10.4274/jcrpe.galenos.2022.2022-8-12

Case report

A New Variant of the IER3IP1 Gene: The First Case of Microcephaly, Epilepsy, and Diabetes Syndrome 1 from Turkey

Söbü E et al. Microcephaly, Epilepsy, and Diabetes Syndrome 1

Elif Söbü[1], Gül Demet Kaya Özçora[2], Elif Yılmaz Güleç[3], Bahtiyar Şahinoğlu[4], Feride Tahmiscioğlu Bucak[5]
[1]Kartal Dr. Lutfi Kirdar City Hospital, Department of Pediatric Endocrinology, Istanbul, Turkey
[2]Gaziantep Hasan Kalyoncu University, Faculty of Medical Sciences Pediatric Neurology Dept, Gaziantep, Turkey
[3]Istanbul Medeniyet University Medical School, Istanbul Goztepe Prof Dr Suleyman Yalcin City Hospital, Department of Medical Genetics, Istanbul, Turkiye
[4]Dr. Ersin Arslan Education and Research Hospital, Medical Genetics Department, Gaziantep, Turkey
[5]Bağcılar Education and Research Hospital, Pediatric Endocrinology Department, İstanbul, Turkey

What is already known on this topic?
MEDS1 manifests as microcephaly with simplified gyral pattern in combination with severe infantile epileptic encephalopathy and early-onset permanent diabetes.

What this study adds?
This is the first case reported from Turkey, differs from other cases due to the absence of a typical simplified gyral pattern on early brain MRI, the late onset of diabetes, and the presence of a new genetic variant.

Abstract
Microcephaly, Epilepsy, and Diabetes Syndrome 1 (MEDS1) is a rare autosomal recessive disorder and caused by defects in the IER3IP1 (Immediate Early Response 3 Interacting Protein 1) gene. Only 9 cases have been described in the literature. MEDS1 manifests as microcephaly with simplified gyral pattern in combination with severe infantile epileptic encephalopathy and early-onset permanent diabetes. A simplified gyral pattern has been described in all cases reported to the date. Diagnosis is made by demonstration of specific mutations in the IER3IP1 gene. In this study, we present an additional case of a patient with MEDS1 who is homozygous for the c.53C >T p.(Ala18Val) variant. The case, the first to be reported from Turkey, differs from other cases due to the absence of a typical simplified gyral pattern on early brain MRI, the late onset of diabetes, and the presence of a new genetic variant. The triad of microcephaly, generalized seizures and permanent neonatal diabetes should prompt screening for mutations in *IER3IP1*.
Keywords: Developmental delay, diabetes mellitus, epilepsy, IER3IP1, MEDS1

Elif Söbü MD, Kartal Dr. Lütfi Kırdar City Hospital, Department of Pediatric Endocrinology, Istanbul, Turkey
+90(507) 6457646
elifsobu@yahoo.com
24.08.2022
20.11.2022
0000-0002-2037-7046

Published: 23.11.2022

Introduction
The term monogenic diabetes (infantile-onset diabetes) refers to diabetes associated with monogenic defect and diagnosed usually in the first six months of life (1). Recent developments in the field of molecular genetics indicate that diabetes occurring very early in life is mostly caused by underlying monogenic defects (2,3). In fact, current studies indicate that monogenic diabetes should be considered in cases of diabetes diagnosed in the first two years of life, and these studies report that approximately 1%–6% of pediatric diabetes cases are actually neonatal diabetes (2,3,4). Microcephaly, epilepsy, and diabetes syndrome 1 (MEDS1) is an autosomal recessive neurodevelopmental disorder that was first described by Poulton et al. in 2011 and is characterized by microcephaly, simplified gyral pattern, severe epilepsy, and infantile diabetes (5). The disease is known to result from homozygous and compound heterozygous mutations in the *IER3IP1* gene, and it has so far been reported in a total of nine cases (5,6,7,8,9).
In this study, we present an additional case of a patient with MEDS1 who is homozygous for the c.53C >T p.(Ala18Val) variant. The case, the first to be reported from Turkey, differs from other cases due to the absence of a typical simplified gyral pattern on early brain MRI, the late onset of diabetes, and the presence of a new genetic variant. The triad of microcephaly, generalized seizures and permanent neonatal diabetes should prompt screening for mutations in *IER3IP1*.

Case Report
The patient was born of the first live birth from the first pregnancy of a healthy father and mother, who were first cousins. He had no siblings, was born at term, and had no complications during pregnancy or the perinatal period. He had a birth weight of 3.400 kg (−0.24 SD) with a height of 49 cm (−0.37 SD) and a head circumference of 34 cm (−0.42 SD). At the age of 11 weeks, he presented to the pediatric neurology outpatient clinic with complaints of spasms, crying, and restlessness. Neurological examination performed at presentation revealed that he had no eye contact, object tracking, and head control and that he had central hypotonia and flexor spasms. Physical examination at presentation revealed that he weighed 4.700 kg (−0.83 SD), measured 55 cm (−1.31 SD), and had a head circumference of 35.5 cm (−2.46 SD) and a conspicuous microcephaly. He had hypertelorism, depressed nasal bridge and micrognathia (Figure 1). Laboratory tests revealed blood amino acid, cerebrospinal fluid (CSF) amino acid, acyl-carnitine, and urine organic acid levels within normal limits. Electroencephalogram (EEG) showed a burst suppression pattern. Brain MRI performed at the age of 2 months revealed normal cortical sulci and gyri with normal widths for age as well as normal ventricular system with normal width for age (Figure 2). Diagnosed with epilepsy, he was started on vigabatrin and pyridoxal 5 phosphate therapy. Owing to first-degree consanguineous marriage in the family and the co-occurrence of epilepsy and dysmorphic features, whole-exome sequencing (WES) was performed on DNA obtained from the proband and parents. He was found to have a homozygous missense variation (c.53C>T/p.Ala18Val) in *IER3IP1*. We could not find any phenotype–genotype study about this mutation in the literature. Homozygous pathogenic variants of this gene have been associated with autosomal recessive microcephaly, epilepsy, and diabetes syndrome type 1 (OMIM: 614231), and *IER3IP1* is a highly conserved protein with marked

expression in the cerebral cortex and in beta cells. As the patient's seizures did not respond to the initial treatment, other drugs were introduced in the following order: levatiracetam, topiramate, clonazepam, and clobazam. Brain Computed tomography (CT) performed at the age of 9 months revealed increased distance in the CSF space, particularly remarkable in the frontal lobe (Figure 3).
While there were no clinical signs of hypogonadism that might occur with MEDS1, thyroid function tests revealed thyroid stimulating hormone (TSH) level of 0.89 IU/ml (normal range: 0.27–4.2) and free T4 level of 0.96 ng/ml (normal range: 0.87–1.76). At the age of 18 months, he presented with rapid breathing, and further tests revealed a blood glucose level of 311 mg/dl, insulin level of 4.9 mIU/L, C-peptide level of 0.43 µg/L, and HbA1c level of 7.09%; upon establishing a diagnosis of diabetes, insulin therapy was started at a dose of 0.4 U/kg. Diabetes antibodies (anti-glutamic acid decaboxylase, anti-insulin, and islet antibodies) were negative. There was no acidosis or ketonuria. Medical history was negative for polydipsia, polyuria, and significant weight loss. This variant has not been previously reported. Both parents were found to be heterozygous for the mutation.
The patient's parents provided informed consent for publication of this case report.

Preparation for Genetic Analysis
Genomic DNA extraction was performed according to manufacturer's instruction (Maxwell RSC Blood DNA kit, Promega, USA) using Maxwell RSC Instrument (Promega, USA). 30 µl of Proteinase K (PK) Solution was added into 200 µl blood sample. 300 µl of Lysis Buffer was added to blood and PK mix and incubate at 56°C for 20 minutes. After this step, each blood lysate sample was transferred to the cartridges. At the end of assay in the instrument, 50 µl DNA was eluted. The concentration of DNA was determined spectrophotometrically by measurement of the absorbance at 260/280 nm using a Nanodrop 1000 apparatus (Thermo Fisher Scientific). The concentration of DNA samples for libraries were determined by using Qubit 3.0 (Thermo Fisher Scientific). The sequencing libraries for exome sequencing were prepared according to Twist Human Core Exome Kit protocol (Twist Bioscience, USA). Paired-end 150 bp read sequencing was performed on a NovaSeq system (Illumina, USA).Ana
Results
Raw data were uploaded to the Sophia DDM (Sophia Genetics-Lausanne-Switzerland) platform and for further analysis, which detected homozygous *c.53C*>T p.(Ala18Val) (NM_016097) variation in *IER3IP1*. This detected variant could not be found in any literature report or in the healthy population database (gnomAD; https://gnomad.broadinstitute.org/). However, *in silico* prediction databases (MutationTaster, PROVEAN, SIFT) stated, in consensus, that the variation was "deleterious." The American College of Medical Genetics (ACMG) 2015 criteria qualified the variant as "Class 3 - variant of uncertain clinical significance" (10). The segregation analysis for the variation was performed with Sanger sequencing and Integrative Genomics Viewer (IGV) using samples collected from the patient's parents, and both parents were found to be heterozygous carriers of the mutation (Figure 4, Figure 5). Because the patient's clinical findings were similar to the expected symptoms of the "Microcephaly, epilepsy, and diabetes syndrome 1 (OMIM: 614231)" phenotype caused by homozygous pathogenic variants in *IER3IP1*, this mutation was thought to account for the patient's phenotypic features.

Discussion
This case report presented a male patient with homozygous variation in *IER3IP1*; this is the first case reported from Turkey and the 10th case in the literature. It differs from other cases due to absence of a typical simplified gyral pattern on brain MRI and later onset of diabetes compared with other reported cases.
MEDS1 syndrome was first reported by Poulton et al. in 2011 in two cases from two unrelated families. Common findings in these cases were microcephaly with simplified gyral pattern in combination with severe infantile epileptic encephalopathy and early-onset permanent diabetes. An autopsy specimen from one patient showed increased apoptosis in the cerebral cortex and pancreas beta cells, implicating premature cell death as the pathogenetic mechanism (5).
Microcephaly, epilepsy, and diabetes syndrome type 1 (MEDS1) (OMIM: 614231), which shows an autosomal recessive pattern of inheritance, results from a defect in the production of immediate early response 3 interacting protein 1 (IER3IP1) expressed in beta cells of the cerebral cortex and pancreas. IER3IP1 is localized to the endoplasmic reticulum (ER) and is thought to play a role in the transport of proteins between the ER and Golgi apparatus and to be involved in the ER stress response (5). The association of neonatal diabetes with *IER3IP1* mutations suggests that IER3IP1 regulates β-cell survival and/or function. Increased apoptosis in the cerebral cortex and pancreatic beta cells in autopsy samples with *IER3IP1* mutation points at early apoptosis as the pathogenic mechanism (5,7).
Neonatal diabetes refers to diabetes that is associated with a monogenic defect and is usually diagnosed in the first 6 months of life. The age at diagnosis of diabetes in the reported MEDS1 cases ranges from 14 days to 2 months (Table 1). In our case, however, diabetes emerged at age 18 months of age, later than in other reported cases (6,7,9). Although current studies have shown that monogenic diabetes usually occurs in the first 6 months, recent studies have shown that it can rarely occur at the age of 12 or even 24 months (3,11,12). The important characteristics of the cases reported in the literature are summarized in Table 1.
The detection of c.62 T > G and c.233 T > C variants in all but one of the cases reported to date, and the fact that most of the cases are in Middle Eastern and North African countries or in countries receiving immigration from these regions, indicate that these variants are probably not mutational hotspots, but rather are rare ancestral variants unique to these regions. In the case of Shalev et al, the common c.62 T > G missense variant and the novel c.79delT frameshift variant were compound heterozygous, and although this novel variant was a frameshift variant, the patient was more mildly affected than previously reported ones and survived to 8 years of age (8). This shows that variants other than two common mutations can cause different phenotypes. The c.62 T > G (p.Val21Gly) variant affects the first transmembrane hydrophobic domain of the protein, and the c.233T>C (p.Leu78Pro) variant affects the second transmembrane hydrophobic domain of the protein, impairing the protein's expression and/or function. The variant in our patient affects amino acid at position 18 in the first transmembrane hydrophobic domain, probably its mechanism of action is similar to c.62T>G, which affects amino acid at position 21. In addition, the c.62T>G variant is adjacent to the protein cleavage site. The milder phenotype of our case may be due to the fact that our variant is not so close to this cleavage site (5). Another piece of evidence supporting the pathogenicity of the variant in our patient is that the residues affected by both our patient's variant (18th residue) and the c.62T>G (21st residue) variant are located within a highly conserved 12-residue region among the species as shown below.

```
11          18 21          32
AALLCVNAIAVLHEERFLKNIG      human
AALLCVNAIAVLHEERFLKNIG    mouse
TAILFTNAIAVLHEERFLSKIG    zebrafish
AALLCVNAIAVLHEERFLKNIG    cow
```

AALLFVNAIAVLHEERFLRR blue-ringed sea krait

In differential diagnosis, Wolcott–Rallison syndrome has been reported to be the most common cause of neonatal diabetes in families with consanguine marriages (13). This syndrome, which results from a homozygous mutation in *EIF2AK3*, is characterized by insulin-dependent diabetes mellitus before 6 months of age, skeletal dysplasia after 6 months of age, and liver failure. This syndrome manifests as renal failure, microcephaly, epilepsy, and central hypothyroidism and it must be ruled out in the differential diagnosis of MEDS1 (14). Increased ER stress, and thus beta-cell death, constitutes the pathogenesis of the disease, and management requires insulin replacement (15). This syndrome may also include episodes of liver failure and skeletal anomaly in later ages, indicating the importance of early genetic diagnosis. A study that presented 4 cases of MEDS1 reported that three of the patients had skeletal findings, including osteoporosis, metaphyseal changes, osteopenia, pathological fractures, and poor modeling of long bones (6). Our patient had no skeletal anomaly.

IER3IP1 has an unclear role in the development of the cortex and in the pathogenesis of epilepsy and diabetes, but it is thought to be required during early stages of neural development, for instance, during neural progenitor proliferation. Presence of microcephaly with simplified gyration has a distinctive role in differential diagnosis and already exists during gestation. Severe infantile epileptic encephalopathy is highly unusual in primary microcephaly and has been reported only in patients with *WDR62* mutations (16). In addition, a rare combination of primary microcephaly and severe infantile epilepsy in patients with *PNKP* mutations has been reported (17).

Because our patient had refractory epilepsy, microcephaly, and axial hypotonia at the time of presentation, no specific complication at birth, and was born of parents who were first cousins, he underwent WES early and was diagnosed with MEDS1. The patient's family was asked to be vigilant about symptoms of potential diabetes with blood glucose being monitored. Diabetes emerged later than reported in other cases in the literature, but early genetic analysis allowed for diagnosing diabetes before acidosis developed. The patient did not present with microcephaly at birth, but with increasing age, it became evident. It was remarkable that the simplified gyral pattern, which was detected in all other cases, was absent on early MRI. Continued apoptosis in the postnatal period was thought to be the cause of magnetic resonance imaging (MRI) findings and microcephaly. This hypothesis was supported by increased distance in the CSF space detected on brain CT performed at the age of 9 months.

In conclusion, this is the first case of MEDS1 reported from Turkey and shows a variant that has not been previously described in the literature. Although the simplified gyral pattern, which co-occurs with the triad of microcephaly, epilepsy, and diabetes, may guide the diagnosis of MEDS1, manifestation of the symptoms may sometimes take time. Early genetic counseling should be considered in families where consanguine marriage is accompanied by epilepsy and microcephaly.

Acknowledgements

None

Ethics Informed Consent

The patient's parents provided informed consent for publication of this case report.

References

1. Lemelman MB, Letourneau L, Greeley SAW. Neonatal Diabetes Mellitus: An Update on Diagnosis and Management. Clin Perinatol. 2018 Mar;45(1):41-59. doi: 10.1016/j.clp.2017.10.006. Epub 2017 Dec 16. PMID: 29406006; PMCID: PMC5928785.
2. Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, Oram RA, Knight B, Hyde C, Cox J, Mallam K, Moudiotis C, Smith R, Fraser B, Robertson S, Greene S, Ellard S, Pearson ER, Hattersley AT; UNITED Team. Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. Diabetes Care 2016;39:1879-1888. Epub 2016 Jun 6
3. Denkboy Öngen Y, Eren E, Demirbaş Ö, Sobu E, Ellard S, De Franco E, Tarım Ö. Genotype and Phenotype Heterogeneity in Neonatal Diabetes: A Single Centre Experience in Turkey. J Clin Res Pediatr Endocrinol. 2021 Feb 26;13(1):80-87. doi: 10.4274/jcrpe.galenos.2020.2020.0093. Epub 2020 Aug 21. PMID: 32820876; PMCID: PMC7947723.
4. Delvecchio M, Mozzillo E, Salzano G, Iafusco D, Frontino G, Patera PI, Rabbone I, Cherubini V, Grasso V, Tinto N, Giglio S, Contreas G, Di Paola R, Salina A, Cauvin V, Tumini S, d'Annunzio G, Lughetti L, Mantovani V, Maltoni G, Toni S, Marigliano M, Barbetti F; Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetes (ISPED). Monogenic Diabetes Accounts for 6.3% of Cases Referred to 15 Italian Pediatric Diabetes Centers During 2007 to 2012. J Clin Endocrinol Metab 2017;102:1826-1834.
5. Poulton, C. J., Schot, R., Kia, S. K., Jones, M., Verheijen, F. W., Venselaar, H., de Wit, M.-C. Y., de Graaff, E., Bertoli-Avella, A. M., Mancini, G. M. S. Microcephaly with simplified gyration, epilepsy, and infantile diabetes linked to inappropriate apoptosis of neural progenitors. Am. J. Hum. Genet. 89: 265-276, 2011. [PubMed: 21835305, images, related citations]
6. Abdel-Salam GM, Schaffer AE, Zaki MS, Dixon-Salazar T, Mostafa IS, Afifi HH, Gleeson JG. A homozygous IER3IP1 mutation causes microcephaly with simplified gyral pattern, epilepsy, and permanent neonatal diabetes syndrome (MEDS) Am J Med Genet A. 2012;158A:2788–2796.
7. Valenzuela I, Boronat S, Martínez-Sáez E, Clemente M, Sánchez-Montañez Á, Munell F, Carrascosa A, Macaya A. Microcephaly with simplified gyral pattern, epilepsy and permanent neonatal diabetes syndrome (MEDS). A new patient and review of the literature. Eur J Med Genet. 2017 Oct;60(10):517-520. doi: 10.1016/j.ejmg.2017.07.007. Epub 2017 Jul 12. PMID: 28711742.
8. Shalev SA, Tenenbaum-Rakover Y, Horovitz Y, Paz VP, Ye H, Carmody D, Highland HM, Boerwinkle E, Hanis CL, Muzny DM, Gibbs RA, Bell GI, Philipson LH, Greeley SA. Microcephaly, epilepsy, and neonatal diabetes due to compound heterozygous mutations in IER3IP1: insights into the natural history of a rare disorder. Pediatr Diabetes. 2014 May;15(3):252-6. doi: 10.1111/pedi.12086. Epub 2013 Oct 21. PMID: 24138066; PMCID: PMC3994177.
9. Rjiba K, Soyah N, Kammoun M, Hadj Hmida I, Saad A, Mcelreavey K, Mougou-Zerelli S. Further report of MEDS syndrome: Clinical and molecular delineation of a new Tunisian case. Eur J Med Genet. 2021 Sep;64(9):104285. doi: 10.1016/j.ejmg.2021.104285. Epub 2021 Jul 3. PMID: 34229114.
10. Rubio-Cabezas O, Ellard S. Diabetes Mellitus in Neonates and Infants: Genetic Heterogeneity, Clinical Approach to Diagnosis, and Therapeutic Options. [cited 2017 Jul 16];Horm Res Paediatr. 2013 80:137–46.
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID: 25741868; PMCID: PMC4544753.
12. Letourneau L, Carmody D, Wroblewski K, Denson A, Sanyoura M, Naylor RN, Philipson LH, Greeley SAW. Diabetes presentation and management in infancy: high risk of diabetic ketoacidosis (DKA).
13. Franco De, Flanagan SE, Houghton JA, Allen HL, Mackay DJ, Temple IK, Ellard S, Hattersley AT. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. [cited 2017 Jul 16];The Lancet. 2015 386:957–63.
14. Davoodi MA, Karamizadeh Z, Ghobadi F, Shokrpour N. Wolcott-Rallison Syndrome With Different Clinical Presentations and Genetic Patterns in 2 Infants. Health Care Manag (Frederick). 2018 Oct/Dec;37(4):354-357. doi: 10.1097/HCM.0000000000000238. Erratum in: Health Care Manag (Frederick). 2019 Apr/Jun;38(2):108. PMID: 30234637.

15. Delépine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet. 2000;25:406–9.
16. Yu, T.W., Mochida, G.H., Tischfield, D.J., Sgaier, S.K., Flores-Sarnat, L., Sergi, C.M., Topc¸u, M., McDonald, M.T., Barry, B.J., Felie, J.M., et al. (2010). Mutations in WDR62, encoding a centrosome-associated protein, cause microcephaly wit simplified gyri and abnormal cortical architecture. Nat. Genet. 42, 1015–1020.
17. Shen, J., Gilmore, E.C., Marshall, C.A., Haddadin, M., Reynolds, J.J., Eyaid, W., Bodell, A., Barry, B., Gleason, D., Allen, K., et al. (2010). Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. Nat. Genet. 42, 245–249.

Table 1. The important characteristics of the cases reported in the literature.

	Poulton et al (2011)		**Abdel-Salem et al. (2012)**				**Shalev et al(2015)**	**Valenzuela et al (2017)**	**Rjiba et al (2021)**	**Current case**
			Family 1251		**Family 1578**					
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9**	**Case 10**
Gender	M	M	M	F	F	F	M	M	M	M
Consanguinity	+	+	+	+	+	+	-	-	+	+
MRI	simplified gyral pattern	simplified gyral pattern	simplified gyration, cortical atrophy, hypoplastic corpus callosum, cerebellar vermis hypoplasia	simplified gyral pattern and agenesis of corpus callosum with mild cerebellar vermis hypoplasia without atrophy	cerebral atrophywith simplified gyral pattern, and agenesis of the corpus callosum	simplified gyral pattern and agenesis of corpus callosum with normal cerebellum	simplified gyral pattern	simplified gyral pattern, ventriculomegaly and hypoplastic corpus callosum	atrophy of the supra-tentorial level without pituitary anomaly	Normal
EEG	High voltage asymmetric multifocal activity with abnormal background	hypsarrythmia	polyspikes and slow waves with burst suppression	generalized epileptic abnormalities with sharp and slow-waves	burst suppression pattern	burst suppression pattern	hypsarrythmia	Low-amplitude background in the theta-delta range, suggesting diffuse neuronal dysfunction, with no epileptiform discharges.	NA	burst suppression pattern
Genetic analysis	c.62 T > G p.Val21Gly Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.233 T > C p.Leu78Pro Homozygous	c.62 T > G/ p.Val21Gly and c.79delT/p.Phe27fsSer*25 Compound heterozygous	c.233 T > C p.Leu78Pro Homozygous	c.62 T > G p.Val21Gly Homozygous	c.53C> T p.(Ala18Val) Homozygous
Diabetes	+	+	+	+	+	+	+	+	+	+
Age at diabetes onset	NA	NA	NA	NA	40 days	14 days	NA	5 Weeks	2 months	18 months
Hypogo	+	NA	bilatera	NA	NA	NA	retractil	NA	unilater	-

nadism			l undescended testes				e testes		al cryptorchidism and small genitalia	
Skeletal findings	NA	NA	osteoporosis, metaphyseal changes	pathological fracture	poor modeling of long bones and osteopenia	NA	NA	-	NA	-
Death	18 months	27 months	5 1/2 years	26 months	31/2 years	-	8 years	7 weeks	1 year	-

Table 1. General characteristics of MEDS patients
MRI: magnetic resonance imaging, EEG: electroencephalogram , NA: not available, M: Male, F:Female.

Figures

Figure 1. Patient's facial appearance.

Figure 2. Brain MR images of the patient at the age of three months old.

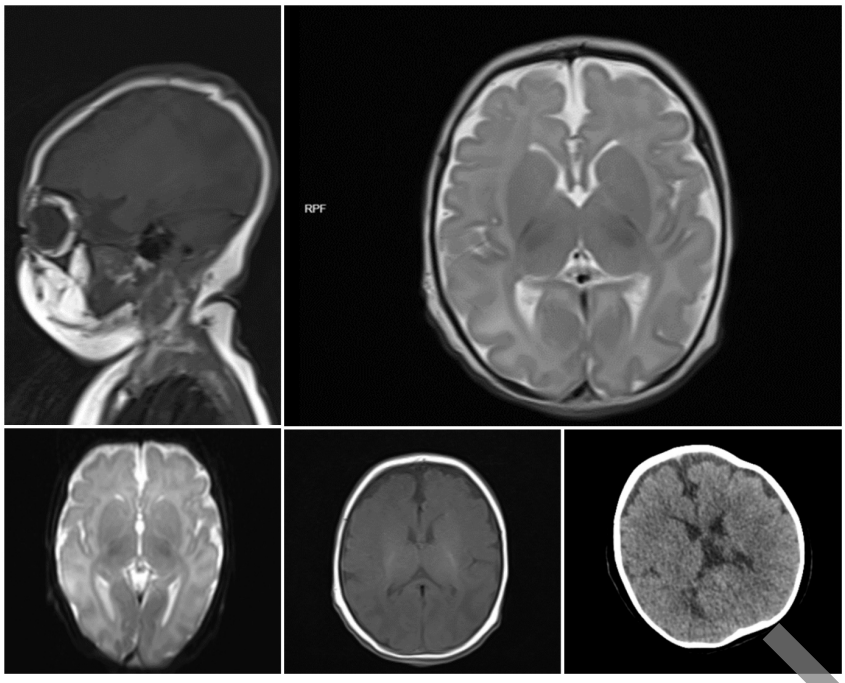

Figure 3. Brain CT at the age of 9 months old.

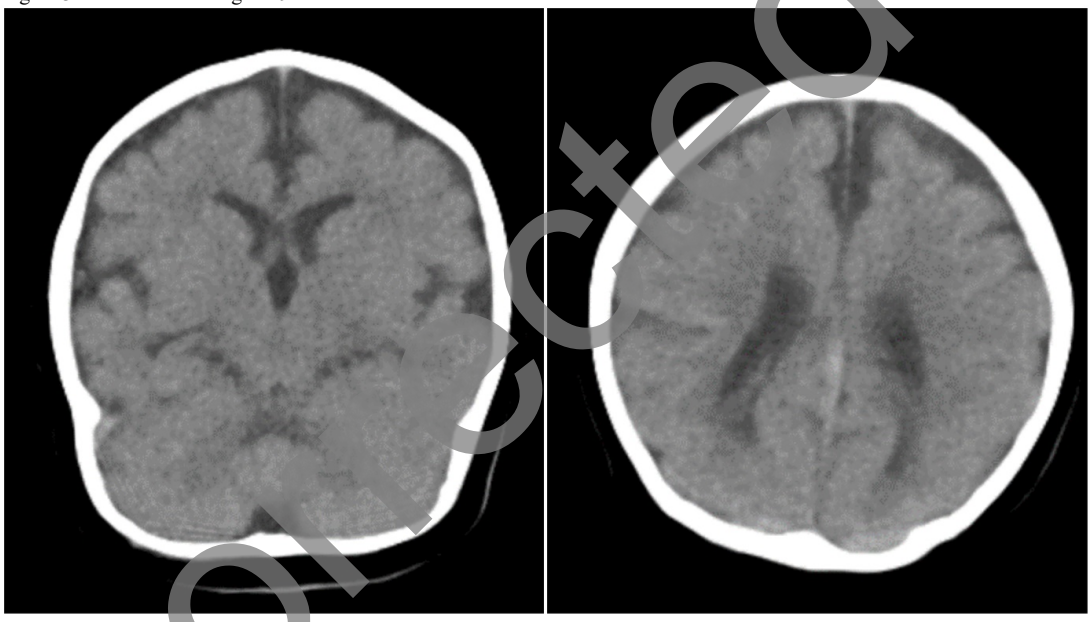

Figure 4. Results of Next-generation sequencing at the mutation locus c.53C >T p.(Ala18Val).

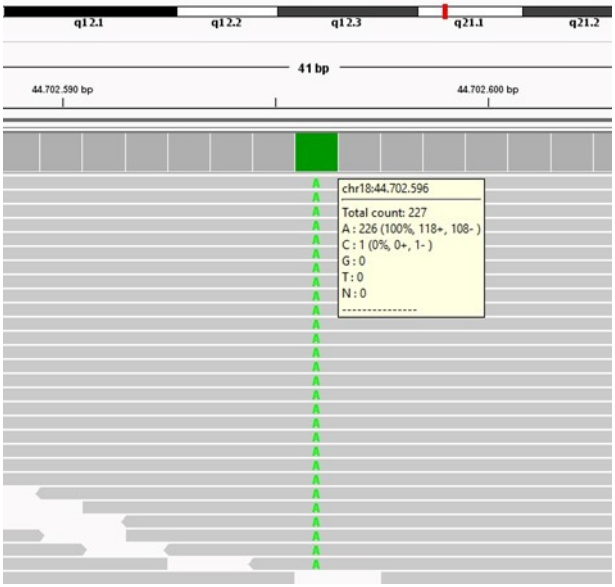

Figure 5. Integrative Genomics Viewer were used to analyse the characteristics of the mutated MEDS1 protein.