Muhsin Elmas et al, 2019;2(1):77–80.
https://doi.org/10.24911/JBCGenetics/183-1546931990

CASE REPORT

Turkish family with dysequilibrium syndrome with a novel mutation in the *VLDLR* gene

Muhsin Elmas[1]*, Basak Gogus[1], Ayse Tolunay Oflu[2], Aysegul Bukulmez[2], Ebru Elmas[3], Mustafa Solak[1]

ABSTRACT

Background: A very few diseases are reported caused due to cerebellar hypoplasia and neuronal migration defects such as pachygyria. Cerebellar Ataxia, mental retardation, and Dysequilibrium Syndrome 1 (DES) (Online Mendelian Inheritance in Man # 224050) are one among such group of diseases. DES is caused due to a homozygous mutation in the *VLDLR* gene involved majorly in neuronal migration.

Case Presentation: Two members (siblings) from a Turkish family presented with neuromotor developmental delay, moderate learning disability, delayed psychosocial development, and strabismus complaints. Whole exome sequencing (WES) was performed as consanguinity existed between the parents and specific pre-diagnosis could not provide a satisfactory conclusion for the patients. WES revealed a homozygote novel mutation in the *VLDLR* gene.

Conclusion: Evaluation of WES data resembled a process of finding a needle in a haystack; therefore, the present study recommended clinical information and anamnesis to be very important in understanding and interpreting the WES result.

Keywords: VLDL receptor, dysequilibrium syndrome, pachygyria.

Introduction

Cerebellum acts as the control center for the central nervous system muscle tone, coordination of movement, and balance. Cerebellar malformations result in walking disabilities and problems with coordination of gait and limbs (1). Pachygyria is a congenital brain malformation disorder with severe developmental delay, seizures, poor muscle tone and control, feeding or swallowing difficulties, a nd m icrocephaly fi ndings. Pachygyria also presents migration defects along with the presence of broad sulcus and abnormal brain convolutions (2). Dysequilibrium Syndrome 1 [DES 1, Online Mendelian Inheritance in Man (OMIM) #224050] is a non-progressive cerebellar disorder characterized by ataxia associated with an intellectual disability, delayed ambulation and cerebellar hypoplasia, moderate-to-severe intellectual disability, dysarthria, strabismus, and seizures (3). The *VLDLR* gene encodes the very low-density lipoprotein receptor, a component of the signaling pathway that mediates neuroblast migration in the cerebral cortex and cerebellum (4). A homozygous mutation in this gene is reported to cause DES. The first reported mutation associated with DES was a 199 kb homozygous deletion involving the VLDLR coding region in the Hutterites population (5). Herein, we report clinical, laboratory, and radiological findings of DES among two siblings with homozygous mutations in the *VLDLR* gene.

Case Presentation

A 9-year-old girl and 2-year-old boy (Turkish siblings) was presented with neuromotor developmental delay, moderate learning disability, delayed psychosocial development, chronic constipation, and strabismus complaints (1). Patient 1: A 9-year-old girl (older sibling) who did not show any special features during the prenatal period. Her birth weight was 3,730 g and she was born with spontaneous vaginal delivery at full term. Her

Correspondence to: Muhsin Elmas
*Medical Genetics Department, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey.
Email: drmelmas@gmail.com
Full list of author information is available at the end of the article.
Received: 08 October 2018 | **Accepted:** 23 December 2018

fifth-minute appearance, pulse, grimace, activity, and respiration (APGAR) score was 8–9 and she did not stay in the intensive care unit at the post-term period. She had been fed with breastfeeding until the age of 2 years. Her motor developmental stages were delayed (head and neck control at 7-month old, sitting with supporting at 15-month-old, sitting alone at 18-month old, walking at 36-month old). She still cannot walk independently and presented chronic constipation. At physical examination, neuromotor developmental delay and psychosocial developmental delay were determined. Her head circumference was above 97% according to the age criteria. But, her height and weight were normal. At the dysmorphic examination high anterior hairline, long face, narrow forehead, narrow jaw, pointed chin, tall chin, hypertelorism, sparse eyebrow, long palpebral fissure, telecanthus, prominent inferior crus of antihelix, prominent antihelix stem, prominent superior crus of antihelix, everted antitragus, expanded terminal portion of crus helix, prominent crus helix, low insertion of columella, prominent nasal bridge, broad nasal tip, bulbose nose, long nose, short philtrum, smooth philtrum, wide mouth, and microdontia were found (Figure 1). Even though the patient could walk with support, she lacked the ability to speak. There was bilateral strabismus found in the eyes of the patient. At the same time, the patient's hair was fragile. Magnetic resonance imaging (MRI) reported dilated fourth ventricles, vermis, and bilateral cerebellar hemisphere hypoplasia and pachygyria. Biochemical examinations did not show any pathological value except lactate dehydrogenase (LDH) elevation. The result of the karyotype was 46, XX (2). Patient 2: A 2-year-old boy (younger sibling) who did not show any special features during the prenatal period. His birth weight was 5,500 g and was born with a cesarean section at term due to macrosomia at full term. Her fifth-minute APGAR score was 8–9 and stayed 2 hours at the intensive care because of hypoglycemia after birth. The patient still feeds on breastfeeding. He had neuromotor retardation delayed (head and neck control at 1-year old, still cannot sit with support). He had lingual frenulum operation one time and also reports chronic constipation. At the physical examination determined neuromotor and psychosocial developmental delay. The height, weight, and head circumference of the patient were within normal range according to his age. At the dysmorphic examination, prominent forehead, full cheeks, premaxillary prominence, short chin, deeply set eye, laterally extended eyebrow, sparse eyebrow, long eyelashes, proptosis, telecanthus, prominent inferior crus of antihelix, prominent antihelix stem, prominent antitragus, low-set ears, expanded terminal portion of crus helix, prominent crus helix, localized underdeveloped helix, bifid tragus, broad columella, depressed nasal bridge, wide nasal bridge, broad nasal tip, bulbose nasal tip, and broad philtrum were found (Figure 2). The patient had a disability in speaking. MRI found periventricular hyperintensity, vermis, and bilateral cerebellar hemisphere hypoplasia and pachygyria. The result of the karyotype was 46, XY.

The mother of the patients did not have diabetic features during both the pregnancy periods. In the pedigree of the patients, they had consanguineous parents (second-degree cousins, Figure 3). Since no specific pre-diagnosis could be thought for both the siblings and consanguinity existed between the parents, whole exome sequencing (WES) was considered as the most suitable genetic test to be performed for further evaluation. The WES analysis found *VLDLR* gene homozygous NM_003383.4:c.1459G>T (p.Asp487Tyr) novel mutation in both siblings. The parents were heterozygous for the mutation detected. Furthermore, *VLDR* c.1459G>T (p.Asp487Tyr) novel mutation was confirmed by Sanger Sequencing. The mutation was categorized as "Damaging" according to the prediction scores (MutationTaster, FATHMM, FATHMM-MKL, MetaSVM, MetalR). The American College of Medical Genetics and Genomics (ACMG) tag for this mutation was PM2, PP3, and BP1 with an ACMG score showing variant of unsignificance. Furthermore, the DANN score was 0.9957 and the disease reported to be caused by this mutation was "cerebellar ataxia, mental

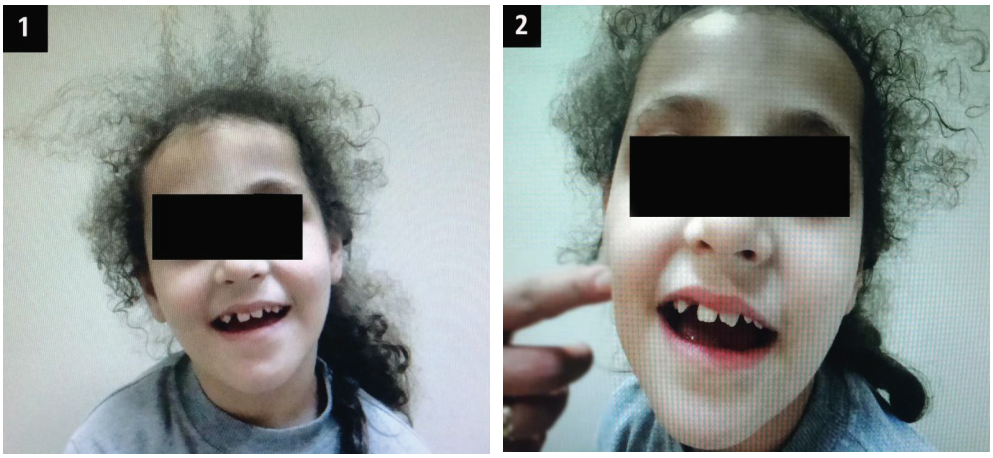

Figure 1. *Dysmorphologic findings of patient 1 (9-year-old girl).*

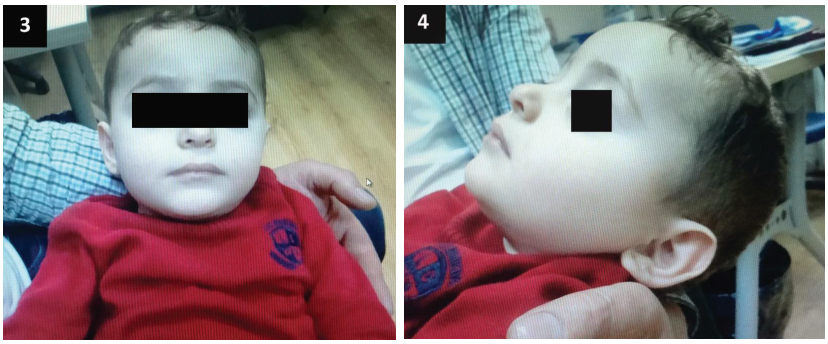

Figure 2. *Dysmorphologic findings of patient 2 (2-year-old boy).*

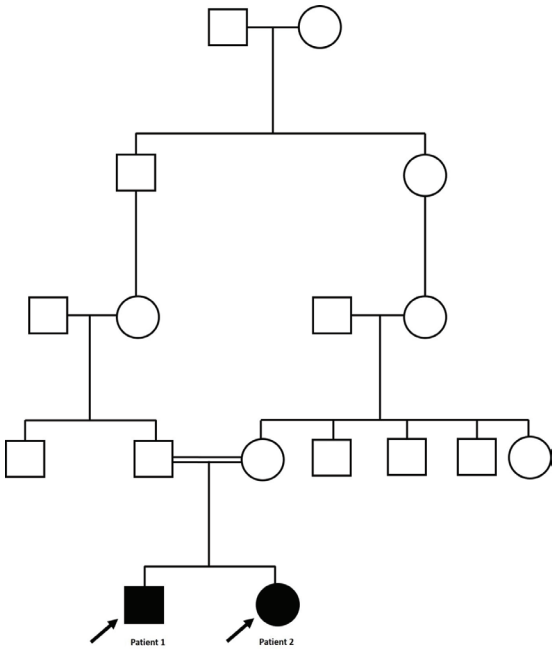

Figure 3. *Pedigree of the family with DES.*

retardation, and dysequilibrium syndrome 1 (DES 1)" (OMIM # 224050). The clinical findings of the disease were the same as the findings of the study cases. Thus, a definitive diagnosis was possible.

Discussion

Most cases of DES have been described among Hutterite families and Turkish families (6,7). However, there were clinical differences between the cases of the present study and cases previously reported by Ozcelik et al. for DES (4). Also, a study reported by Uner Tan among Turkish family showed clinical findings of walking on

Table 1. *Comparison of the patients' findings with the clinical synopsis according to OMIM.*

Clinical synopsis at OMIM	Presence of findings in our patients
Inheritance	
Autosomal Recessive	+
Growth	
Short stature	–
Head & Neck	
Strabismus	+
Cataracts, Postnatal	–
Skeletal	
Pes Planus	–
Neurologic	
Psychomotor retardation	+
Mental retardation	+
Poor speech development	+
Ataxia	+
Disturbed equilibrium	+
Quadrupedal gait	–
Intention tremor	+
Dysarthria	+
Dysmetria	+
Dysdiadochokinesis	+
Hypotonia	–
Seizures (rare)	–
Cortical gyral simplification	+
Pachygyria	+
Cerebellar hypoplasia	+
Cerebellar ataxia	+
Small brainstem	–

all four extremities from the early childhood period (7). Although our case was from a Turkish family, both the cases lacked the above mentioned clinical findings. In addition, our case had pachygyria, which could be attributed to diversity in the clinical effects due to the difference in mutations reported. The clinical findings of patients previously reported in the literature had variations (1,5,8). Table 1 summarizes the patients' findings with the clinical synopsis according to the OMIM database.

In addition, one of our patients (Patient 1: 9-year-old girl) had macrocephaly, unlike the other cases reported in the literature. Also, the macrosomic birth history reported in patient 2 (2-year-old boy) has not been reported in the literature previously. The authors suspect the novel mutation to be the causative factor for the macrocephaly and macrosomic birth history observed among the respective cases.

Conclusion

The WES was proved useful and the best available option among genetic analysis tools to be employed when there has been no specific pre-diagnosis available to be considered and there exist consanguinity among the parents. The present study recommended clinical information and anamnesis to be very important in understanding the WES result.

Acknowledgment
The authors would like to thank the patient and his family and also thank the Intergen Genetic Center for molecular analysis.

Funding
None.

Declaration of conflicting interests
The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
Informed consent was obtained from the parents.

Author details
Muhsin Elmas[1], Basak Gogus[1], Ayse Tolunay Oflu[2], Aysegul Bukulmez[2], Ebru Elmas[3], Mustafa Solak[1]
1. Medical Genetics Department, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
2. Pediatric Department, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
3. Pediatric Department, Afyonkarahisar Public Hospital, Afyonkarahisar, Turkey

References

1. Hoffmann K, Demirhan O, Aruoba D, Humphrey N, Tu S. Cerebellar hypoplasia, with quadrupedal locomotion, caused by mutations in the very low-density lipoprotein receptor gene Eur J Hum Genet 2008; 16(9):1070–4. https://doi.org/10.1038/ejhg.2008.73
2. Aicardi J. The agyria-pachygyria complex : a spectrum of cortical malformations. Brain Dev 1991; 13(1):1–8. https://doi.org/10.1016/S0387-7604(12)80289-0
3. Schurig V, Van Orman A, Bowen P, Opitz JM. Nonprogressive cerebellar disorder with mental retardation and autosomal recessive inheritance in Hutterites. Am J Med Genet 1981; 9(1):43–53. https://doi.org/10.1002/ajmg.1320090109
4. Ozcelik T, Akarsu N, Uz E, Caglayan S, Gulsuner S, Onat OE, et al. Mutations in the very low-density lipoprotein receptor VLDLR cause cerebellar hypoplasia and quadrupedal locomotion in humans. Proc Natl Acad Sci USA 2008; 105(11):4232–6. https://doi.org/10.1073/pnas.0710010105
5. Boycott KM, Bonnemann C, Herz J, Neuert S, Beaulieu C, Scott JN, et al. Mutations in VLDLR as a cause for autosomal recessive cerebellar ataxia with mental retardation (dysequilibrium syndrome). J Child Neurol 2009; 24(10):1310–5. https://doi.org/10.1177/0883073809332696
6. Pallister PD, Opitz JM, Reynolds JF. Disequilibrium syndrome in Montana Hutterites. Am J Med Genet 1985; 22(3):567–9. https://doi.org/10.1002/ajmg.1320220314
7. Tan U. Unertan syndrome: review and report of four new cases. Int J Neurosci 2008; 118(2):211–25. https://doi.org/10.1080/00207450701667808
8. Kolb LE, Arlier Z, Yalcinkaya C, Ozturk AK, Moliterno JA, Erturk O, et al. Novel VLDLR microdeletion identified in two Turkish siblings with pachygyria and pontocerebellar atrophy. Neurogenetics 2010;11(3):319–25. https://doi.org/10.1007/s10048-009-0232-y