Whole Exome Sequencing Identifies ARCN1 Pathogenic Variant in a 4-Year-Old Female with Developmental Delay and Dysmorphic Features

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Background

This case study involves a 4-year-old female proband presenting with significant clinical manifestations and the identification of a pathogenic variant through whole exome sequencing (WES).

Clinical data

The proband presented with delayed milestones and was evaluated by a pediatrician. Physical examination revealed short stature, microcephaly, micrognathia, and bilateral cataracts. No abnormalities were detected respiratory, and cardiovascular systems. Brainstem evoked response audiometry (BERA) was normal for both ears. Electroencephalography (EEG) showed generalized epileptiform discharges.

Family history

The parents are consanguineous, and pedigree analysis indicated a history of consanguineous marriages within the family.

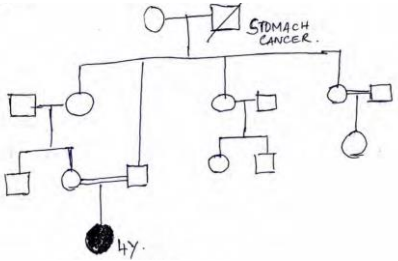
Investigations

Initial investigations included chromosomal microarray and a metabolic screening profile, which were negative for common aneuploidies and metabolic disorders. Given the clinical presentation and family history, WES was pursued after obtaining informed consent.

Results

WES revealed a pathogenic variant in the ARCN1 gene (c.1388A>G). Sanger sequencing confirmed this variant.

Pedigree chart



ARCN1 is involved in vesicle transport and intracellular trafficking, and mutations in this gene are associated with short stature-micrognathia syndrome and developmental delay.

Genetic counselling

Pretest counselling:

It was emphasized that negative chromosomal microarray result does not mean there is no genetic cause for this primary indication.

Details regarding whole exome sequencing, its cost and turnaround time was discussed. Informed consent for was obtained to perform whole exome sequence in the proband.

Posttest counselling:

Test results were conveyed to the patient by a team of genetic counsellors and the pediatrician. The genetic variant detected in ARCN1 gene and the related phenotypes were discussed with the parents. The recurrence risk and reproductive options for a next pregnancy were briefly discussed. Sanger sequencing of ARCN1 gene was recommended for both the parents for prediction the risk of reoccurrence in the next pregnancy.