement disorder	Yes	Yes	Yes	Yes
Speech	No	2-3 words	2-3 words	2-3 words
Seizure	Stopped at 8 years	Yes	No	No
Visual impairment	Hyperopia, Astigmatism	Hyperopia, Astigmatism	No	No
Anaemia	Mild, microcytic	Yes	No	No
Brain MRI	Hypoplasia of corpus callosum, thickened cortical grey matter, and reduced white matter arborization.	Normal	Thinning of the deep white matter in the parieto-occipital region and in both cerebral hemispheres. High signal in the maxillary sinus indicative of sinusitis. Thinning of the corpus callosum noted on sagittal images	Not performed

Genetic finding

Our analysis identified a novel homozygous missense variant (chr1:g.42807490A>G; c.125T>C, p.Leu42Pro) located in exon 3 of SVBP gene (NM_199342.4) in all four patients. This rare variant segregated with disease in both families (parents and siblings). The variant is classified as likely pathogenic (PM2, PP3, PP1-STR) based on ACMG/ClinGen guidelines.

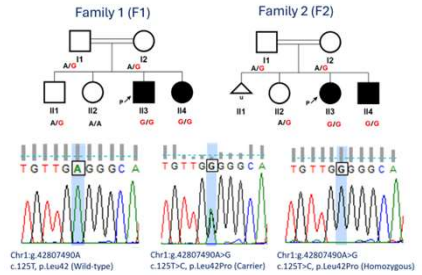

Figure 1: Pedigrees and electropherogram of individuals with/out SVBP variants.

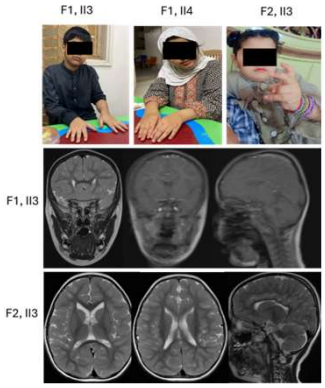

Figure 2: Pictures of affected individuals and brain MRI from individuals F1, II3 and F2, II3 with MRI abnormality.

CONCLUSION

Our findings expand the SVBP gene mutation spectrum, identified in patients with autosomal recessive neurodevelopmental disorder with ataxia, hypotonia, and microcephaly (NEDAHM). Further functional studies are necessary to elucidate the pathogenic mechanisms associated with missense variants in this gene.

CONFLICT OF INTEREST STATEMENT: AR, SK and GO are current employees at Arcensus Diagnostics.

Acknowledgement: This work was made possible by all patients who participated in this study; we also thank SMS Pakistan for referring the patient.

References:
[a] Iqbal ***et al***, Genet. Med 2019
[b] Pagnamenta ***et al***, Hum. Molec. Genet. 2019

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