Donnai–Barrow Syndrome in Two Sisters with a Homozygous LRP2 Mutation and Renal Dysfunction: Integral Management of the Disease with Review of the Literature

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Abstract

Objectives: Donnai–Barrow syndrome (DBS) or facio occulo acoustic renal (FOAR) syndrome, DBS/FOAR (MIM# 227290) is caused by mutations in the LRP2 gene (MIM# 600073). Disease severity and penetrance vary greatly among patients carrying the same pathogenic variant(s) and single-gene variants often do not reliably predict the disease phenotypes.

Background: The LRP2 gene located on chromosome 2q31.1 band encodes megalin, a multi-ligand endocytic receptor. There are less than 50 cases reported worldwide.

Cases presentation: We report two Ecuadorian sisters born from consanguineous parents carrying a homozygous LRP2 mutation in intron 44 NM_004525.2:c.8452+1G>A. Both individuals, aged 23 and 20 years respectively, presented classical clinical features of the DBS/FOAR including craniofacial dysmorphology, hypertelorism, ocular anomalies, cataracts, high myopia, and sensorineural deafness associated with renal dysfunction (proteinuria, hypercalciuria and hypocitraturia). Both sisters were treated with hearing aids, cochlear implants, corrective lenses, cataracts surgery, vitamin D and potassium citrate supplementation, and renal protection with angiotensin II receptor antagonists.

Conclusion: As far as we know, this is the first family of DBS/FOAR resulting from consanguineous parents with a LRP2 splice site mutation NM_004525.2:c.8452+1G>A, with a complete characterization of the renal phenotype and follow-up.

Keywords: Donnai–Barrow syndrome • Facio-oculo-acoustico-renal syndrome • DBS/FOAR • LRP2 • Renal dysfunction • Ocular anomalies • Sensorineural hearing loss

Introduction

Donnai–Barrow syndrome or facio occulo acoustic renal syndrome (DBS/FOAR) (MIM# 222448) is a rare autosomal recessive disorder characterized by facial dysmorphism, agenesis/hypogenesis of the corpus callosum, enlarged anterior fontanelle, hypertelorism, high myopia, severe sensorineural deafness, congenital diaphragmatic hernia, developmental delay and low molecular weight (LMW) proteinuria with notable excretion of retinol-binding (RBP) and vitamin D-binding (DBP) proteins [1-5]. The disease had been reported as separate entities, however when more patients were described it became evident that both phenotype corresponded to the same disease. Affected people often have mild to moderate intellectual disability. Although, there is variability in the expression of some features (agenesis/hypogenesis of the corpus callosum, and proteinuria), both disorders are now considered as the same entities [3]. Focal segmental glomerulosclerosis and proximal tubule dysfunction (rarely progressing to renal insufficiency) are reported occasionally [6-8].

DBS/FOAR is an extremely rare, inherited syndrome with less than 50 cases reported worldwide [9,10]. The disease is caused exclusively by mutations of the gene LRP2 (low-density lipoprotein receptor-related protein 2); LRP2 within 79 exons (NM_004525.2) mapping to human chromosome 2q31.1, encodes megalin, an endocytic transmembrane glycoprotein [11]. Megalin plays an important role in endocytosis of numerous ligands and in various signaling pathways. The LRP2 gene is a member of a family of receptors with structural similarities to the low density lipoprotein receptor expressed in specialized epithelia, including those of the inner ear, neural tube, lower airways, epididymis, yolk sac, gonad, and proximal renal tubules [11,12]. Data are lacking regarding initial and long-term evolution of kidney function in DBS/FOAR patients. Thus, we addressed the diagnosis of two affected DBS/FOAR girls, siblings of healthy first-cousin parents, presenting with classical manifestations of this syndrome, including renal dysfunction. We described the follow-up and treatment for ocular, acoustic, renal and intellectual pathological manifestations.
Materials and Methods

Clinical report

**Patient 1:** Individual IV.1 in figure 1 is a 23-year-old girl that was the first child of healthy first cousins Ecuadorian parents, who was remitted for renal evaluation (Figure 1A). She was born at term after an uneventful pregnancy and vaginal delivery. Clinical history revealed that, at birth, she had a large anterior fontanelle, hydrocephaly and dysmorphic facial features. She also showed hypertelorism, prominent eyes, exophthalmos and short anterior fontanelle, suborbital skin creases, short nose, flat nasal bridge and broad nasal tip. She presented bilateral sensorineural deafness needing hearing aids in the infancy. Clinical examination at age 19 years revealed a still-opened anterior fontanel and myopia magna. She had prominent eyebrows, flat nasal bridge, hypertelorism, exophthalmos and low set ears (Figure 1B). Ophthalmological examination revealed high myopia and bilateral astigmatism, posterior staphyloma, left iris coloboma, macular atrophy, and congenital cataracts for which she was eventually operated at age 20 and 21, respectively. Menarche was at age 12 years-old. The patient was seen for genetic diagnosis when she was 21. Due to severe bilateral sensorineural deafness, left cochlear implant was successfully inserted at age of 22. Physical examination at the time of renal evaluation revealed a normal blood pressure. Her weight was 60 Kg, height was 150 cm and her body mass index (BMI) was 26.7 Kg/m². She had slight cognitive impairment performing a transition module to adult age. Family history revealed that she had one younger sister who had similar dysmorphic features. Another half-paternal sister was normal. At age of 21, serum creatinine was 1.18 mg/dl with an estimated glomerular filtration rate (eGFR) of 66 ml/min/1.73 m² according to chronic kidney disease epidemiology collaboration (CKD-EPI) formula; proteinuria was 1.660 mg/g creatinine. Computed tomography (CT) and magnetic resonance image (MRI) of the brain showed no anomalies. Abdominal ultrasound (US) revealed bilateral kidneys with decreased size (right-kidney 71 mm, left-kidney 78 mm), without evidence of nephrocalcinosis or nephrolithiasis. At the last visit, she had a serum creatinine of 1.10 mg/dl, a CKD-EPI of 71 ml/min/1.73 m², and proteinuria 1.720 mg/g creatinine. Urine pH and sediment were normal. The levels of serum 25(OH) vitamin-D were 9 ng/ml (normal: 30-100 ng/ml) and iPTH 108.6 pg/ml (normal: 18.5-88.0 pg/ml). We treated the patient with telmisartan (10 mg/day), potassium citrate (2.5 g/8 h) and 25(OH) vitamin D (0.266 mg/2 weeks) (Table 1).

**Patient 2:** Patient 2 IV.2 in Figure 1 is a 20-year-old woman and the younger sister of Patient 1 who visited our outpatient clinic for renal evaluation. She was the second child of healthy first cousins Ecuadorian parents (Figure 1A). She was born at term after an uneventful pregnancy and vaginal delivery. Clinical history revealed that, at birth, she had a large anterior fontanelle and dysmorphic facial features. Hearing loss was first detected at aged 2 years and

![Figure 1](image.png)

**Figure 1.** A) Pedigree (up to 4 generations) of the family with Donnai-Barrow syndrome. Black arrows indicate probands. B) Photographs of the Patient 1 (IV.1) at age 19 year-old (top), and the Patient 2 (IV.2) at age 16 year-old (bottom). Note the flat nasal bridge, broad nasal tip, prominent eyebrows, exophthalmos, hypertelorism, under orbital skin creases and retrognathia.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case IV.1</th>
<th>Case IV.2</th>
<th>Normal range</th>
</tr>
</thead>
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<td>1.25</td>
<td>1.10</td>
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<tr>
<td>eGFR, ml/min/1.73 m²</td>
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<td>61</td>
<td>71</td>
</tr>
<tr>
<td>Proteinuria, mg/g creatinine</td>
<td>1660</td>
<td>1226*</td>
<td>1720*</td>
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<tr>
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<tr>
<td>Citraturia, mg/g creatinine</td>
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<td>48***</td>
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<td>9.8</td>
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<td>-</td>
</tr>
<tr>
<td>Urine pH</td>
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<td>7</td>
<td>6.5</td>
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</tbody>
</table>

Note: *Telmisartan treatment; **Potassium citrate supplement; ***25(OH) vitamin D supplement
she started to use bilateral hearing aid at aged 5 years. Soon after birth, she was diagnosed to have a severe myopia compared with glasses from infancy. Menarche was at age 12. At age 16 years, she had also a large head with open anterior fontanelle, hypertelorism, large eyes, depressed nasal bridge and broad nasal tip (Figure 1B). Ophthalmological examination revealed high myopia bilaterally, posterior staphyloma, cataracts, and retinal dystrophy. Her glasses prescription is currently -23 diopters. Due to progression of severe bilateral sensorineural deafness, bilateral cochlear implants were inserted at age 16 and 20, respectively. She had very high cognitive deficiency; she was able to attend high-school. Physical examination at the time of renal evaluation revealed a normal blood pressure. Her weight was 58 kg, height 150 cm and her BMI 25.8 kg/m². At age of 18, her renal function showed a serum creatinine of 0.80 mg/dl and CKD-EPI of 90 ml/min/1.73 m², and proteinuria was 1.442 mg/g creatinine. Proteinuria included albumin but not LMW proteins. Urine pH and sediment were normal. CT and MRI of the brain showed no abnormalities. Abdominal US revealed kidneys with normal size without other findings. Currently, at age of 20, she has a serum creatinine of 0.88 mg/dl and CKD-EPI of 90 ml/min/1.73 m², proteinuria 1.360 mg/g creatinine, 25(OH) vitamin D 12 ng/ml (30-100 ng/ml) and iPTH 53 pg/ml (18.5-80 pg/ml). She is currently under treatment with telmisartan 10 mg/day, potassium citrate (2.5 g/8 h) and 25(OH) vitamin D (0.266 mg/2 weeks) (Table 1).

Biochemical and radiological studies

Urinal samples were collected for urinalysis: first-voided morning urine and 24-hour collection. Serial measurement of serum and urine levels of sodium, potassium, chloride, bicarbonate, uric acid, creatinine, calcium, phosphate, vitamin-D, iPTH and other biochemical values such as proteinuria, calciumuria, phosphaturia and citraturia were analyzed using standard procedures. Serial measurement of estimated glomerular filtration rate (eGFR) evolution was also analyzed in both patients. The eGFR was determined by chronic kidney disease epidemiology collaboration (CKD-EPI) equation using the serum creatinine. Patients were evaluated for nephrolithiasis, nephrolithiasis or other renal diseases by abdominal US. CT and MRI of the brain were performed by standard procedures. Intellectual development was evaluated after passing psychological tests.

Genetic analysis

DNA was extracted from peripheral blood using Chemagen technologies by The Chemagic TM360 (Perkin-Elmer, Waltham, MA), under standard procedures.

Massive parallel sequencing: After obtaining the patient’s consents, patient 1 F1V1 in Figure 1 and their parents were analyzed using next-generation sequencing (NGS; massive parallel sequencing) using a custom panel containing 1586 genes involved in known inherited diseases (gene list is available upon request). Optimizing libraries was done with Kappa, the generation patient 1 procedures.

Results

Clinical diagnosis

We ascertained two siblings with symptoms reminiscent of DBS/FOAR, with an initial suspected diagnosis of Stickler Syndrome. The evolution of craniofacial, oculo-acoustic and renal manifestations confirmed that the patients’ clinical features were consistent with DBS/FOAR. Both patients shared the characteristic dysmorphic features (hypertelorism, exophthalmos, depressed nasal bridge, short nose and posteriorly rotated ears) (Figure 1B). Serial ophthalmologic surveillance performed in both sisters revealed high bilateral myopia, posterior staphyloma, cataracts and retinal dystrophy. They underwent surgery for cataracts (Patient 1) or corrective lenses for myopia (Patient 2). Audiological examinations revealed in both individual’s bilateral sensorineural deafness needing hearing aids and/or cochlear implants. Finally, CT and MRI of the brain showed no significant anomalies. Patient 1 had mild cognitive deficiency performing a transition module-school to adult age and Patient 2 was normally schooled.
Renal dysfunction

Table 1 summarizes the evolution of biochemical data in both patients. Analysis of urine demonstrated in both patient proteinuria, hypercalciuria and hypocitraturia. In addition, both presented hypovitaminoses D. Patient 1 also showed proteinuria and chronic renal failure (CRF) stage-2 (CKD-EPI 60-90 ml/min/1.73 m²) associated to decreased kidneys size, whereas Patient 2 showed similar range of proteinuria than her sister, but with normal renal function (CKD-EPI >90 ml/min/1.73 m²) and normal size of the kidneys. There was no associated glycosuria or amino aciduria. In the context of middle proteinuria, treatment initially included angiotensin-II receptor antagonists. As can be observed this treatment had no initial impact on proteinuria after 18 months. Supplements of potassium citrate and 25(OH) vitamin-D3 were also administered (Table 1).

Figure 2. A) Next generation sequencing analysis using a clinical custom panel designed by us, Clinica v4 (see Methods), in Patient 1 (top) detecting the SNV NM_004525.2:c.8452+1G>A in homozygosity or any of her parents in heterozygosity (bottom) B) Detailed Sanger sequencing chromatogram of the LRP2 gene confirming homozygous mutation NM_004525.2:c.8452+1G>A in the first proband. C) Confirming Sanger sequencing for all family members.

Figure 3. Schematic representation of all pathogenic/likely pathogenic variants (P/LP); in box the splice junction loss described in the two patients (NM_004525.2:c.8452+1G>A). *Interestingly, it is the number of homozygous biallelic variations among P/LP (13/45; 28.9%). **As LRP2 is among the longest genes in the human genome and contains several private benign variants, extreme caution must be used in interpreting sequence changes [10]. In this case c.2522C>T(p.Thr841Met), ClinVAR classifies this variant as benign. However DECEPHER (#259113) classified this paternally inherited variant as LP in a patient with another maternally inherited LRP2 variant and the following clinical features: Blepharophymosis, cleft palate, postaxial polydactyly, preauricular skin, seizures, short stature, stenosis of the external auditory canal, talipes equinovarus.
Genetic data

Genomic analysis by NGS in the proband (Patient 1) and her parents identified a previously described LRP2-SNV: NM_004525.2:c.8452+1G>A [3], but in homozygosis, confirming diagnosis of DBS/FOAR (Figure 2A). Sanger sequencing confirmed the mutation in the proband and her sister (Patient 2), and demonstrated co-segregation with the phenotype, as parents (II-2 and II-3) were found to be heterozygous carriers (Figure 2B). The variant evolutionary conserved is classified using ACMG/AMP criteria as a pathogenic variant (PVS1, PM2, PM3, PP3, PP4, PS5), and it was previously classified as pathogenic in databases (Varsome, HGMD®, ClinVAR) [13].

The c.8452+1G>A, a splice donor variant (ADRA score 0.9999 y RBase score 0.938), seemed to be associated with megalin dysfunction [3]. We also reviewed and schematized different pathogenic/likely pathogenic (P/LP) variants currently reported in several free databases (ClinVar, Varsome, LOVD) and different articles [3, 6-10, 14-19] (Figure 3).

SNP-arrays analysis confirmed the presence of a large homozygosity block in both patients (12.2 Mb and 19.4 Mb in Patient 1 and 2, respectively) at chromosome band 2q24.2-2q31.3 (Figure 1 Supplemental Data). Overlapped region including LRP2 between the sisters was 12.2 Mb.

Discussion

Megalin and renal dysfunction

Megalin/LRP2 mediates the uptake of vitamins and proteins and is critical for clearance of amyloid-β protein from the brain [20]. Megalin is essential for the uptake of the 25(OH) Vitamin D3-DBP complexes in renal proximal tubules [21]. In addition, megalin is responsible for the normal tubular reabsorption of virtually all filtered proteins, mediating the recovery of essential substances that otherwise would be lost in the urine [22]. Furthermore, dysfunction in proximal tubules receptor-mediated endocytosis leads to protein overload in the distal nephron, which mediates inflammation and secretion of proinflammatory factors, which may be responsible of progression to CRF [22]. In fact, glomerular proteinuria and LWM proteinuria in two patients with renal biopsy revealed focal glomerulosclerosis [9]. In both affected patients a slow, progressive loss of renal function was identified at the age of 20 years. Focal segmental glomerulosclerosis was reported in other patients with Donnai-Barrow syndrome [6,7]. Although the functional implications of glomerular expression in humans have not been investigated, this points to the possibility of megalin being important for maintaining normal glomerular function [9].

Our patients affected with this homozygous LRP2 pathogenic variant (NM_004525.2:c.8452+1G>A) presented with most of the cardinal features of renal dysfunction of DBS/FOAR, including mild proteinuria, severe vitamin D deficit, hypercalcemia and hypoprotinemia without evidence of nephrocalcinosis or nephrotitis; They are receiving supplements of potassium citrate and 25(OH) vitamin D3. Currently, no other data of proximal tubulopathy (Fanconi syndrome) were detected. These findings were consistent with previous data of two patients with similar age and persistent, non-nephrotic proteinuria, with a homozygous LRP2 mutation, NM_004525.2:c.8269+1G>A, located at the full conserved donor splice site of intron 18 [9].

Intrafamilial variability of phenotypic renal features has been also previously reported [3,9,23]. Our study supports this observation; although both affected sisters presented proteinuria, Patient 1 had a reduced eGFR at the age of 23 years, whereas Patient 2 had well conserved eGFR at 20 years. In the context of mild proteinuria, treatment initially included angiotensin-II receptor antagonists in both individuals. Despite treatment with renin-angiotensin system blockers, proteinuria was refractory and unchanged during the 18 months-treatment (Table 1).

Individuals with DBS/FOAR show proteinuria, including increased spilage of RBP and DBP [3]. More recently, hypercalcemia, nephrocalcinosis, nephrotitis, and focal segmental glomerulosclerosis have been also reported [8]. Progression to nephropathy and end-stage renal disease (ESRD) is a rare but life-threatening complication, especially in adults, and urinary function should be monitored in individuals with DBS/FOAR. In fact, one of the first reported individuals eventually died due to renal failure at age 30 years [10,19]. However, only other two adults older than 50 years with molecularly confirmed LRP2 pathogenic variants have been reported [8,19]. Focal segmental glomerulosclerosis was also reported in patients with Donnai-Barrow syndrome [6,7,9]. Although the functional implications of glomerular expression in humans have not been investigated, it has been suggested the possibility of megalin as being important for maintaining normal glomerular function [9].

There is scant information on the long-term prognosis of patients with DBS/FOAR, since several individuals died early in utero or in the neonatal period. The rarity of DBS/FOAR hampers efforts to assess long-term prognosis, and on the other hand, therapeutic options to slow the progression to ESRD in patients with DBS/FOAR related nephropathy have been lacking. Regarding treatment, blockade of the renin-angiotensin system through the administration of angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists seems to decrease proteinuria and preserve renal function, perhaps owing to the direct effects of these agents on podocytes [7].

DBS/FOAR prevalence and LRP2 mutation

The prevalence and incidence of DBS/FOAR are difficult to estimate. Prevalence about <1/1000000 has been reported. Fewer than 50 individuals from around 30 families worldwide have been reported so far. DBS/FOAR affects all ethnicities, including northern and central Europeans, Middle Eastern, American of European origin, and African Americans; males and females are equally affected. As expected, it is more commonly diagnosed in the offspring of consanguineous unions (13/45; nearly 30%), where any of these individuals are members of a few large consanguineous families from: Iraq (p.Asp3828Gly), Pakistan (p.Asp3779Asn), South Arabia (p.Tyr1656Ter and p.Cys4021Tyr), United Arab Emirates (p.Y4252H), Qatar (p.Ser3120fs) or an African American family (c.6978dupG; p.Thr2327Aspfs) [3,16-18,24,25] (Table 2, Figure 3).

We describe two additional individuals from an Ecuadorian family of consanguineous parents with DBS/FOAR associated with a homozygous LRP2 mutation previously described in a patient from UK associated with DBS/FOAR (NM_004525.2:c.8452+1G>A) and discuss the clinical features, molecular details, treatment and management [3]. The mutation reported in our work had been described previously as a compound heterozygous in three affected sibs (a male of 19 years and two fetuses) from a family with DBS/FOAR originally reported by Donnai and Barrow, Kantarci et al. and Pober et al. [2,3,23]. To our knowledge, our patients would be the second family with this specific splice site mutation at intron 44 (NM_004525.2:c.8452+1G>A), but the first case reported as homozygous (biallelic inheritance of this variant).

To date, different LRP2 pathogenic or likely pathogenic variants associated with DBS/FOAR have been documented within the gene, from different parts of the world supporting that apparently all LRP2 domains are associated with similar phenotype and clinical features of the syndrome, and that all domains are required for a proper function of the protein [3,6-10,14-19,26] (Figure 3). We denoted a slightly increase of mutational events in the LDR-receptor class B domains within LRP2, but it is not significant. In fact, there seems to be no

Table 2. Updating list-number of the LRP2 variants.

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<th>Coding Impact</th>
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<th>Missense</th>
<th>Splice Junction Loss</th>
<th>Synonymous</th>
<th>Others</th>
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<tr>
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<td>11</td>
<td>11</td>
<td>0</td>
<td>-</td>
<td>45*</td>
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<tr>
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</tbody>
</table>
mutational hotspot, and no obvious genotype/phenotype correlation has been made. It is noteworthy that many mutations reported to date are expected to lead to the absence of LRP2 synthesis [16]. Indeed, nearly 40% discussed by Stora et al. or 25% (our review) are splice site mutations, and around 50% are frameshift/nonsense [19] (Table 2, Figure 3). Coding sequence variations are also all over the gene. This observation does not support previous comments of Stora and colleagues that 75% of splice site variations were located between exon 7 and exon 18, and 67% of mutations in coding sequence were located between exon 40 and exon 50. However, it is remarkable a prevalence of the homozgyous biallelic variations between exons 30 and 65 [19] (Figure 3).

In addition, different pathogenic copy number variations (upto 30 deletions and 10 duplications, ranging from 23.06 Kb to 147.54 Mb) were also reported affecting partial or the whole LRP2 gene (CLinVar, LOVD).

Management and outcome

Remarkably, there is scant clinical information on the follow-up due to the high number of non-survivors for this syndrome. For example, our family (with two members affected) represented the second series in the world of DBS/FOAR treated successfully with cochlear implants. In Patient 1 left cochlear implant was inserted at age 22 years and in Patient 2 bilateral cochlear implants were inserted at age 16 and 20 years, respectively. We found only a few isolated cases reported of Donnai–Barrow syndrome who underwent cochlear implants [10,15,27]. Recently, a series of cochlear implantation in patients with agenesis of the corpus callosum without genetic confirmation of DBS/FOAR has been reported [28].

We also observed variability in the expression of some features. This family shows a milder phenotype in the younger sister who presented with a predominant cochlear affection and milder intellectual, ocular and renal phenotype. In fact, Patient 1 underwent catacacts surgery at age 20 and 21, respectively, and Patient 2 was only treated with corrective lenses for vision problems (myopia). Therefore, the lifetime expectancy of individuals with relatively rare genetic conditions and its increasing treatment of this condition is based on the signs and symptoms present in each person, but may include hearing aids and/or cochlear implants for hearing loss, corrective lenses for vision problems and/or surgery for certain physical abnormalities such as cataracts. In addition, schooling can allow an educational development and intellectual rehabilitation management [29].

Conclusion

In conclusion, the present clinical, biochemical, and genetic investigations of two girls with DBS/FOAR provide new insights into this rare clinical entity and help further understand the pathophysiology of the renal dysfunction. We discuss the impact of homozygous LRP2 mutation on the severity of the disease, as well as the convenience of supplement of potassium citrate and 25(OH) vitamin D3 as previously suggested. Despite the initial absence of efficacy of treatment with angiotensin-II receptor antagonists on proteinuria we believe that, based in a hypothetical effect as podocytes protector, it should be maintained for long-term treatment. In addition, both sisters were good candidates for cochlear implant surgery. Corrective lenses for vision problems and/or cataracts surgery were also performed.

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Contributorship Statement

All authors were involved in drafting the manuscript, gave final approval for the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RP and JN and made substantial contributions to the concept/design and acquisition, analysis, interpretation of data, and writing the article. RM, CP, FSS, PL, and RS made substantial contributions to the acquisition, analysis, interpretation of data and figures. MP and VR made NGS studies and variant interpretations. MSL made bioinformatic alignment analysis and VCFs. RM made Sanger Sequencing analysis.

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The authors thank the affected individuals and their family who contributed to this study. The study was conducted following the Declaration of Helsinki. Written informed consents were obtained from the patients for publication of this case report and any accompanying images.

Financial Disclosure

The authors declare that they have not relevant financial interests.

References

15. Kantarci, Sibel, Ragge NK, Thomas NS and Robinson DO, et al. “Pattern in


Supplementary Figure 1: SNP-arrays analysis confirmed the presence of a large homozygosity block in both patients (12.2 Mb and 19.7 Mb in Patient 1 and 2, respectively) at chromosome band 2q24.2-2q31.3.