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CASE REPORT

A novel frameshift homozygous mutation in *FAT1* gene causes ptosis, nephropathy, and syndactyly in an Emirati family: case report and literature review

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ABSTRACT

Background: Single gene mutations are important causes of glomerular disease in children. Of these genes, mutations in the *FAT1* gene have been recently described in the literature as a cause of nephropathy in isolated form or multisystem involvement. The spectrum of renal disease associated with *FAT1* gene mutations varies from asymptomatic proteinuria and hematuria to severe nephrotic syndrome and end-stage renal disease.

Case Presentation: In this case report, we describe a 3-year-old child and two other family members with a novel frameshift homozygous mutation in the *FAT1* gene consistent with the diagnosis of autosomal recessive colobomatous-microphthalmia, ptosis, nephropathy, and syndactyly syndrome with variable expression of the phenotype.

Conclusion: This report adds to the genotype-phenotype correlation, highlighting the clinical importance of considering *FAT1* gene defects as part of the differential diagnosis for congenital ptosis, syndactyly and nephropathy, especially with multiple affected family members.

Keywords: *FAT1* gene, ptosis, nephropathy, syndactyly, hearing loss.

Introduction

Chronic kidney disease (CKD) in children is a significant health problem worldwide. Data about CKD's actual incidence and prevalence in children is limited (1). In Europe, the incidence of children with moderate to severe CKD is reported at about 11-12 per million of the age-related population (pmarp), while the prevalence ranged between 56-74 pmarp (1). Data from the Gulf Cooperation Council (GCC) countries which consist of Saudi Arabia, the United Arab Emirates, Kuwait, Qatar, Bahrain, and Oman is very limited. In Saudi Arabia, a study involving 36 hospitals showed the prevalence of CKD of 20.4 per million children (2). In Oman, a study on patients less than 13 years of age between 2004 and 2015 showed a mean incidence rate of CKD at 24 pmarp (3). In Kuwait, the mean incidence of CKD in children aged 0-15 years. Glomerular filtration rate (GFR) < 50 ml/minute/1.73 m^2 from 1996 to 2003 was reported at 38 pmarp, while the peak prevalence was reported at 329 pmarp in 2003 (4).

According to Kidney Disease Improving Global Outcome guidelines, CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health (5). Causes of CKD vary according to the age. Younger patients have higher rates of congenital kidney disease compared to older patients and adolescents who are more likely to have glomerular disease (6,7). Congenital anomalies of the kidney and urinary tract are the most common causes of CKD in children, and they account for about 60% of all CKD cases (6). Glomerular causes of CKD, on the other hand, account for only 10-20% of children with CKD (8,9). However, they account for a more significant proportion of patients with ESRD (10).

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With the advancement in molecular genetics testing, many single gene mutations have been linked to glomerulotubular disease. One of these important genes is the FAT1 gene, which was recently described as a cause of nephropathy. The FAT1 gene has been linked to podocyte differentiation and function. It is part of a small family of cadherin-like genes designated as FAT1-FAT4 in humans (11,12). The FAT1 proteins are involved in fundamental developmental processes, including cellular polarization, cellular migration, and cell-cell adhesion. Loss of FAT1 function causes decreased epithelial cell adhesion and effacement of the podocyte foot process, resulting in abnormal glomerular filtration and nephropathy (11,12).

The clinical manifestations of *FAT1* gene-related disorders may include ophthalmologic, central nervous system, musculoskeletal, and renal abnormalities. The data about *FAT1* gene mutation as a cause of nephropathy are evolving, and the number of affected families reported is limited. Therefore, the phenotype may not be thoroughly described. Both autosomal dominant and recessive patterns of inheritance have been described with variable degrees of disease penetrance and expression. The renal manifestations of *FAT1* gene mutation can be divided into isolated glomerulotubular nephropathy and multisystem involvement. Two distinct multisystem disorders with *FAT1* gene mutations have been described, which are characterized by 1) a combination of steroid-resistant nephrotic syndrome (SRNS), tubular ectasia, hematuria, and facultative neurological involvement (13), and 2) a combination of facial dysmorphism, colobomatous-microphthalmia, ptosis, and syndactyly with or without nephropathy (14). In this report, we describe a 3-year-old child with congenital bilateral ptosis and bilateral syndactyly without nephropathy. His father and paternal uncle manifested with the same clinical picture in addition to bilateral hearing loss and chronic kidney disease progressing to ESRD.

Case Presentation

Three Emirati patients with congenital ptosis and syndactyly were identified by the genetic team in Tawam Hospital (Al-Ain City) for clinical evaluation and follow-up. Those patients were born in consanguineous marriages (Figure 1). After obtaining written informed consent, blood samples from the patients were collected in ethylenediaminetetraacetic acid tubes.

According to the manufacturer's protocol, two affected individuals' DNAs were extracted from peripheral blood cells using a Flexigene DNA extraction kit (Qiagen Gmbh, Germany). The whole-exome sequencing was carried out by CENTOGENE AG laboratory in Rostock, Germany (www.centogene.com). Genomic DNA is enzymatically fragmented, and libraries are generated by *polymerase chain reaction*-mediated addition of Illumina compatible adapters. The libraries are paired-end sequenced on an Illumina platform to yield an average coverage depth of ~30×. An in-house bioinformatics pipeline includes reading alignment to GRCh37/hg19 genome assembly, variant calling, and annotation. Structural variant (SV) calling is based on the DRAGEN pipeline from Illumina. All variants with minor allele frequency of less than 1% in the gnomAD database and disease-causing variants reported in HGMD®, ClinVar or CentoMD® are considered. While the evaluation is focused on coding exons and flanking ±20 intronic bases, the complete gene region is interrogated for candidate variants with plausible association to the phenotype. All potential modes of inheritance patterns are considered. In addition, family history and clinical information are used to evaluate identified variants concerning their pathogenicity and causality. Variants are categorized into five classes (pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign). All variants related to the phenotype of the patient are reported. SVs of unknown significance are not reported. Orthogonal methods confirm variants with low quality

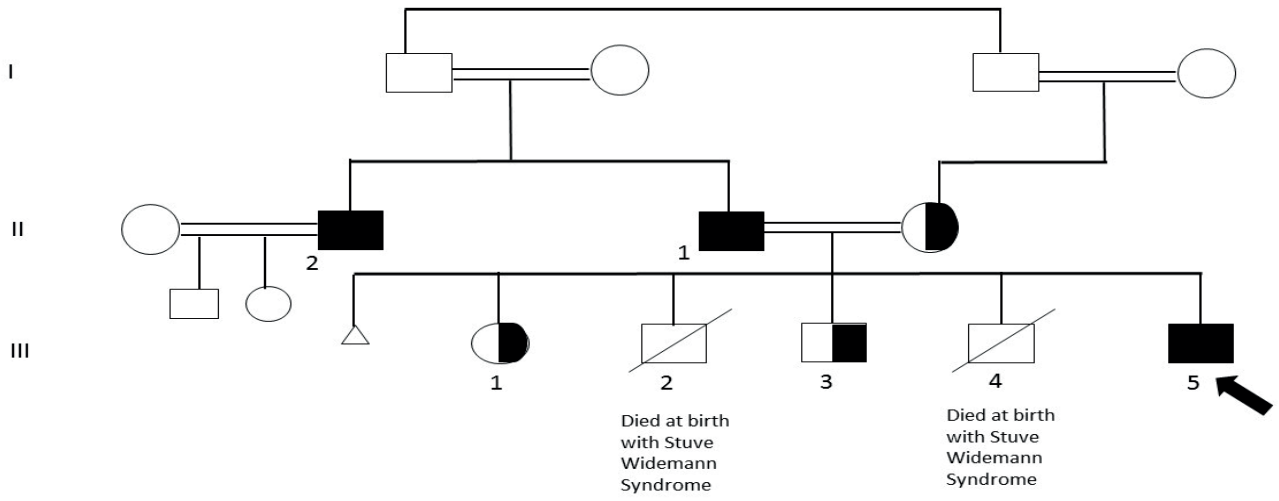

Figure 1*. Family pedigree. Circles and squares are females and males, respectively; filled symbols are affected members; half-filled symbols are carrier members; roman numbers indicate the generations; and Arabic numbers indicate offspring.*

and/or unclear zygosity. Consequently, a specificity of >99.9% for all reported variants are warranted. For the mitochondrial genome, sequence reads are aligned to the Revised Cambridge Reference Sequence of the Human Mitochondrial DNA (NC_012920) and variant calling is carried out using validated in-house software. The pipeline confidently detects heteroplasmy levels down to 15%. Structural variant (SV) calling is based on the DRAGEN pipeline from Illumina. All identified variants are evaluated concerning their pathogenicity and causality. Variants are categorized into five classes (pathogenic, likely pathogenic, VUS, likely benign, and benign). All variants related to the phenotype of the patient are reported. Centogene has established stringent quality criteria and validation processes for variants detected by NGS. Orthogonal methods confirm variants with low quality. Consequently, a specificity of >99.9% for all reported variants are warranted.

Results

Patient 1 (III-5)

A 3-year-old child, with unremarkable prenatal history and delivery history with appropriate birth growth parameters: weight = 2.92 kg, length = 53 cm, and head circumference = 35 cm, was found to have bilateral toes syndactyly at birth (right foot: first and second toes syndactyly and third and fourth toes syndactyly with mild deformity; left foot: first and second toes syndactyly and fourth and fifth toes with mild deformity, and missing the third toe). He was also noted with droopy eyelids soon after birth with no other neurological deficits or dysmorphic features. Due to similar presentation in other family members (father with congenital ptosis and toes syndactyly and unilateral polydactyly; and paternal uncle with toes syndactyly and unilateral missing toes), the child was referred to specialists for genetic evaluation, ophthalmology examination and neurological assessment. His skeletal survey showed bilateral syndactyly with absent left foot middle toe pharyngeal bone, with no abnormality in other bone structures.

Chromosomal microarray did not reveal any abnormalities. The family was requested to go for whole-exome sequencing, singleton (WES) of the child at 7 months, which was also unremarkable. The child remained otherwise in his usual state of health and continued to develop milestones appropriate for his age. With further follow-up visits, the mother revealed important history about the child's father and paternal uncle, both having CKD, which progressed to ESRD and required renal transplant. The cause of CKD was unidentified in both. The family was recounseled about sending genetic studies to the father and the uncle and agreed. When the child was 2.5 years old, whole-genome sequencing was carried out and confirmed a homozygous likely pathogenic variant in the *FAT1* gene [*FAT1* NM_005245.3: c.12990del p.(Phe4330Leufs*19)] which is consistent with the genetic diagnosis of autosomal recessive colobomatous-microphthalmia, ptosis, nephropathy, and syndactyly syndrome. His father (patient 2) is homozygous, and his mother is heterozygous for the variant. After diagnosis, the nephrology team followed the child, and he is currently 4 years old with unremarkable screening tests, including kidney function tests and urinalysis. A detailed eye exam did not show coloboma or other abnormalities apart from ptosis, and there was no issue with hearing (audiology was normal). His cardiac evaluation did not reveal any structural anomalies or arrhythmias. He had no feeding or swallowing problems, and his weight and height were within the 25th centile. He achieved all developmental milestones normally, at the time of writing this report, at 4 years of age.

Patient 2 (II-1)

Patient 2 is the father of patient 1, who is 43 years old and is known to have bilateral toes syndactyly, unilateral polydactyly, bilateral ptosis since birth, and bilateral hearing loss with unknown etiology, with CKD with complications progressing to ESRD in his early 20s. The etiology of CKD was unclear, but he was labeled as having Alport disease without genetic confirmation. As per his wife, he was initially diagnosed to have proteinuria, which progressed to renal failure. He underwent a renal transplant from an unrelated living donor at the age of 23. After 10 years of the first transplant, he presented with lower limbs edema (which worsened over time) with on/off diarrhea and increasing creatinine level. His renal graft biopsy showed chronic graft rejection with about 40-50% fibrosis. He had a second transplant at the age of 38 years. The second renal failure was thought to be due to either poor compliance to medications or reoccurrence of his undiagnosed primary disease. WES was carried out on him and showed *FAT1* gene mutation similar to his son in homozygous status. His eye exam did not show coloboma. His acoustic reflex testing thresholds were absent in both ears. His pure tone audiometry (air and bone) indicated a mixed hearing loss in both ears, more on the right side. He had normal life performance, including academic and work achievements, with no developmental or cognitive problems since early life. His skeletal survey showed bilateral toes with left foot 6th toe (polydactyly). His cardiac evaluation showed concentric left ventricular hypertrophy with septal predominance, dilated right atrium, and ventricle with good systolic function.

Patient 3 (II-2)

Patient 3 is the brother of patient 2, who is 47 years old and is known to have bilateral toes syndactyly and bilateral ptosis since birth. He had CKD in his 20s, and it progressed to ESRD in his early 30s. The etiology of CKD was also unclear. He underwent a renal transplant at the age of 30. The eye exam did not show coloboma. He started to complain of intermittent hearing loss at 25 years of age. His pure tone audiometry (air and bone) indicated sensory neural hearing loss. After finding the homozygous variant in the *FAT1* gene in his first relatives, he was tested for it and confirmed to have the same.

He had a normal life performance, including academic and work achievements, with no developmental or cognitive problems reported. He is married to his far cousin, and none of his children have ptosis or syndactyly

(none was interested in doing the genetic tests while writing this report). He did not have a cardiac evaluation at our institute.

Genetic analysis

After WES variant filtering, the same homozygous variant [GenBank NM_005245.3: c.12990del p.(Phe4330Leufs*19)] in the *FAT1* gene was identified in all affected patients in this family.

Discussion

Variants in *FAT1* have been identified in various disorders, including multiple cancer types and patients with facioscapulohumeral dystrophy-like phenotype. Coloboma and syndactyly are consistent with the clinical features seen in the new *FAT1*-associated multisystemic disorder, which is characterized by colobomatous-microphthalmia, facial dysmorphism, and ptosis, syndactyly, and occasional glomerulotubular nephropathy (15).

The reported spectrum of renal disease in *FAT1* gene mutation may range from asymptomatic proteinuria and hematuria to severe nephrotic syndrome and end-stage renal disease. In a report by Gee et al. (13), four families with *FAT1* mutations presented with SRNS, tubular ectasia, hematuria, and facultative neurological involvement. In a study by Lahrouchi (14), two patients had severe nephrotic syndrome, while three patients were found to have asymptomatic proteinuria. Milder expression of the renal disease with *FAT1* mutation was also reported by Rossanti et al. (16). In a study by Fabretti et al. (17), four patients from three families with *FAT1* mutation were reported to have heterogeneous renal phenotypes ranging from normal kidney function to early-onset ESRD.

Table 1 summarizes all reported mutations of the *FAT1* gene and the number of cases with each one. The variant c.2207dupT is the most common variant in the *FAT1* gene-associated autosomal recessive colobomatous-microphthalmia, ptosis, nephropathy, and syndactyly syndrome.

Table 1. *Reported mutations in the FAT1 gene.*

Nucleotide change	Amino acid change	Number of patients reported	Reference
c.9259C>G	p.Arg3087Gly	1 patient (double heterozygous with other variant)	Gee et al. [13]
c.5671C>A	p.Pro1891Thr	1 patient (double heterozygous with other variant)	Gee et al. [13]
c.4517G>A	p.Arg1506His	1 patient (double heterozygous with other variant)	Gee et al. [13]
c.3008C>T	p.Ala1003Val	1 patient (double heterozygous with other variant)	Gee et al. [13]
c.857A>G	p.Asn286Ser	1 patient	Gee et al. [13]
c.10570C > A	Q3524K	1 patient	Serajpour et al., [23]
c.2207dupT	p.I737NfsX7	6 patients	Lahrouchi et al. [14]
c.2600_2601delCA	p.T867IfsX4	2 patients	Lahrouchi et al. [14]
c.9729del	p. V3245LfsX25	1 patient	Lahrouchi et al. [14]
c.3093_3096del	p.P1032CfsX11	2 patients	Lahrouchi et al. [14]; Rossanti et al. [16]
c.5648T>A	p.Leu1883*	2 patients	Fabretti et al. [17]
c.8446_8447dupGC	p.Phe2817Hisfs*13	1 patient	Fabretti et al. [17]
c.2563G>A	p.Gly855Arg	1 patient (double heterozygous with other variant)	Fabretti et al. [17]
c.5539G>A	p.Val1847Ile	1 patient (double heterozygous with other variant)	Fabretti et al. [17]
c.10570C>A	p.Q3524K	1 patient	Rossanti et al. [16]
c.5480_5483del	p.Gly1827ValfsTer6	2 patients (double heterozygous with other variant)	Rossanti et al. [16]; Nagano et al., 2020 [24]
c.12867dup	p.Glu4290ArgfsTer30	2 patients (double heterozygous with other variant)	Rossanti et al. [16]; Nagano et al., 2020
c.5970_5971del	p.Asn1991PhefsTer19	1 patient	Haug et al. [15]
c.12990del	p.Phe4330Leufs*19	3 patients	This study

Here, we report three patients from the same family with variable phenotypes and have the same homozygous mutation in the *FAT1* gene. This variant is reported for the first time in humans, and both family segregation analysis and clinical correlation are strongly suggestive that this variant is pathogenic.

All of our reported patients here had congenital bilateral ptosis and syndactyly. Renal assessment in patient 1 was unremarkable, while patients 2 and 3 had proteinuria, which progressed to renal failure, and required transplant.

Two of our patients had hearing impairment in their early adulthood without identifying any genetic causes in WES apart from *FAT1* mutation. Hearing impairment has been described by Haug et al. (15) with sequence variant c.5970_5971del. In addition, a previously reported case with terminal deletion of chromosome 4q, corresponding to a heterozygous 6.9-Mb deletion in the 4q35.1–q35.2 region, including *FAT1*, presented with hearing impairment in addition to other features (18). However, further research is required to elucidate and determine the potential role of *FAT1* in hearing impairment.

Early detection of CKD in children is important to optimize patient outcomes. Among the several factors associated with CKD progression to ESRD, nephrotic range proteinuria, low baseline glomerular filtration rate (GFR), and high blood pressure were found to be the most important predictors of CKD progression to ESRD (6,10). In asymptomatic patients, kidney function is recommended to be tested and followed up regularly (14). Patients who develop CKD need to be followed for progression. In mild CKD, GFR and albuminuria need to be assessed annually, and the follow-up intervals may be shortened in patients with a higher risk of progression or where measurement will affect therapeutic decisions (5). Whether patients with recessive *FAT1* mutations are at greater risk for cancer is unclear (13,19).

Managing patients with *FAT1* mutation will require a multidisciplinary team approach to address the various issues related to their disease. As congenital anomalies of the eyes and limbs are commonly encountered in these patients, early referral for surgical correction is important to avoid potential functional loss (e.g., correction of severe bilateral ptosis to avoid poor vision). Patients with *FAT1* mutations may also have neurological manifestations, including intellectual disability, developmental delay, seizures, poor muscle tone, motor dysfunction, and poor feeding and swallowing (13). Early referral and follow-up with appropriate specialties and rehabilitation services are important in these patients. Patients who develop CKD are at risk of multiple complications, including growth retardation, cardiovascular problems, neurocognitive problems, and lower quality of life than healthy children (20). These patients need multidisciplinary team care to address all issues related to CKD. In addition, patients with progressive CKD need a timely referral for dietary counseling; education about RRT; kidney transplant options; vascular access surgery; and ethical, psychological, and social care (5). The most common causes of death in these patients are cardiovascular disease and infection (21,22). Patients undergoing renal transplants may have a fourfold survival benefit compared to dialysis patients (21). More studies are needed to explore the various aspects of prognosis and treatment strategies in patients with *FAT1* mutation.

Conclusion

In summary, to authors' knowledge, this is the first report about three Emirati patients with a novel variant in the *FAT1* gene. This report adds to the genotype-phenotype correlation, highlighting the clinical importance of considering *FAT1* gene defects as part of the differential diagnosis for congenital ptosis, syndactyly, and nephropathy, especially with multiple affected family members. More studies are needed to explore the role of *FAT1* mutation in cardiomyopathy, as one of our patients has it. This report also highlights the importance of identifying gene mutations for decision-making in terms of future surveillance, treatment strategies, and predicting prognosis. It also helps in providing genetic counseling.

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Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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 patients for publication of this case report.

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REFERENCES

1. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children [published correction appears in Pediatr Nephrol. 2012;27(3):507]. Pediatr Nephrol. 2012;27(3):363–73. https://doi.org/10.1007/s00467-011-1939-1
2. Aldrees A, Kurpad R, Al-Sabban EA, Ikram M, Abu-Aisha H. Chronic renal failure in children in 36 Saudi Arabian hospitals. Saudi Kidney Dis Transplant Bull. 1991;2(3):134–8.

3. Al Riyami MS, Al Shehhi M, Al Sulaimi T, Al Mamary L, Al Maskari A, Al Ghaithi B, et al. Epidemiology and outcome of CKD in Omani children. Kidney Int Rep. 2019;4(5):727–32. https://doi.org/10.1016/j.ekir.2019.02.014
4. Al-Eisa A, Naseef M, Al-Hamad N, Pinto R, Al-Shimeri N, Tahmaz M. Chronic renal failure in Kuwaiti children: an eight-year experience. Pediatr Nephrol. 2005;20(12):1781–5. https://doi.org/10.1007/s00467-005-2000-z
5. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco ALM, De Jong PE, et al. Kidney disease: improving global outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(1):1–150.
6. Ardissino G, Testa S, Daccò V, Viganò S, Taioli E, Claris-Appiani A, et al. Proteinuria as a predictor of disease progression in children with hypodysplastic nephropathy. Data from the Ital Kid Project. Pediatr Nephrol. 2004;19(2):172–7. https://doi.org/10.1007/s00467-003-1268-0
7. Ferris ME, Gipson DS, Kimmel PL, Eggers PW. Trends in treatment and outcomes of survival of adolescents initiating end-stage renal disease care in the United States of America. Pediatr Nephrol. 2006;21(7):1020–6. https://doi.org/10.1007/s00467-006-0059-9
8. Ardissino G, Daccò V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003;111(4 Pt 1):e382–7. https://doi.org/10.1542/peds.111.4.e382
9. NAPRTCS 2008 Annual Report: renal transplantation, dialysis, chronic renal insufficiency [cited 2021 Nov 20]. Available from: https://naprtcs.org/system/files/2008_Annual_CKD_Report.pdf
10. Warady BA, Abraham AG, Schwartz GJ, Wong CS, Muñoz A, Betoko A, et al. Predictors of rapid progression of glomerular and nonglomerular kidney disease in children and adolescents: the chronic kidney disease in children (CKiD) cohort. Am J Kidney Dis. 2015;65(6):878–88. https://doi.org/10.1053/j.ajkd.2015.01.008
11. Yaoita E, Kurihara H, Yoshida Y, Inoue T, Matsuki A, Sakai T, et al. Role of Fat1 in cell-cell contact formation of podocytes in puromycin aminonucleoside nephrosis and neonatal kidney. Kidney Int. 2005;68(2):542–51. https://doi.org/10.1111/j.1523-1755.2005.00432.x
12. Sadeqzadeh E, de Bock CE, Thorne RF. Sleeping giants: emerging roles for the fat cadherins in health and disease. Med Res Rev. 2014;34:190–221. https://doi.org/10.1002/med.21286
13. Gee H, Sadowski C, Aggarwal P, Porath JD, Yakulov TA, Schueler M, et al. FAT1 mutations cause a glomerulotubular nephropathy. Nat Commun. 2016;7:10822. https://doi.org/10.1038/ncomms10822
14. Lahrouchi N, George A, Ratbi I, Schneider R, Elalaoui SC, Moosa S, et al. Homozygous frameshift mutations in FAT1 cause a syndrome characterized by colobomatous-microphthalmia, ptosis, nephropathy and syndactyly. Nat Commun. 2019;10:1180. https://doi.org/10.1038/s41467-019-08547-w
15. Haug P, Koller S, Maggi J, Lang E, Feil S, Wlodarczyk A, et al. Whole exome sequencing in coloboma/ microphthalmia: identification of novel and recurrent variants in seven genes. Genes. 2021;12:65.
16. Rossanti R, Watanabe T, Nagano C, Hara S, Horinouchi T, Yamamura T, et al. FAT1 biallelic truncating mutation causes a non-syndromic proteinuria in a child. CEN Case Rep. 2021;10(1):100–5. https://doi.org/10.1007/s13730-020-00529-y
17. Fabretti F, Tschernoster N, Erger F, Hedergott A, Buescher AK, Dafinger C, et al. Expanding the spectrum of FAT1 nephropathies by novel mutations that affect hippo signaling. Kidney Int Rep. 2021;6(5):1368–78.
18. Vona B, Nanda I, Neuner C, Schröder J, Kalscheuer VM, Shehata-Dieler W, et al. Terminal chromosome 4q deletion syndrome in an infant with hearing impairment and moderate syndromic features: review of literature. BMC Med Genet. 2014;15:72.
19. Peng Z, Gong Y, Liang X. Role of FAT1 in health and disease (Review). Oncol Lett. 2021;21:398. https://doi.org/10.3892/ol.2021.12659
20. Greenbaum LA, Warady BA, Furth SL. Current advances in chronic kidney disease in children: growth, cardiovascular, and neurocognitive risk factors. Semin Nephrol. 2009;29(4):425–34. https://doi.org/10.1016/j.semnephrol.2009.03.017
21. McDonald SP, Craig JC; Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62. https://doi.org/10.1056/NEJMoa031643
22. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002;61(2):621–9. https://doi.org/10.1046/j.1523-1755.2002.00156.x
23. Serajpour N, Serajpour N, Karimi B, Hooman N, Hosseini R, Khosravi P. Molecular genetic analysis of steroid resistant nephrotic syndrome, detection of a novel mutation. Iran J Kidney Dis. 2019;13(3):165–72.
24. Nagano C, Yamamura T, Horinouchi T, Aoto Y, Ishiko S, Sakakibara N, et al. Comprehensive genetic diagnosis of Japanese patients with severe proteinuria. Sci Rep. 2020;10(1):1–14.