Received: 11 January 2018 | Revised: 12 February 2018 | Accepted: 16 February 2018

DOI: 10.1111/cge.13242

WILEY CLINICAL GENETICS

LETTER TO THE EDITOR

Hypercalciuria and nephrolithiasis: Expanding the renal phenotype of Donnai-Barrow syndrome

To the Editor:

Low molecular weight proteinuria (LMWP) is a defining feature of 2 rare genetic conditions, namely Donnai-Barrow/facio-oculo-acusti-co-renal (DB/FOAR) syndrome and Dent disease (DD).

DB/FOAR syndrome (MIM #222448) is an autosomal recessive disorder caused by mutations in the *LRP2* gene and characterized by typical craniofacial features, agenesis/hypogenesis of the corpus callosum, high-grade myopia, sensorineural hearing loss, and LMWP. Congenital diaphragmatic hernia and omphalocele are frequent additional findings.[1] Hypercalciuria, nephrocalcinosis/nephrolithiasis, and rickets have not been reported in DB/FOAR,[2] but they are, in association with LMWP, classical findings in DD, a group of X-linked renal tubulopathies caused by defects in the *CLCN5* gene encoding the Cl−/H+ antiporter ClC-5 (DD 1; MIM #300009) or in the *OCRL* gene (DD 2; MIM#300555).[3] Whereas DD 1 only affects the kidney, the spectrum of symptoms in DD 2 can range from apparent exclusive kidney manifestations to the involvement of other organs, notably brain, muscle, and eyes.

We report novel *LRP2* likely pathogenic variants in 2 patients presenting with LMWP, hearing and vision loss, and the DD classical renal phenotype.

Case 1 is a 69-year-old male presented with chronic kidney disease (CKD), incomplete Fanconi syndrome, and nephrolithiasis. At age 14, he showed progressive bilateral hearing loss and left eye blindness and at age 40 glaucoma of his right eye. At age 25, he developed acute kidney injury (AKI) with microhematuria, glomerular proteinuria, and LMWP. AKI remitted completely after tonsillectomy but mixed proteinuria persisted with incomplete Fanconi syndrome. A kidney biopsy showed hyaline glomeruli, PAS-positive mesangial hyperplasia, focal sclerosis of Bowman capsule, tubular cells with granular cytoplasm and few hyaline intraluminal casts. A bone biopsy showed osteomalacia, consistent with a diagnosis of renal rickets. He then developed calcium oxalate kidney stones, hypertension and slow progressive CKD with mixed proteinuria, and hypercalciuria with renal glycosuria.

Case 2 is a teenager of Senegalese origin with LMWP, hypercalciuria and nephrocalcinosis. Omphalocele repair surgery was performed at 6 months. As a child, he showed marked growth failure, hypertelorism, flat and wide nasal bridge, broad forehead and prominent parietal bossing, and mild psychomotor retardation. Hypophosphatemia and hypovitaminoses D and A were noted. He manifested

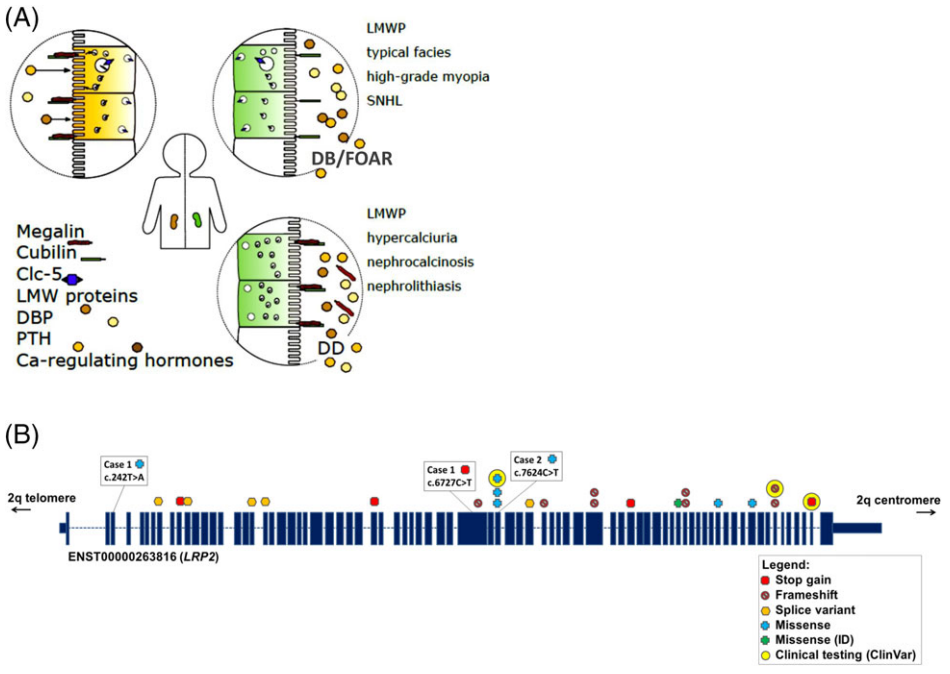

FIGURE 1 (A) Comparison of proximal tubular dysfunction in Dent disease (DD) and Donnai-Barrow/facio-oculo-acustico-renal (DB/FOAR) diseases because of ClC-5 and Megalin impairment, respectively. (B) Sequence variants in the probands and DB/FOAR patients. p.(Ile81Asn) (Case 1) and p.(Arg2542Cys) (Case 2) are in a LDL-receptor class A and B, respectively

retinal detachment and cataract in his left eye and severe myopia with peripapillary atrophy in his right eye.

Both patients had received a provisional diagnosis of DD because their renal phenotypes were consistent with the classical DD symptoms.[3]

Sanger sequencing excluded *CLCN5* and *OCRL* mutations in both cases. Whole exome sequencing discovered the c.[242T>A]; [6727C>T] variants in *LRP2* (NM_004525.2) in Case 1. One change was predicted to cause the non-conservative p.(Ile81Asn) substitution, the other to introduce a premature stop codon leading to p.(Arg2243Ter). Parental DNA was not available for testing. The homozygous c.7624C>T variant was identified in Case 2, resulting in the p.(Arg2542Cys) missense change. Both parents were unaffected carriers. These variants are not present in dbSNP, 1000 Genome, EVS, or ExAC.

The *LRP2* gene encodes Megalin, a large single-spanning transmembrane multiligand receptor, expressed in absorptive epithelia including adult kidney proximal tubules. Together with ClC-5, Megalin forms the endocytic macromolecular complex dedicated to albumin and LMW protein reabsorption (Figure 1A).[4] Case 1 is a compound heterozygote for a likely null variant and a missense variant at the N-terminus of the protein. The other missense variants previously reported in DB/FOAR patients are instead localized to the C-terminal half of Megalin (Figure 1B). We speculate that the p.(Ile81Asn) could act as a hypomorph, thus explaining the milder phenotype in Case 1.

We propose that a subset of patients presenting as DD may represent unrecognized cases or mild forms of DB/FOAR, or be on the phenotypic continuum between the 2 conditions.

Institutional review boards of Padua University Hospital and Massachusetts General Hospital approved the study. Informed consent was obtained from all the participants.

ACKNOWLEDGEMENTS

This work was supported by the University of Padua, Project BIOINFOGEN prot. STPD11F33L and by US NICHD P01HD068250.

ORCID

F. Anglani http://orcid.org/0000-0003-1534-4458

F. Anglani[1]
L. Terrin[1]
M. Brugnara[2]
M. Battista[3]
V. Cantaluppi[3]
M. Ceol[1]
L. Bertoldi[4]
G. Valle[4]
M.P. Joy[5]
B.R. Pober[5]
M. Longoni[5]

[1]*Clinical Nephrology Division, Department of Medicine-DIMED, University of Padua, Padua, Italy*
[2]*Pediatric Division, Department of Life and Reproduction Sciences, University of Verona, Verona, Italy*
[3]*Nephrology and Transplantation Division, Department of Clinical and Experimental Medicine, Amedeo Avogadro University, Novara, Italy*
[4]*CRIBI Biotechnology Centre, University of Padua, Padua, Italy*
[5]*Pediatric Surgical Research Laboratories, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*

Correspondence
Dr Franca Anglani, Dipartimento di Medicina-DIMED, Università di Padova, Via Giustiniani no. 2, 35128 Padova, Italy.
Email: franca.anglani@unipd.it

DOI 10.1111/cge.13242

REFERENCES

1. Pober BR, Longoni M, Noonan KM. A review of Donnai-Barrow and facio-oculo-acoustico-renal (DB/FOAR) syndrome: clinical features and differential diagnosis. *Birth Defects Res A Clin Mol Teratol*. 2009;85:76-81.
2. Dachy A, Paquot F, Debray G, et al. In-depth phenotyping of a Donnai-Barrow patient helps clarify proximal tubule dysfunction. *Pediatr Nephrol*. 2015;30:1027-1031.
3. Devuyst O, Thakker RV. Dent's disease. *Orphanet J Rare Dis*. 2010;5:28.
4. Gorvin CM, Wilmer MJ, Piret SE, et al. Receptor-mediated endocytosis and endosomal acidification is impaired in proximal tubule epithelial cells of Dent disease patients. *Proc Natl Acad Sci U S A*. 2013;110:7014-7019.