Renal Phenotype in Lowe Syndrome: A Selective Proximal Tubular Dysfunction

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Background and objectives: Lowe syndrome is defined by congenital cataracts, mental retardation, and proximal tubulopathy and is due to mutations in OCRL. Recently, mutations in OCRL were found to underlie some patients with Dent disease, characterized by low molecular weight proteinuria, hypercalciuria, and nephrocalcinosis. This phenotypic heterogeneity is poorly understood.

Design, setting, participants, & measurements: The renal phenotype of 16 patients with Lowe syndrome (10.9 ± 7.0 yr) under care of the authors was characterized to define overlap of symptoms with Dent disease and infer clues about OCRL function. Medical charts of patients were reviewed for data regarding glomerular filtration rate and markers of proximal tubular function.

Results: All patients had low molecular weight proteinuria and albuminuria. Lysosomal enzymuria was elevated in all 11 patients assessed. Fifteen patients had hypercalciuria, and 14 aminoaciduria. Seven patients required bicarbonate and three required phosphate replacement; all others maintained normal serum values without supplementation. None of the patients had detectable glycosuria, and none had clinically overt rickets. GFR was mildly to moderately impaired and highly variable, with a trend of deterioration with age.

Conclusions: Patients with Lowe syndrome do not have renal Fanconi syndrome but a selective proximal tubulopathy, variable in extent and dominated by low molecular weight proteinuria and hypercalciuria, the classical features of Dent disease. These findings suggest that OCRL and CIC-5, the chloride channel mutated in Dent disease, are involved in similar reabsorption pathways in the proximal tubule.


Lowe oculocerebrorenal syndrome (OMIM #309000), as originally described, consists of the triad of congenital cataracts, mental retardation, and renal tubular dysfunction (1). The molecular basis was later identified as mutations in the gene OCRL, encoding a phosphatidylinositol (4,5)-biphosphate phosphatase (PIP2P) (2).

Recently, mutations in OCRL were also found to underlie some patients with Dent disease (OMIM #300009), now called Dent2, raising the question of how mutations in the same gene could cause two seemingly distinct diseases (3). The discovery that patients with Dent2 have some evidence of systemic involvement suggested that there may be a spectrum of symptoms associated with OCRL mutations (4). It is interesting that mice deleted for OCRL function have no clinical phenotype, possibly because of compensation from other PIP2P (5). To elucidate the role of OCRL in kidney function and to define the overlap of symptoms with Dent disease, we set out to characterize the renal phenotype in all patients who had Lowe syndrome and were under care at centers in London, Nijmegen, Leiden, and Skopje.

Materials and Methods

All patients who had Lowe syndrome and were under current care at Great Ormond Street Hospital London (n = 12), Nijmegen (n = 2), Leiden (n = 1), and Skopje (n = 1) were reviewed. For all patients, the diagnosis of Lowe syndrome was based on clinical criteria; that is, all patients were boys who had the characteristic eye symptoms (cataract/glaucoma), muscular hypotonia, mental retardation, and a proximal tubulopathy. Mutational analysis of OCRL was performed for 14 patients by direct sequencing with parental consent, for which institutional ethical approval had been obtained. Mutations were classified according to GenBank accession no. NM_000276. The actual initiation codon is still controversial, and we followed the classification used by Hoopes et al. (3) using Met-18 as amino acid 1 (Swiss-Prot entry Q01968) with its A of the ATG codon as nucleotide 1, located at position...
217 to 219 in GenBank entry NM_000276. Missense mutations identified were absent in 75 control samples (50 male samples and 25 female samples = 100 X chromosomes). For two patients, consent could not be obtained. Patient charts were reviewed, and data were obtained from routine clinical assessment for GFR, glycosuria, phosphaturia, acidosis, low molecular weight proteinuria (LMWP), albuminuria, lysosomal enzymeuria, calcium, and nephrocalcinosis. For patients for whom formal GFR measurements (two-point slope clearance using $^{51}$Chromium-EDTA) were available, a modified factor k for each patient was derived from individual $^{51}$Cr-EDTA GFR measurements, when available. Otherwise, mean k of 26 was used (for further details, see text).

## Results

A summary of the results is given in Table 1. Individual patients are identified by the number indicated in column 1 of Table 1. Listed are the means of all available results for each patient. Although individual results varied over time, no trend in the change of the assessed tubular functions was discernible.

### Mutational Analysis

We identified 12 different mutations in the 14 patients analyzed. Premature termination codons (Q198X, K674X [observed twice], and R827X) were seen in four patients, and an additional six patients carried either small deletions/insertions or splice mutations that were predicted to result in the translation of an aberrant protein. Four additional patients had missense mutations (A311P, L617P, and A844T [observed twice]). Apart from the R827X nonsense mutation (8), all mutations identified have not been previously reported, consistent with the observation that OCRL mutations are generally heterogeneous (9).

### GFR

A total of 14 Chromium$^{51}$-GFR determinations were obtained for seven patients. Means ± SEM Chromium$^{51}$-GFR was 57 ± 4 ml/min per 1.73 m$^2$. Mean ± SEM value for k in the Schwartz-Haycock formula, derived from the Chromium$^{51}$-GFR measurements and simultaneous height and creatinine determinations, was 26 ± 1. Individual eGFR values, derived from serum creatinine values, are plotted in Figure 1. Individual mean

### Table 1: Summary of renal-related findings in 16 patients with Lowe syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>C Level</th>
<th>Mutation</th>
<th>eGFR (ml/min per 1.73 m$^2$) $^{k}$</th>
<th>LMWP/Chromosome (mg/mmol)</th>
<th>Albumin/Chromatin (mg/mmol)</th>
<th>Enzymuria/Chromatin (mg/mmol)</th>
<th>Amino aciduria</th>
<th>Normalized Urine Ca/Chromatin</th>
<th>Nephrocalcinosis (Age at Renal Ultrasonography)</th>
<th>HCO$_3^-$ Dosage (mmol per kg per d)</th>
<th>Normalized TMp/GFR $^{b}$</th>
<th>Glycosuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>251G/–A</td>
<td>A844T</td>
<td>27 ± 4 (20)</td>
<td>181.0 ± 268.0</td>
<td>70 ± 12</td>
<td>ND</td>
<td>Yes</td>
<td>0.9</td>
<td>ND</td>
<td>0.53</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>231G/–G</td>
<td>A844T</td>
<td>28 ± 2 (26)</td>
<td>13.8 ± 30</td>
<td>2</td>
<td>ND</td>
<td>Yes</td>
<td>1.20 ± 0.18</td>
<td>No</td>
<td>1.02 ± 0.01</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>249C/–T</td>
<td>R287X</td>
<td>40 ± 12 (26)</td>
<td>21.3 ± 2.5</td>
<td>64 ± 12</td>
<td>86 ± 14</td>
<td>Yes</td>
<td>1.32 ± 0.20</td>
<td>No</td>
<td>1.20 ± 0.12</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>1872/36</td>
<td>S625C/36X365</td>
<td>74 ± 23 (26)</td>
<td>31.1 ± 4.5</td>
<td>136 ± 27</td>
<td>244 ± 32</td>
<td>Yes</td>
<td>3.25 ± 0.36</td>
<td>No</td>
<td>1.10 ± 0.10</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>590C/–T</td>
<td>Q198X</td>
<td>60 ± 3 (26)</td>
<td>26.2 ± 3.0</td>
<td>69 ± 10</td>
<td>143 ± 18</td>
<td>Yes</td>
<td>3.37 ± 0.46</td>
<td>No</td>
<td>1.03 ± 0.08</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>203A/–T</td>
<td>K674X</td>
<td>44 ± 4 (26)</td>
<td>5.6 ± 5</td>
<td>105 ± 5</td>
<td>ND</td>
<td>Yes</td>
<td>2.47 ± 0.05</td>
<td>No</td>
<td>4.0</td>
<td>N°</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>ND</td>
<td>–</td>
<td>59 ± 2 (26)</td>
<td>53.5 ± 6</td>
<td>52 ± 27</td>
<td>46 ± 24</td>
<td>Yes</td>
<td>1.44 ± 0.10</td>
<td>No</td>
<td>2.0</td>
<td>N°</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>1552/2A/–C</td>
<td>Splice defect</td>
<td>72 ± 2 (26)</td>
<td>5.3 ± 5</td>
<td>37 ± 25</td>
<td>278 ± 41</td>
<td>Yes</td>
<td>1.42 ± 0.10</td>
<td>No</td>
<td>1.20 ± 0.05</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>203A/–C</td>
<td>K674X</td>
<td>66 ± 2 (26)</td>
<td>28.5 ± 4</td>
<td>75 ± 15</td>
<td>216 ± 21</td>
<td>Yes</td>
<td>1.34 ± 0.12</td>
<td>No</td>
<td>4.0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>2501/1, 1 + 6 del</td>
<td>Splice defect</td>
<td>47 ± 4 (27)</td>
<td>53.2 ± 5</td>
<td>143 ± 23</td>
<td>573 ± 135</td>
<td>Yes</td>
<td>1.36 ± 0.20</td>
<td>No</td>
<td>1.0</td>
<td>0.08 ND</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>2501/6 del</td>
<td>E346Q/3X35</td>
<td>50 ± 2 (26)</td>
<td>155.0 ± 64</td>
<td>208 ± 52</td>
<td>ND</td>
<td>No</td>
<td>1.32 ± 0.18</td>
<td>No</td>
<td>1.33 ± 0.14</td>
<td>No</td>
<td></td>
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<tr>
<td>12</td>
<td>5</td>
<td>1850/–C</td>
<td>L617P</td>
<td>71 ± 2 (26)</td>
<td>49.3 ± 5.2</td>
<td>138 ± 11</td>
<td>604 ± 137</td>
<td>Yes</td>
<td>1.35 ± 0.27</td>
<td>No</td>
<td>1.22</td>
<td>No</td>
<td></td>
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<tr>
<td>13</td>
<td>4</td>
<td>ND</td>
<td>–</td>
<td>49 ± 3 (26)</td>
<td>35.5 ± 13.1</td>
<td>87 ± 30</td>
<td>142 ± 72</td>
<td>Yes</td>
<td>1.47 ± 0.24</td>
<td>No</td>
<td>3.0</td>
<td>1.19 ± 0.40</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>9/3G/–C</td>
<td>A311P</td>
<td>61 ± 8 (26)</td>
<td>90.7 ± 11.3</td>
<td>185 ± 31</td>
<td>949 ± 373</td>
<td>Yes</td>
<td>1.51 ± 0.26</td>
<td>No</td>
<td>1.06 ± 0.06</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>9/3–G/A</td>
<td>Splice defect</td>
<td>74 ± 7 (26)</td>
<td>15.0 ± 3.4</td>
<td>226 ± 9</td>
<td>ND</td>
<td>No</td>
<td>1.18 ± 0.16</td>
<td>No</td>
<td>1.33 ± 0.15</td>
<td>No</td>
<td></td>
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<tr>
<td>16</td>
<td>0.7</td>
<td>1444/1445/51/21</td>
<td>D482del/drin GRP-VATCY</td>
<td>47 (26)</td>
<td>65.6 ± 155</td>
<td>719 ± 35</td>
<td>No</td>
<td>Yes</td>
<td>1.21 ± 0.24</td>
<td>No</td>
<td>1.0</td>
<td>1.28 ± 0.02</td>
<td>No</td>
</tr>
</tbody>
</table>

*Data are means ± SEM, where applicable. Abnormal values are highlighted in bold. Note the selective proximal tubular dysfunction with increased losses of amino acids, albumin, low molecular weight proteinuria (LMWP), and calcium present in all patients, whereas symptomatic renal tubular acidosis and phosphaturia were seen in only a few patients and none had glycosuria. Mutations have been classified according to reference sequence NM_000272, using Methionine encoded by c.217–219 as start codon (p.M1). For details, see text. Ca, calcium; eGFR, estimated GFR; NAG, N-acetyl-β-d-glucosaminidase; ND, no data available; TMp/GFR, tubular maximum for phosphate reabsorption.

In parentheses is given factor k from Schwartz-Haycock formula (GFR = [height [cm] * k/creatinine [μmol/L])]. K was derived from individual $^{51}$Cr-EDTA GFR measurements, when available. Otherwise, mean k of 26 was used (for further details, see text).

Measured is retinol-binding protein, except for patients 1 and 11 (α1-microglobulin) and patients 2 and 15 (β2-microglobulin).

Data are normalized to age-appropriate lower limit of normal.

Patient on phosphate supplementation.

Calciu.
values ranged between 40 and 75 ml/min per 1.73 m², but there was high intraindividual variability.

LMWP
All patients had highly elevated urinary LMWP ratios with a mean ± SEM of 40.9 ± 2.3 mg/mmol for RBP, or approximately 1000-fold the upper limit of normal (<0.04), consistent with severe LMWP.

Albuminuria
Urinary albumin/creatinine ratios were moderately elevated, with individual mean values between 64 and 284 mg/mmol (normal <10) and an overall mean ± SEM of 107 ± 12.1 mg/mmol, or approximately 10-fold the upper limit of normal.

Lysosomal Enzymuria
Data on urinary NAG excretion were available for 11 patients and elevated in all of them (see Table 1). Individual mean values were between 88 and 948 U/mmol creatinine (normal <27), and the overall mean ± SEM was 403 ± 89 mg/mmol, or approximately 15-fold the upper limit of normal.

Aminoaciduria
Fourteen patients had generalized aminoaciduria but with concentration ratios to creatinine just above the normal range in some patients but up to 10-fold the upper limit of normal in others. Two patients (patients 11 and 15) had urine amino acid concentrations in the normal range.

Hypercalciuria
Fifteen patients had elevated calcium/creatinine ratios in the urine. In the one patient (patient 1) with normocalciuria, only a single value was available. Overall mean ± SEM of calcium/creatinine ratios for the 16 patients was 1.98 ± 0.13-fold the age-adjusted upper limit of normal. There was no evidence for progression of calciuria with age.

Nephrocalcinosis
Of the 15 patients assessed, eight had ultrasound evidence of medullary nephrocalcinosis. One of those eight also had multiple echogenic foci visible on ultrasound and repeatedly passed concrements in the urine. Laboratory analysis identified them as mixed calcium oxalate and calcium phosphate stones. In addition, one of the seven patients (patient 13) without medullary nephrocalcinosis had a 4-mm echogenic focus visible on ultrasound with acoustic shadowing.

Renal Tubular Acidosis
Seven patients required bicarbonate (or equivalent citrate) supplementation with dosages between 0.4 and 4 mmol/kg per d to maintain plasma bicarbonate values in the normal range. In addition, one patient (patient 14) received citrate supplementation because of the concrement formation in his urine but had plasma bicarbonate values at the lower limit of normal before citrate therapy.

Phosphaturia
TmP/GFR values were available for 15 patients, and mean values were in the age-appropriate normal range for 12 of them. One patient (patient 9) had a borderline low value but maintained normal plasma phosphate levels without supplementation. Two patients (patients 6 and 7) required phosphate supplements, although no urine phosphate value was available for...
throughout the is, all patients exhibited oculocerebrorenal involvement. Mutation of Lowe syndrome was established on clinical grounds; that they actually have Dent2 disease, yet, importantly, the diagnosis of our patients as having Lowe syndrome, when first described in 1952, was defined as “organic aciduria, decreased renal ammonia production, hydrocephalus, and mental retardation,” thus, with respect to manifestations in the kidney, referring to impairments in specific renal tubular pathways (1). Over time, however, the definition of Lowe syndrome has been simplified to the triad of oculocerebrorenal involvement. Indeed, in our series here, LMWP was a uniform abnormality, in Lowe syndrome in concordance with our findings (12–16). Although this potentially exceeds the upper limit of normal for adults (<1.6 mmol/L) (10), the exact amount lost is unclear, of course, because of the threshold limit of the assay.

Discussion

Lowe syndrome, when first described in 1952, was defined as “organic aciduria, decreased renal ammonia production, hydrocephalus, and mental retardation,” thus, with respect to manifestations in the kidney, referring to impairments in specific renal tubular pathways (1). Over time, however, the definition of Lowe syndrome has been simplified to the triad of oculocerebrorenal involvement, mental retardation, and a renal Fanconi syndrome, the last usually suggesting a generalized proximal tubular dysfunction (11). In contrast, our results clearly point to specific tubular dysfunctions, albeit to a variable extent. This discrepancy is a consequence of the term “renal Fanconi syndrome” being applied to diseases in which more than one transport pathway in the proximal tubule is affected; however, with the increasing recognition of the distinct molecular pathways of proximal tubular function, a careful definition of clinical renal manifestations is critical to elucidate the pathophysiology of the affected proteins, such as OCRL in the kidney.

Possible explanations for this discrepancy include a mischaracterization of our patients as having Lowe syndrome, when they actually have Dent2 disease, yet, importantly, the diagnosis of Lowe syndrome was established on clinical grounds; that is, all patients exhibited oculocerebrorenal involvement. Muta
tional analysis cannot distinguish between Lowe syndrome and Dent2, because there is no clear genotype–phenotype correlation (4,12); however, mutations are not uniformly distributed throughout the OCRL gene, and there seem to be remarkable differences in their allocation leading to either Lowe syndrome or OCRL-related Dent2 (4). Mutations detected in our patients follow the distribution seen in Lowe syndrome.

Progression of the tubulopathy with age could be another potential explanation, so our almost exclusively pediatric patients may not yet exhibit the full spectrum of symptoms; however, no trend toward progression could be detected, as can also easily be seen from Table 1, in which patients are listed according to age. In fact, a detailed look at the individual features of the renal manifestations in our patients shows that, as far as available, they are comparable to those reported in other series of patients with Lowe syndrome, suggesting that the term renal Fanconi syndrome, when defined as a generalized proximal tubulopathy, has been misapplied.
three patients described by Lowe or in a large series of patients described almost 40 yr later (1,20), yet it was already described as uniformly present in 1958 and confirmed subsequently (12,22,23). The transport pathway for calcium in the proximal tubule is not yet defined but clearly is affected by OCRL dysfunction. Nephrocalcinosis and/or calculi occurred in 67% of our patients (nine of 15 assessed). It is interesting that it was not explainable by the degree of hypercalciuria, because the patients without nephrocalcinosis actually had higher urinary calcium/creatinine ratios (mean ± SEM 2.1 ± 0.45-fold the upper limit of normal) than those with nephrocalcinosis (mean ± SEM: 1.60 ± 0.15-fold the upper limit of normal). Neither was it obviously related to age, because nephrocalcinosis was already present in one patient at 1 yr of age and absent in another at 15 yr of age. Mean ± SEM age of patients with and without nephrocalcinosis at time of last ultrasound was comparable at 7.4 ± 2.0 versus 7.8 ± 2.9 yr, respectively. It is interesting that a similar variability of calcium excretion and nephrocalcinosis was observed in patients with Dent disease resulting from a CLCN5 mutation, highlighting further the phenotypic similarities in the kidney of these two diseases (24).

Acidosis. Metabolic acidosis was present in all three originally described children (1). In a subsequent review of 70 cases, 65 had values for blood carbon dioxide content available, which was normal in 12 (18%) (21). Similarly, in a later review of 23 children, eight (35%) did not require alkali substitution to maintain acid-base balance (20). In our series, nine (56%) patients maintained acid-base homeostasis without supplementation; however, plasma total carbon dioxide concentration was typically at the lower end of normal. A more detailed investigation of renal ammonia production and urine acidification, as performed originally by Lowe, might well reveal subclinical abnormalities in this group. It is interesting that Lowe argued that the decreased production of ammonia actually set his patients apart from those with renal Fanconi syndrome, in whom a strongly increased amount of ammonia was detected (25).

Phosphaturia. Lowe did not comment on phosphaturia in his three patients, but they had low to normal serum phosphate levels, as in the subsequent review of 70 cases (1,21). In the review by Charnas et al. (12), 14 (61%) of 23 patients did not require phosphate supplementation, and four of seven recently described Korean patients with Lowe syndrome developed hypophosphatemia. Obviously, the assessment of phosphaturia is complicated by the often-present elevated parathyroid hormone levels (PTH). TmP/GFR values in our patients were obtained while PTH levels were normal, and seven of the 16 patients required 1-OH cholecalciferol substitution to keep PTH in the normal range. Thus, the low serum phosphate values in the original series of patients may be partly due to secondary phosphaturia mediated by PTH, rather than primary phosphaturia from tubular dysfunction. Consistent with the normal to only slightly elevated phosphaturia is that clinical rickets was essentially absent in our patients with no obvious bone deformities.

Glycosuria. Lowe noted the absence of glycosuria in his first three patients, even when blood glucose levels were increased to 150 mg/dl in two patients (1). Similarly, in other reviews of patients with Lowe syndrome, glucose was only occasionally detected in the urine and then in marginal amounts (12,20,21). This is obviously in stark contrast to other patients with renal Fanconi syndrome, in whom glycosuria is a defining feature (26–30). The absence of glycosuria in our patients clearly argues strongly for a selective proximal tubular dysfunction in Lowe syndrome.

GFR: Comparison with the Literature

Lowe did not comment on glomerular filtration in his original description but in the subsequent review noted that creatinine clearance was variable and normal in some patients. In the later review by Charnas et al., serum creatinine values were available from 13 patients who were older than 10 yr and suggested a slow decline of GFR with age; however, a large variability in these patients was also noted. Our data are based on several formal GFR measurements, because creatinine values can be misleading in patients with abnormal muscle mass. Indeed, the mean factor k in the Schwartz-Haycock formula, derived from the formal GFR measurements in our patients, is substantially lower (k = 26) than that used for healthy children (k = 40, corresponding to a value of 0.3, when measuring creatinine in mg/dl). We suggest that using this derived factor will allow for a more accurate estimation of GFR in patients with Lowe syndrome.

Overall, our series shows a high inter- and intra-individual variability with a trend to deteriorate with age (see Figure 1). Mean GFR values were below the normal range in all patients (see Table 1).

One Gene, Two Diseases? Obligatory Symptoms with Loss of OCRL Function

The results here clearly demonstrate that the renal involvement consists of a spectrum of selective proximal tubular dysfunctions. Importantly, LMWP, albuminuria, aminoaciduria, and hypercalciuria/nephrocalcinosis, the defining features of Dent disease, predominate also in patients with Lowe syndrome. These results thus provide a better understanding of the OCRL conundrum of “one gene, two diseases”: Loss of OCRL function can cause a spectrum of renal as well as systemic symptoms. Presumably, other PIP2P can compensate for loss of OCRL, as suggested by the lack of clinical symptoms in the OCRL-deleted mouse (5). Under this model, individual variability in such compensation would explain the differing extent of symptoms.

Two Genes, One Disease: Functional Implications for OCRL and CLC-5

That loss of function in both OCRL and CLC-5 can cause Dent disease suggests that the involvement in endocytic pathways of the two proteins overlaps in the proximal tubule. Our results show an obligatory impairment of those pathways that rely on subsequent intracellular vesicle formation, whereas the reuptake of substances that are directly released in the cytosol, such as glucose, phosphate, and bicarbonate, are less affected. Indeed, OCRL has been shown to interact with clathrin and regulate vesicular transport, and the details of this interaction have been elucidated (31,32). Similarly, CLC-5 is involved in...


27. Debre R, Marie J, Cleret F, Messimy R: Late rickets coexistent with chronic nephritis and glycosuria. *Archives de Medicine des Enfants* 37: 597–606, 1934