PS-15

Karayol-Borroto-Haghshenas syndrome, *MSL2* associated neurodevelopmental disorder : A case report

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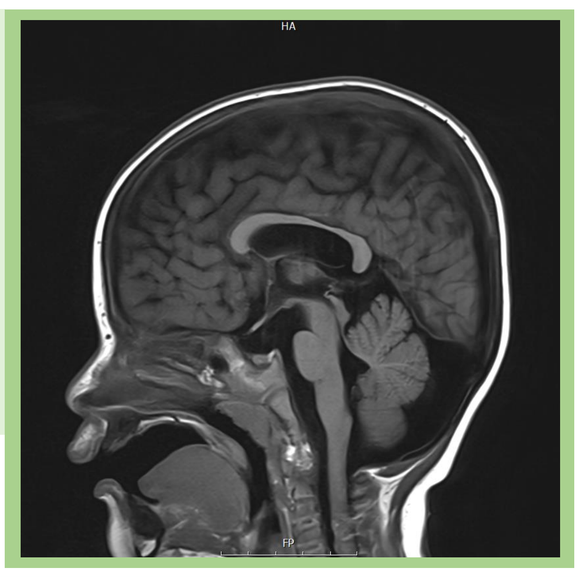
BACKGROUND

- *MSL2*, a core MSL complex component, is an epigenetic regulator that mediates histone H4K16 acetylation during neurodevelopment.
- Recent studies have identified heterozygous de novo variants in *MSL2* as the cause of *MSL2*-associated neurodevelopmental syndrome (MANDS; also referred to as Karayol-Borroto-Haghshenas syndrome), showing global developmental delay, intellectual disability, and distinctive dysmorphic features.
- Here, we describe a patient diagnosed with *MSL2*-associated neurodevelopmental syndrome.

CASE REPORT

- A 4-month-old boy, born at 39 weeks of gestation via spontaneous vaginal delivery with a birth weight of 3640 g and no perinatal complications, was referred for evaluation of gross motor delay. He was the second child of non-consanguineous parents.
- The patient exhibited poor head control, decreased trunk tone, reduced spontaneous movements, and infantile strabismus at initial presentation.
- The patient showed initial gross motor improvement followed by a plateau phase. Serial Bayley Developmental Assessments confirmed persistent global developmental delay with uneven progress across domains; the Childhood Autism Rating Scale (CARS) score at 28 months was 29.5, at the upper limit of the non-autistic range.
- The patient also exhibited mild dysmorphic features and had undergone surgical correction for infantile strabismus before 12 months of age.
- Comprehensive evaluation, including brain MRI and electrodiagnostic study, was performed around 20 months of age. Brain MRI revealed an enlarged cisterna magna, mild lateral ventricular dilatation, and subtle thinning of the corpus callosum (Figure 1). Nerve conduction study was unremarkable.

Figure 1. Brain MRI of the patient showing enlarged cisterna magna, mild lateral ventricle dilatation, and subtle thinning of the corpus callosum.



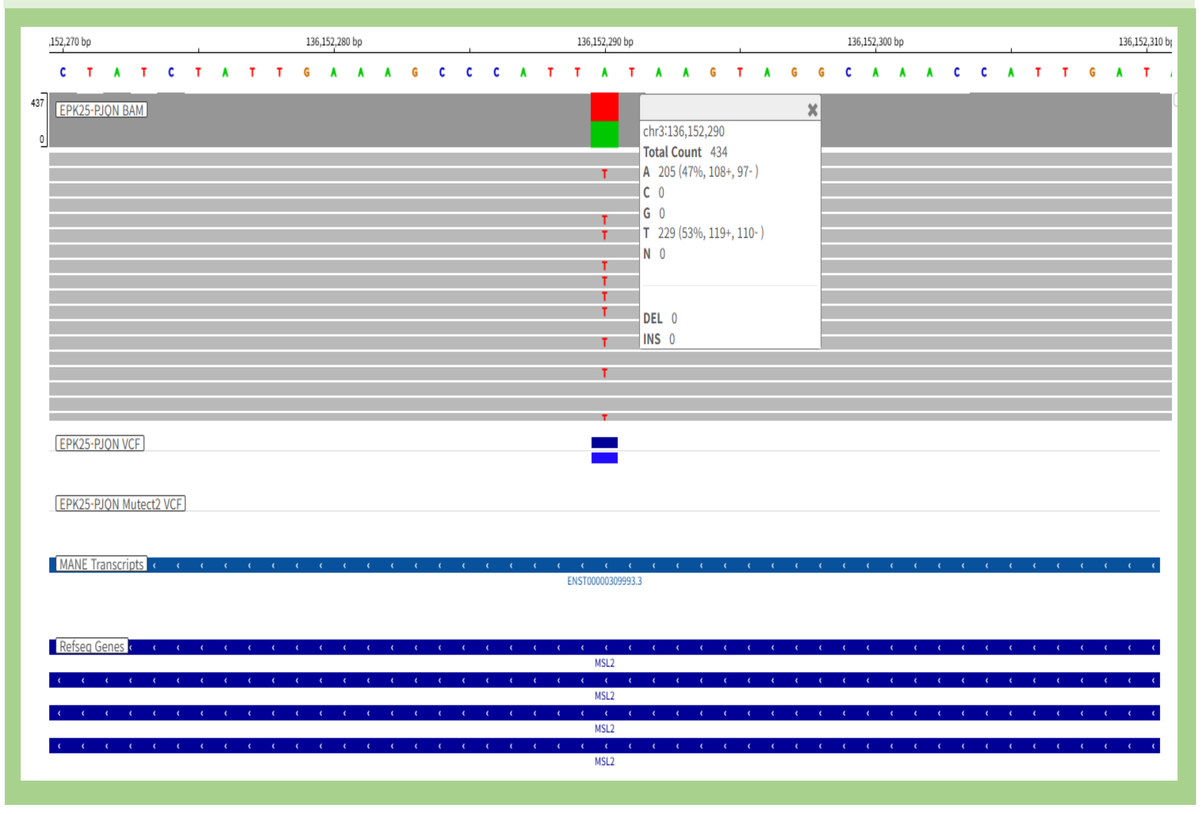
INITIAL GENETIC STUDY

- Given the clinical presentation of global developmental delay with structural brain anomalies of uncertain etiology, genetic investigations were initiated.
- Chromosome analysis, chromosome microarray, and targeted gene sequencing panel analyzing 981 genes associated with hereditary delayed development were simultaneously performed.
- However, these tests did not identify any pathogenic variants.

WHOLE EXOME SEQUENCING TEST

- Therefore, whole exome sequencing was performed.
- Whole exome sequencing (WES) identified a heterozygous nonsense variant in *MSL2* (NM_018133.4: c.591T>A, p.Tyr197*) (Figure 2).
- This variant introduced a premature stop codon in *MSL2*, leading to protein truncation (p.Tyr197*) and loss of normal protein function.
- Sanger sequencing of the parents confirmed that the variant was de novo.
- The variant was classified as pathogenic according to ACMG guidelines, and the patient was diagnosed with Karayol-Borroto-Haghshenas syndrome (*MSL2*-related neurodevelopmental disorder).

Figure 2. Integrative Genomics Viewer image of the patient shows nonsense variant in *MSL2*. (NM_018133.4:c.591T>A, p.Tyr197*)



DISCUSSION

- This patient's WES identified a de novo nonsense variant in *MSL2* (c.591T>A, p.Tyr197*).
- In the cohort of Karayol et al. (2024), nonsense variants accounted for 5 of 25 cases (20%), and predicted loss-of-function variants were identified in 23 of 25 cases (92%).
- This patient exhibits a relatively mild phenotype within the broad and heterogeneous severity spectrum reported in the same cohort, notable for persistent global developmental delay, emerging social-behavioral concerns, and mild dysmorphic features, in the absence of seizures or major systemic involvement.

CONCLUSION

- To our knowledge, this is the first report of *MSL2*-associated neurodevelopmental syndrome in an East Asian population, with fewer than 30 cases reported worldwide to date.
- Notably, the truncating *MSL2* variant identified in this patient appears to be novel.
- This case highlights the clinical significance of WES, as targeted gene panel-based next-generation sequencing failed to detect the variant, whereas whole exome sequencing successfully identified a pathogenic variant.