Новая мутация c.2010delG гена *CLCN5* при болезни Дента у 11-летнего мальчика, страдающего нефролитиазом и нефрокальцинозом

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A novel mutation c.2010delG of *CLCN5* gene associated with Dent disease-1 in an 11-year-old male with nephrolithiasis and nephrocalcinosis

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Болезнь Дента-1 (ген *CLCN5*) наследуется рецессивно, сцепленно с Х-хромосомой, и характеризуется протеинурией за счет низкомолекулярных белков, гиперкальциурией, нефрокальцинозом, рецидивирующей мочекаменной болезнью и нарастающей почечной недостаточностью. Женщины являются носителями и обычно страдают незначительно. Мы представляем наблюдение 11-летнего ребенка с нефрокальцинозом и нефролитиазом с мутацией c.2010delG (или p.Asp671fs) гена *CLCN5*, которая ранее не была описана при болезни Дента-1.

У бабушки пробанда была диагностирована почечная недостаточность неясного генеза. При физикальном обследовании мальчика патологии не обнаружено, рост и артериальное давление в пределах возрастных параметров. Оксалаты в моче, цитраты натрия, мочевая кислота, бикарбонат натрия, витамин D и уровень паратгормона были в пределах нормальных значений. Определялась гиперкальциурия (9 мг/кг в сутки), протеинурия за счет низкомолекулярных белков (уровень β_2-микроглобулина 5280 мкг/л, норма менее 250 мкг/л) в суточной моче. Реабсорбция фосфатов (TPR) находилась на низком уровне – 88%. По данным ультрасонографии выявлен двусторонний (размером до 4 мм) необструктивный нефролитиаз и нефрокальциноз. Молекулярно-генетический анализ обнаружил мутацию гена *CLCN5* c.2010delG (или p.Asp671fs) со сдвигом рамки, которая была идентифицирована как стоп-кодон (см. рисунок). Учитывая выраженную гиперкальциурию, пациенту были назначены цитрат калия и тиазидные диуретики.

Почечный тубулярный ацидоз, дистальный тип, медуллярная губчатая почка, неонатальный нефрокальциноз, воздействие петлевых диуретиков, наследственная тубулопатия, хроническая гипокалиемия и бета-талассемия являются основными заболеваниями, приводящими к нефрокальцинозу как с гиперкальциурией, так и без таковой. Нормальный уровень pH крови, низкомолекулярная протеинурия, гиперкальциурия и низкий уровень тубулярной реабсорбции фосфатов без гиперкальциемии указывают на наследственную тубулопатию – болезнь Дента у нашего пациента. Генетический анализ также подтвердил диагноз – выявлена мутация гена *CLCN5*.

Ключевые слова: *дети, нефролитиаз, тубулопатия, нефрокальциноз, болезнь Дента, CLCN5.*

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Dent's disease-1 (*CLCN5* gene) is a rare X-linked recessive tubulopathy characterized by low molecular weight proteinuria, hypercalciuria, nephrolcalcinosis or nephrolithiasis, proximal tubular dysfunction and renal failure in adulthood. Females are carriers and usually mildly affected. We present an 11-year-old child with nephrocalcinosis and nephrolithiasis with c.2010delG (or p.Asp671fs) mutation in *CLCN5* gene which had not previously been reported in the Dent's disease-1.

Keywords: *child, tubulopathy, nephrolithiasis, nephrocalcinosis, Dent's disease, CLCN5.*

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INTRODUCTION

Nephrocalcinosis is characterized by the deposition of calcium in the kidney paranchyma and tubules. It is associated with conditions that cause hypercalcemia, hyperphosphatemia, and the increased excretion of calcium, phosphate, and/or oxalate in the urine. According to the laboratory results, three groups can be formed in patients with nephrocalcinosis to make a differential diagnosis; hypercalciuria with hypercalcemia, hypercalciuria without hypercalcemia and hyperphosphaturia [1].

Dent's disease-1 is a rare cause of hypercalciuria without hypercalcemia. It is characterized by low molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and chronic renal failure. In about 60% of patients with X-linked nephrolithiasis, a mutation in the *CLCN5* gene is detected (Dent disease type 1), whereas in 15%, the disease is due to a mutation in the *OCRL* gene (Dent disease type 2) [2–4]. Due to be X-linked, males are affected more severely, but females are carriers and usually only mildly affected in both forms of Dent's disease [5].

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CASE REPORT

An 11-year old boy was referred for nephrolithiasis and nephrocalcinosis. He denied any renal disease, trauma, diarrhea or constipation at past medical history. The grandmother had renal failure of unknown origine at medical family history. There was no pathological finding on the physical examination, including growth parameters and blood pressure according to age group. Laboratory findings were normal except hypercalciuria (9 mg/kg/d), 88% tubular phosphore reabsorbtion rate, low molecular weight proteinuria (B_2 microglobulin 5080 mcg/L, n <250 mcg/L) in 24 hour urine, bilateral 4 mm non obstructive nephrolithiasis and nephrocalcinosis at ultrasonography. Urinary oxalate, citrate, uric acid, serum bicarbonate, vitamin-D and parathormone values were also normal. Genetic analysis revealed mutation c.2010delG (p.Asp671fs) in the *CLCN5* gene that was detected in frame shift and identified as a stop codon (Figure). The patient was given potassium citrate and thiazide for persistant hypercalciuria.

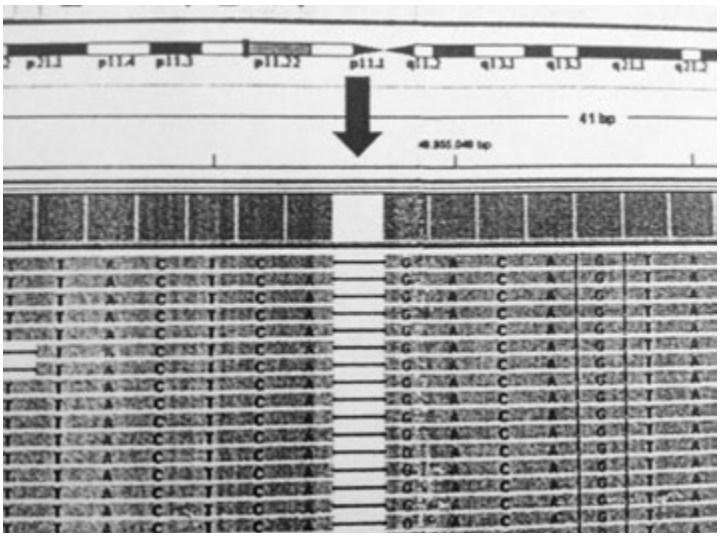

Figure. **The mutation c.2010delG (p.Asp671fs) in the *CLCN5* gene**

DISCUSSION

The clinical diagnosis of Dent's disease is based on the presence of LMW proteinuria, (elevation of B_2-microglobulin, clara cell protein RBP – retinol-binding protein) and/or about five fold above the upper limit which is pathognomonic for Dent's disease), hypercalciuria (>4 mg/kg per days characteristic for Dent's disease) and diagnosis should include at least one of the presence: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia or chronic renal disease [6, 7]. Our patient fulfilled the criteria of the group of hypercalciuria without hypercalcemia rather than the groups of hypercalciuria with hypercalcemia and hyperphosphaturia among the three groups of nephrocalcinosis. Distal renal tubuler acidosis, medullar sponge kidney, neonatal nephrocalcinosis, loop diuretics, inherited tubulopathies, chronic hypokalemia and beta thalassemia are the underlying diseases in association with the group of hypercalciuria without hypercalcemia at nephrocalcinosis [1]. Normal blood pH, low molecular weight proteinuria, hypercalciuria and lower tubular phosphore reabsorbtion rate (TPR) without hypercalcemia pointed out inherited tubulopathy and Dent's disease in our patient. Genetical analysis also confirmed the diagnosis with the mutation in *CLCN5* gene.

The exact prevalence of Dent's disease is undefined; to date, >250 families have been described [8]. Hypercalciuria and nephrocalcinosis are prevalent at a rate of 95% and 75% in affected males, respectively. Progression to end-stage renal failure are at the 3rd–5th decades of life in 30–80% of affected males [9]. In the absence of therapy targeting for the molecular defect, the current care of patients with Dent's disease is supportive, focusing on the prevention of nephrolithiasis and nephrocalcinosis. Thiazide diuretics can be used to treat hypercalciuria [10, 11].

In summary, a new mutation c.2010delG (p.Asp671fs) in the *CLCN5* gene that was first detected in frame shift and identified as a stop codon in our patient. Dent's disease should be kept in mind in nephrocalcinosis with hypercalciuria, low molecular weight proteinuria and normal blood pH at male patients.

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