Pontocerebellar Hypoplasia Associated With TTC 1 Mutation: Case Series

Gamze Sarıkaya Uzan [1] , Ahmet Yaramış[2], Ece Sönmezler [3], Semra Hız Kurul [1,3,4], Uluç Yiş [1], Çağatay Günay [1], Hanns Lochmüller [5,6,7,8], Rita Horvath [9,10], Yavuz Oktay [3,4,11]

1: Department of Pediatric Neurology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey 2: Pediatric Neurology Clinic, Diyarbakır, Turkey 3: International Biomedicine and Genom Institute, Dokuz Eylül University, İzmir, Turkey 4: Izmir Biomedicine and Genome Center, Dokuz Eylul University Health Campus, İzmir 35340, Turkey 5: Division of Neurology, Department of Medicine, Children's Hospital of Eastern Ontario Research Institute, The Ottawa Hospital, University of Ottawa, Ottawa, Canada 6:CNAG-CRG, Centre for Genomic Regulation, Barcelona Institute of Science and Technology, Barcelona 08003, Spain 7: Department of Neuropediatrics and Muscle Disorders, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg 79106, Germany 8:Division of Neurology, Department of Medicine, The Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, Ottawa ON K1Y 4E9, Canada 9:Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom 10:Department of Clinical Neurosciences, John Van Geest Centre for Brain Repair, School of Clinical Medicine, University of Cambridge, Cambridge CB2 0PY, UK 11:Department of Medical Biology, School of Medicine, Dokuz Eylul University, Izmir 35340, Turkey

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INTRODUCTION and OBJECTIVE

TTC1 (tetratricopeptide repeat domain-containing protein 1) is a member of the Tetratricopeptide repeat (TPR) protein superfamily. TPR is a protein motif that includes degenerate tandem repeats and is found in many proteins involved in regulating cell division and RNA synthesis. The clinical spectrum of the TTC1 gene variants in humans is unclear. In 2015, a variant in this gene was reported as a candidate associated with brain malformations in a patient (NM_003314: c.T784G; p.F262V Hom). But the phenotypic features were not detailed. In the case report, we defined the type of brain malformation by reporting pontocerebellar hypoplasia with the same variant in TTC1 gene. We aimed to highlight its association with PCH by presenting four female patients born from two unrelated first cousin marriages.

CASE PRESENTATIONS

Four female cases had psychomotor retardation that started in early infancy. The physical examinations revealed axial hypotonia and microcephaly. There were no pyramidal signs. Oculomotor apraxia was observed in the ophthalmologic examinations. All of the cases demonstrated PCH and agenesis/dysgenesis of corpus callosum in brain MRIs. DNA isolated from the peripheral blood of four patients and their unaffected parents was subjected to whole exome sequencing. Data analysis was performed using RD-Connect's Genome Phenome Analysis Platform and a homozygous missense variant in the TTC1 gene (NM_003314.3; c.784T>G;p.Phe262Val) was identified in all four patients, while all parents were heterozygous carriers.

TABLE 1. CHARACTERISTIC FEATURES OF OUR PATIENTS

Patiens		Age/Gender	Parents	dysmorphology	Ophtalmologic examination	Seizure
1st family	Case 1	8y/F	1st cousin	• microcephaly (-3.8 SDS) • high frontal hairline • split teeth	Bilateral esotropia	Ø
	Case 2	4y/F		• Microcephaly (-3.77 SDS) • high frontal hairline • split teeth	Bilateral esotropia	Ø
2nd family	Case 3	4y/F	1st cousin	• microcephaly (-3.0 SDS) • high frontal hairline • bullous noise • split teeth	right esotropia	+
	Case 4	17y/F		• microcephaly (-6.32 SDS) • high frontal hairline • bullous noise • split teeth • severe scoliosis	right esotropia	Ø

CONCLUSIONS

Our findings emphasize the association of TTC1 with PCH. More comprehensive studies including functional workup are needed to establish the genotype-phenotype correlations between TTC1 gene and PCH.

Keywords: TTC-1, brain malformations, pontocerebellar hypoplasia

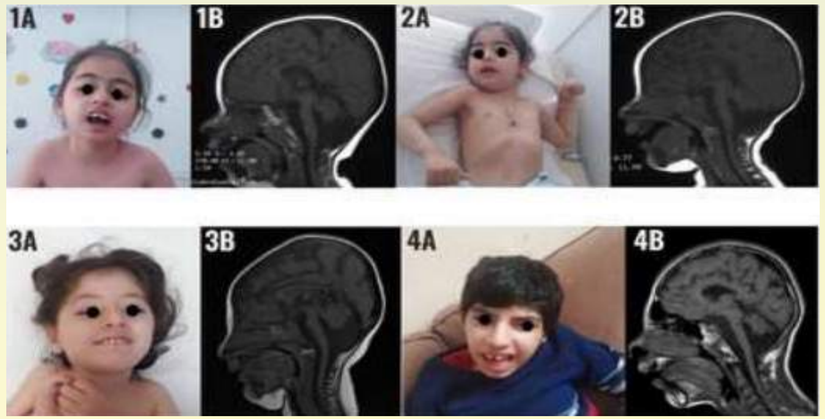

FIGURE 1: Dysmorphological features and MRI findings of our patients: Figure 1A image 1A and 1B: case 1, image 2A and 2B: case 2, image 3A and 3B: case 3, image 4A and 4B: case 4

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Contact: gamzeuzan36@gmail.com