Expanding the Phenotype: A Case Report of a Novel Alanyl-tRNA Synthetase 2 (AARS2) Homozygous Mutation in a 9-Year-Old Child from a Consanguineous Middle Eastern Family Presenting with Global Developmental Delay, Hypotonia, and Dystonia.

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INTRODUCTION

- The mitochondrial alanyl-tRNA synthetase 2 gene (AARS2) mutation is considered one of the ultra-rare genetic diseases that causes affection to mitochondrial metabolism.
- It is estimated to affect 39 individuals so far in published literature.
- The known and most common phenotypes are either an infantile onset lethal hypertrophic cardiomyopathy that is known as Combined oxidative phosphorylation deficiency 8 (COXPD8) or may present later in early adulthood with encephalopathy and regression and at that time it is known as Leukoencephalopathy, progressive, with ovarian failure (LKENP).

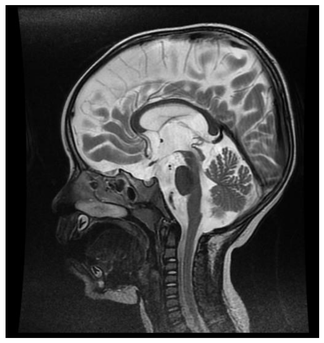
CASE PRESENTATION

- Here, the authors present a 9 years old girl, who presented at 17 months of age with truncal hypotonia, and global developmental delay with a brain MRI showing marginal brain volume reduction with prominent cerebellar folia (suggestive of cerebellar atrophy). She was later diagnosed using whole exome sequencing at 2 years of age with a novel homozygous mutation in AARS2 but her clinical phenotype did not fit either the two ends of the known disease spectrum associated with this mutation, especially that she had a normal cardiac evaluation.
- She continues to follow up with pediatric neurology and metabolic clinics and started to develop movement disorder (dystonia) at the age of 8 years.

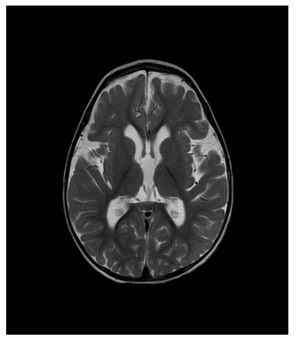
Summary of diagnostic variants detected

Gene & Associated Disease	DNA change	Protein change	rsID	MOI	Zygosity	Effect on Protein		Type
						Polyphen	SIFT	
AARS2; COXPD8/LKENP	NA	Splice site region	Novel	AR	Homo	NA	NA	VUS

Key: AR – Autosomal Recessive, AD – Autosomal Dominant, Het – Heterozygous, Homo – Homozygous, Hemi – Hemizygous, Wt – Wild type (normal), VUS – Variant of uncertain clinical significance, MOI – Mode of Inheritance



Prominent Cerebellar folia



Brain volume reduction

CONCLUSION

- Clinical presentation of AARS2 gene mutation has a wide spectrum with unique presentations in different ages.
- High index of suspicion should be present, especially if symptoms are not fitting into a specific known syndrome and Genetic testing with whole exome sequencing and mitochondrial genome analysis should be included.

REFERENCES

References

Acknowlegment

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