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Case Report

Bi-Allelic Heterozygous Mutations in LPR2, Presenting as Donnai-Barrow Syndrome in Two Brothers

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Abstract

Background: Donnai-Barrow/facio-oculu-acoustico-renal syndrome (DBS) is a hereditary multisystem disease in which renal involvement is characterized by low molecular weight (LMW) proteinuria. It is caused by pathogenic variants in the gene encoding Megalin , a multi-ligand receptor that plays a crucial role in LMW proteins absorption. To date, 32 patients have been described. There is no definitive treatment for this rare condition at this time. **Case-diagnosis:** We present two brothers who exhibit mild facial dysmorphism, severe hearing and vision impairment and mild renal dysfunction with LMW proteinuria. They initial presumed diagnosis was Alport syndrome; however, a final diagnosis of DBS was made by whole exome sequencing (WES). Both patients harbor two distinct novel mutations in LPR2, each inherited from one parent. **Conclusion:** Early recognition and molecular diagnosis of DBS is essential, in order to improve family education and guide treatment interventions. These include cardiac, neurologic, ophthalmologic, audiologic and renal examinations and monitoring. Prenatal and pre-implantation genetic screening should be offered to these families. In addition, special attention is emphasized for low molecular weight proteinuria in young patients.

Introduction

Several unique syndromes characterized by hereditary multisystem diseases involving brain development, somatic growth and renal structure have been described to date. Clinical manifestations include varied degrees of mental and sensorial (such as vision and hearing) insults, body malformations and renal dysfunctions. Clinical features often overlap.

Of the aforementioned syndromes, only Donnai-Barrow syndrome, Dent disease (types 1, 2) and Lowe syndrome are represented by low molecular weight (LMW) proteinuria as the characteristic manifestation of renal pathology. They have in common dysfunction of receptor mediated endocytosis (RME) of LMW proteins in the proximal tubule (PT).

Plasma albumin and LMW proteins are continuously filtered through renal glomeruli and reabsorbed by epithelial cells lining the PT via RME. In the PT, RME is carried out using the megalin/cubilin/amnionless complex [1].

Megalin is a multi-ligand receptor encoded by the LRP2 gene which belongs to the low density lipoprotein (LDL) receptor family. Pathogenic variants of the LRP2 gene cause autosomal recessive Donnai–Barrow/facio-oculo-acoustico-renal syndrome (DBS) [2].

The faciooculoacousticorenal (FOAR) syndrome was first described as comprising facial anomalies, ocular anomalies, sensorineural hearing loss and proteinuria. Facial features include prominent brow, short nose, hypertelorism, ocular anomalies include myopia, iris hypoplasia and/or retinal detachment [3]. Donnai and Barrow first described a syndrome consisting of a diaphragmatic hernia, exophthalmos, absent corpus callosum, hypertelorism, myopia and sensorineural deafness [4].

After more than 30 cases have been described over the years, characteristic clinical finding of DBS were summarized [5].

Facial features:

Large anterior fontanelle in infants and young children.

Wide metopic suture in infants and young children.

Widely spaced eyes typically marked.

Enlarged globes leading to the appearance of prominent eyes.

Down slanted palpebral fissures.

Posteriorly rotated ears.

Depressed nasal bridge.

Short nose with broad or bifid tip.

Multisystemic:

Ophthalmologic abnormalities: High myopia (-6 diopters or worse), retinal detachment (30%), retinal dystrophy and optic nerve hypoplasia, progressive visual loss, iris coloboma or iris hypoplasia in some individuals.

Sensorineural hearing loss: Onset in infancy or childhood (100%).

Developmental delay: Usually present.

Omphalocele (or umbilical hernia): (~40%).

Diaphragmatic hernia (or eventration): (~40%).

Brain malformations: Agenesis of corpus callosum (complete or partial).

Megalin interacts with varoius proteins including cubilin, with which it forms a complex together with its signaling protein, amnionless (AMN). At the apical pole of PT epithelial cells, ligand binding to the megalin/cubilin/AMN complex induces internalization into coated vesicles and delivery to endosomes and lysosomes for ligand processing and receptor degradation or recycling. Progression along the endocytic apparatus requires vesicular acidification, which is driven by the electrogenic vacuolar H+-ATPase and a neutralizing Cl- conductance. Loss of Cl- conductance leads to RME dysfunction in the PT. This is the pathophysiology of Dent's disease, which unlike DBS, is an X-linked renal tubulopathy characterized by LMW proteinuria, hypercalciuria, and renal failure. It is caused by pathogenic variants in the CLCN5 gene encoding the Cl-/ + exchanger, ClC-5.

Similar to Dent's disease, genetic inactivation of ClCN5 in mice induces a severe trafficking defect in PT cells, with loss of megalin and cubilin at the brush border and LMW proteinuria [4, 5].

Studies in patients, animal model and in-vitro preparations, have shown that the megalin-cubilin system plays a key role in the development and function of the choroid plexus, alveoli, retinal epithel, gall bladder, placenta, parathyroid and thyroid [6,7].

In a collaborative study, cellular models of DBS were generated from neuroepithelial and kidney cells, using DBS-patient-derived induced pluripotent stem cell lines. The researchers documented the inability of megalin R3192Q to properly discharge ligand and ligand-induced receptor decay in lysosomes. Thus, mutant receptors are aberrantly targeted to lysosomes for catabolism, essentially depleting megalin in the presence of ligand in affected patients [8].

All these findings shed light on the range of vulnerabilities associated with DBS and Dent disease.

We present here two brothers, sons of non-consanguineous healthy parents, with DBS, caused by bi-allelic novel variants in the LRP2 gene, one inherited from each parent.

Clinical Presentation, Diagnostic Methods

Two brothers, A.L and D.L, 21 and 16-years-old respectively, were referred to our pediatric nephrology clinic for evaluation due to a combination of chronic kidney disease (CKD) and proteinuria accompanied by vision and hearing impairment. Both parents (Romanian Ashkenazi descent, non-related) and two additional siblings of were reportedly as being healthy.

Both affected brothers had congenital exophthalmos, proptosis and severe myopia, which presented in late childhood.

A.L was diagnosed with recurrent ear infections and needed recurrent ventilating tube insertions since the age of 2 years. Hearing continued to deteriorate requiring an audio device from the age of 13 years. Retinal detachment and cataract developed, followed by consistent deterioration in vision. Otherwise, growth and development including cognitive development were normal.

At the age of 20 years, proteinuria, accompanied by microscopic hematuria and elevated serum creatinine (1.5 mg/dl) were first noticed. Over the course of five years, urine protein excretion reached 3 gr/24 H while serum creatinine remained stable. A comprehensive workup including serology tests for Immune mediated diseases, blood count, etc. were all normal. Renal ultrasonography showed normal echogenicity and size of both kidneys.

D.L. presented with a rather similar course, albeit with a normal serum creatinine.

The overall physical examinations were normal in both brothers. Notably, later in the course of the disease, slight facial asymmetry was documented, attributed to ocular and visual impairment.

Relevant laboratory data of the two brothers are summarized in table 1.

Data	A.L	D.L
Serum: creatinine (mg/dl)	1.49	0.98
Urea (mg/dl)	50	38
Na (mmol/L)	140	137
K (mmol/L)	4.5	4.1
Glucose (mg/dl)	98	94
Ca (mg/dl)	9.1	
P (mg/dl)	3.6	
Total protein (g/dl)	7.1	7
Albumin (g/dl)	4.7	4.3
Kappa FLC(mg/L)	24	
Lambda FLC (mg/L)	22.3	
FLC ratio	1.08	
Urine: protein 24 h (mg)	3017	2188
Creatinine 24 h (g)	1.5	1
Albumin/creatinine (mg/g creatinine)	109	87.8
Calcium (8.1-10.4 mg/dl)	10	9.8
Creatinine clearance (ml/min)	72.3	70.9

Table 1: Serum and urine analysis of two affected brothers.

A kidney biopsy was performed for A.L containing 35 glomeruli of which 3 were sclerotic and the remaining were phenotypically normal. Tubulointerstitial histology was normal (Figure 1). No pathology was found on immunofluorescence or electron microscopy. Due to Initial clinical suspicion of Alport syndrome, alpha chains of collagen IV monoclonal antibodies were also tested and found to be normal.

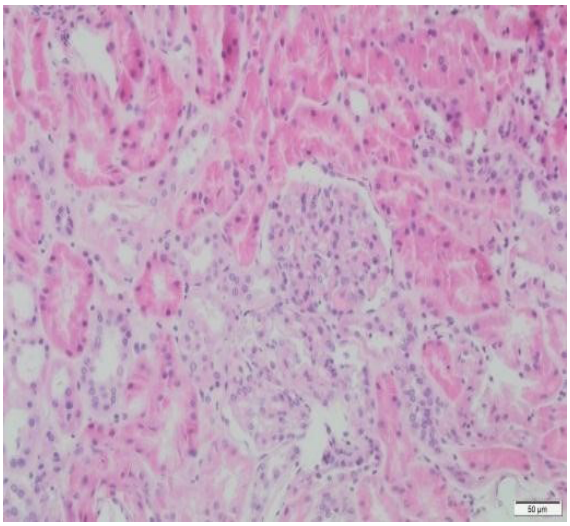

Figure 1: Two sclerotic glomeruli in specimen from kidney biopsy of A.L.

Genetic investigation:

Whole exome sequencing (WES) Quatro was performed on both the affected patients and their parents.

On exome analysis two heterozygote variants were reported as compound heterozygous in the LRP2 gen.:

LRP2:c.6899T>A; p.Ile2300Asn: Exon39/79; Missense; Exon22/79; NM_004525.3, which was found to be maternally inherited.

LRP2: c.3202delT; p.Ser1068HisfsTer118; Exon22/79; frameshift; NM_004525.3, which was found to be paternally inherited.

Both variants are rare according to population databases (frequency less than 0.0001 in Exac, gnomAD database) and predicted to be damaging by various bioinformatic prediction tools.

Following the molecular diagnosis, investigation of possible tubular absorption impairment was carried out, including calcium, lipoprotein-binding and vitamin-binding proteins. In the face of massive proteinuria with a relatively small amount of albumin, we examined the lipid profile, blood levels of vitamins B12 and D and urinary calcium. Vitamin D 25(OH) was 27.4 ng/ml in A.L. and 21 ng/dl in D.L. (normal range 32-100). Lipid profile and B 12 were normal. Urine calcium levels were between middle and high normal in both patients, in repeated tests.

Discussion

Thirty two cases of DBS have been described so far in the literature; variability of the phenotype is extremely wide. Severe phenotype described by Khalifa et al. [9], included global developmental delay, agenesis of corpus callosum (ACC), large anterior fontanel (AF), omphalocele, hearing loss and additional ocular manifestations such as hypertelorism, leucocoria, cataract, vitreous opacity, retinal detachment, myopia and blindness.

A milder phenotype has also been described, as in the report of Schrauwen et al. [10], presenting a case with myopia and mild facial dysmorphic features such as flat malar region and bulbous nose.

Age at diagnosis has been reported as early as prenatally as described by Ozdemir and co. in a case of DBS diagnosed via WES in a fetus, on the basis of congenital diaphragmatic hernia (CDH) and agenesis of corpus callosum (ACC) found by ultrasound [11].

Milder cases are diagnosed as young adults as described in our case, or later.

In the familial case we describe here, Initial suspicion of Alport syndrome delayed the diagnosis, which was finally reached by WES.

Exome sequencing revealed bi-allelic variants the LPR2 gene in the probands, inherited from each of their parents. These variants had not been described in previous cases. To note, this case was included in a series report of our nephrogenic cohort [12].

The patient's clinical and biochemical manifestations correspond to DBS [13].

Kidney histopathological changes seen in our patient were not typically described, progression to nephropathy and end-stage renal disease are rare in DBS. However, focal segmental glomerulosclerosis, nephrocalcinosis and nephrolithiasis, have been reported [14, 15].

In summary, we present two brothers who were referred to our pediatric nephrology clinic due to proteinuria. Clinical and biochemical findings characteristic of DBS were revealed, with a confirmed molecular diagnosis. Both patients harbor two distinct novel mutations in LPR2, each inherited from one parent, a genetic variant that had not been described so far in this syndrome.

In conclusion, early recognition and molecular diagnosis of DBS, like other genetic syndromes with wide phenotypic variability and clinical complications, can improve family education and guide treatment interventions. Patients with DBS should have thorough cardiac, neurologic, ophthalmologic, audiologic and renal examinations and follow up due to the gene mutation effects on those systems. Prenatal and pre-implantation genetic screening must be offered to families when disease-causing variants is suspected or known. The lack of definitive treatment at this time for this rare condition described above emphasizes even more, the necessity of a specialized genetic clinic with a suitable laboratory available, such as our facility, where the diagnosis was made.

Authors' contributions:

Ze'ev Katzir: Pediatric nephrologist in Assuta Ashdod Medical Center. The principal physician of the described patients. The main author of the manuscript.

Avital Angel-Korman: Responsible for the biochemical processing and interpretation of the data

Adi Leiba: Head of the institution of nephrology and hypertension in Assuta Ashdod medical center. Assisted the clinical and academic management of the patients.

Asaf Vivante: Head of the Nephro-genetic clinic and laboratory in Sheba medical center. Led the genetic study of the patients.

Aviva Eliyahu: Senior physician and researcher in the institute of genetics, Sheba medical center. Made the final molecular diagnosis.

References

1. Christensen EI, Birn H, Storm T, Christensen EI, Birn H (2012) Endocytic receptors in the renal proximal tubule. Physiology (Bethesda) 27: 223-236.
2. Kantarci S, Al-Gazali L, Hill RS, Donnai D, Black GC (2007) Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. Nat Genet 39: 957-959.
3. Regenbogen L, Coscas G, DebbascH S (1985) Oculocutaneous syndromes. Metab Pediatr Syst Ophthalmol 11: 14-28
4. Donnai D, Barrow M (1993) Diaphragmatic hernia, exophthalmos, absent corpus callosum, hypertelorism, myopia, and sensorineural deafness: a newly recognized autosomal recessive disorder? Am J Med Genet 47: 679-82.
5. Festa BP, Berquez M, Gassama A, Amrein I (2019) OCRL deficiency impairs endolysosomal function in a humanized mouse model for Lowe syndrome and Dent disease. Human Molecular Genetics 28: 1931-1946.
6. Christensen EI, Birn H (2002) Megalin and cubilin: multifunctional endocytic receptors. Nat Rev Mol Cell Biol 3: 256-66.
7. Fisher CE, Howie SEM (2006) The role of megalin (LRP-2/Gp330) during development. Dev Biol 296: 279-97.
8. Flemming F, Marczenke M, Rudolph IM, Nielsen R (2020) Induced pluripotent stem cell-based disease modeling identifies ligand-induced decay of megalin as a cause of Donnai-Barrow syndrome. Kidney International 98: 159-167.

9. Khalifa O, Al-Sahlawi Z, Imtiaz F, Ramzan K (2015) Variable expression pattern in Donnai-Barrow syndrome: Report of two novel LRP2 mutations and review of the literature. Eur J Med Genet 58: 293-299.

10. Schrauwen I, Sommen M, Claes C, Pinner J (2014) Broadening the phenotype of LRP2 mutations: a new mutation in LRP2causes a predominantly ocular phenotype suggestive of stickler syndrome. Clin Genet 86: 282-6.

11. Ozdemir H, Plamondon J, Gaskin P, Asoglu MR, Tura S (2020) A prenatally diagnosed case of Donnai-Barrow syndrome: Highlighting the importance of whole exome sequencing in cases of consanguinity. Am J Med Genet 182: 289-292.

12. Pode-Shakked B, Ben-Moshe Y, Barel O, Regev LC (2022) A multidisciplinary nephrogenetic referral clinic for children and adults-diagnostic achievements and insights. Pediatr Nephrol 37: 1623-1646

13. Anglani F, Terrin L, Brugnara M, Battista M (2018) Hypercalciuria and nephrolithiasis: expanding the renal phenotype of Donnai-Barrow syndrome. Clin Genet 94: 187-188.

14. Longoni M, Kantarci S, Donnai D (2008) Donnai-Barrow Syndrome. In: Adam MP, Ardinger HH, Pagon RA et al editors GeneReviews®, University of Washington, Seattle: 1993-2021.

15. Shaheen IS, Finlay E, Prescott K, Russell M, Longoni M, Joss S (2010) Focal segmental glomerulosclerosis in a female patient with Donnai-Barrow syndrome. Clin Dysmorphol 19: 35-37.