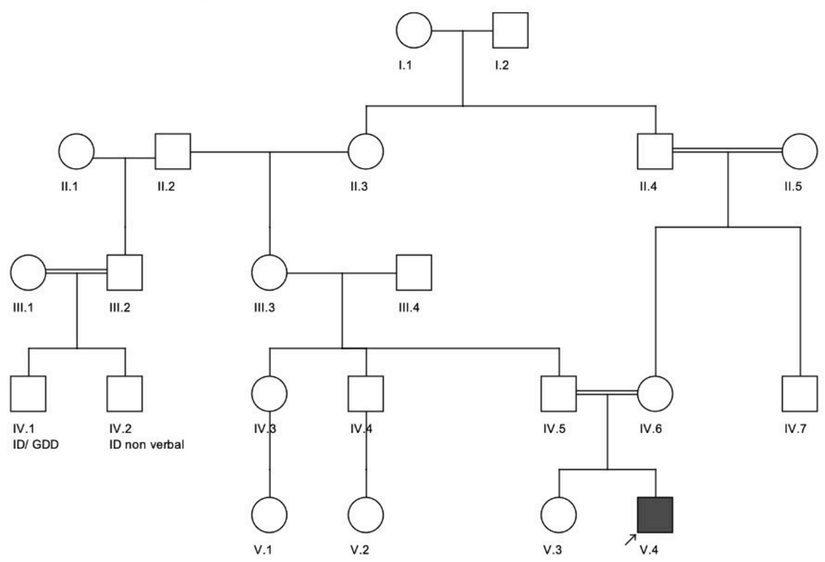
CASE REPORT: RARE *UFSP2* C.344T>A FOUNDER VARIANTS IN A CHILD WITH INFANTILE SPASMS

RUVISHANI SAMARASEKERA, ALISA PHAM, GUNJAN GARG

INTRODUCTION

We report a case of a 4-year-old male with microcephaly, infantile spasms, global developmental delay, unilateral esotropia and autism spectrum disorder, born to consanguineous parents of Palestinian descent. Genetic testing by trio WES identified pathogenic *UFSP2* c.344T>A variants. This is the eleventh reported case of *UFSP2* related neurodevelopmental disorder in the literature. Biallelic *UFSP2* c.344T>A variants were first identified in 8 patients with a severe neurodevelopmental disorder with epilepsy, establishing this as a founder variant by Ni et al in 2021.

Figure 1. Family Pedigree



RESULTS

Trio whole exome sequencing (WES) conducted in 2019 did not report any medically significant variants. Reanalysis of WES genomic data in 2023 identified biparental inheritance of pathogenic *UFSP2* c.344T>A founder variants. The *UFSP2* phenotype was consistent with the patient's features. Table 1 compares the patients in the literature.

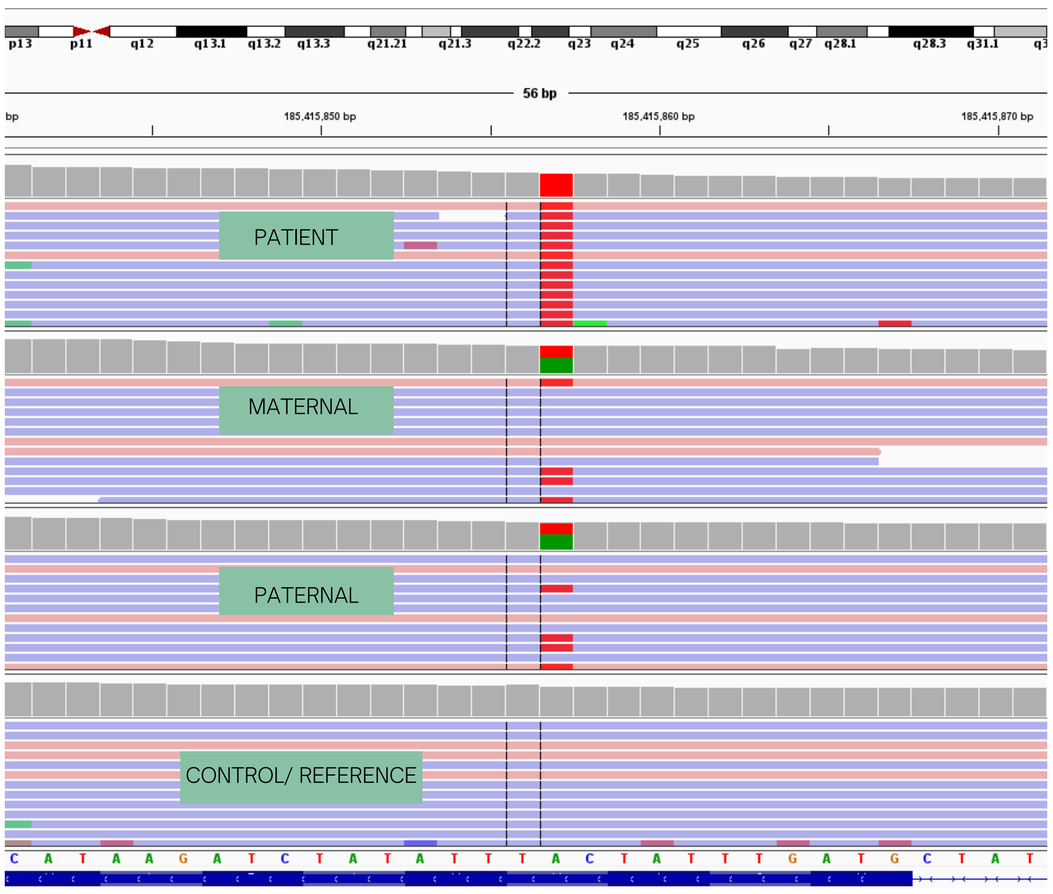


Figure 2. Sequencing data view from Integrative genomic viewer (IGV) for the UFSP2 gene and the UFSP2 c.344T>A variants in our patient.

DISCUSSION

Diagnostic rates in consanguineous populations are highly variable, with Kurul et al. demonstrating a 86% diagnostic yield of trio WES in 190 consanguineous families with neurogenetic phenotypes, with 82% of causative variants being homozygous variants.

Jalkh et al had a diagnostic yield of 49.5% in 200 Lebanese families; 2 years later, the yield was improved to 56% with repeated WES analysis.

Paper		**Our patient V.4**	Ni et al (2021)	Raha et al (2023)
Demographics	Sex	Male	3 males, 5 females	1 female, 1 male
	Current age, years	4	2 - 11 years	4.5 years and 6 months
	Country (Ethnicity)	Palestinian	Pakistani/ Afghani	Not specified
Anthropometry	Weight, age (percentile)	13.7 kg, 4 years (2nd centile)	<3rd centile – 10th centile	<3rd centile, 87th centile
	Height, age (percentile)	96.6 cm, 4 years (1st centile)	<3rd centile – 25th centile	NA
	Occipital Frontal Circumference, age (percentile)	Progressive microcephaly 45cm (age 2 <1st centile) HC at birth 35.5cm (35th centile)	<3rd centile – 10th centile	<3rd centile
Seizures	Initial symptom (age)	Seizures (8 months)	Seizures (2 days - 7 months)	Seizures (5 months)
	Epilepsy type	Infantile spasms (resolved)	Generalised 1 patient with Infantile spasms	Infantile spasms
Delay/ Intellectual disability (ID)		Mod-to-severe GDD	ID not specified	Severe GDD, not specified
Speech		Nonverbal, babbles	Occasionally vocal to nonverbal	Not specified
Tone		Hypotonia	Hypotonia	Not specified, normal
Eyes		Unilateral esotropia (Right)	Convergent squint, alternating esotropia, exotropia And normal	Not specified

Table 1. Comparison of the patient phenotypes across the publications.

CONCLUSION

The genomic result ended the diagnostic odyssey and informed recurrence risk for family planning. The outcome highlights the importance of periodic genomic data reanalysis, given the continual discovery of new gene-disease associations. Concerted efforts to engage with ethnically diverse populations are critical to diversify the reference genome, which in turn increases diagnostic yield in rare disease genomics and improves overall health outcomes.

REFERENCES

Hiz Kurul et al. High diagnostic rate of trio exome sequencing in consanguineous es with neurogenetic diseases. Brain. 2022;145(4):1507-1518.

Jalkh N et al. The added value of WES reanalysis in the field of genetic diagnosis: lessons learned from 200 exomes in the Lebanese population. BMC Med Genomics. 2019;12(1).

Ni M et al. A pathogenic UFSP2 variant in an autosomal recessive form of paediatric neurodevelopmental anomalies and epilepsy. Genet Med. 2021;23(5):900-908.