

TRPC6 mutation in a patient with nephrocalcinosis

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Nephrocalcinosis is characterized by calcium deposition in the renal parenchyma and it is uncommon in childhood.

TRPC6 is a member of the transient receptor potential (TRP) superfamily of cation-selective ion channels proteins. The TRPC subfamily (TRPC1–TRPC7) is a group of calcium-permeable cation channels that is important for the increase in intracellular Ca^{2+} concentration after the engagement of G protein-coupled receptors and tyrosine kinases receptor. Winn et al previously reported that mutations in TRPC6 gene associated with familial form of FSGS, a disease leading to progressive renal failure. TRPC6 is expressed widely in the kidney especially in glomerulus and the tubulointerstitial compartment.

It is known that gene mutations changes protein functions, therefore we thought TRPC6 gene mutation is expressed in kidney cells and control intracellular calcium could have role in nephrocalcinosis.

Case:

A 2,5-year-old girl had referred to the pediatric nephrology department with a compliant polydipsia, polyuria since birth and intermittent abdomen pain. She was normotensive, systemic examination was normal. In laboratory, complete blood count, liver enzymes and bilirubin levels, serum creatinine (0.5 mg/dl) and blood urea (19) were in normal ranges for her age. Urinalysis revealed pH 5.5-6.5, specific gravity 1010. Red and white cell casts were found in the urinary sediment. She had no proteinuria (2.5 mg/m²/h). A defect in urine-concentrating ability was discovered, osmolarity was found 326 mosmol/kg after overnight fluid restriction. Her serum parathyroid hormone level was normal (25 pg/ml). Serum phosphate 5.1 mg/dl (1.63 mmol/L), serum calcium 9 mg/dl (2.25 mmol/L) and urinary calcium excretion levels 2.5 mg/kg/day (<4) were normal. Blood gases revealed normal. A renal and bladder ultrasound showed echogenic foci in both kidneys consistent with extensive medullary nephrocalcinosis. An intravenous pyelogram (IVP) was performed, guided by the appearance of the extensive nephrocalcinosis, not showed obstruction. At 19-years old; laboratory findings including complete blood count, liver enzymes, serum creatinine (0.8 mg/dl) and blood urea (17 mg/dl) were normal. Serum phosphate, serum calcium and urinary calcium excretion levels were normal. Osmolarity was 251 mosmol/kg. She had no proteinuria (1.6 mg/m²/h). The patient was thought to have MSK with nephrocalcinosis and was performed a 3D CT and diagnosed as MKS.

DNA was isolated from the peripheral blood. TRPC6 gene mutations were analyzed by the direct DNA sequencing method all the exons by using exon-intron boundary primers. Following nucleotide exchanges has been detected in TRPC6 gene.

1. c.43C>T; p.Pro15Ser heterozygote missense mutation
2. c.1211C>T; p.Ala404Val homozygote missense mutation
3. c.1683T>C; p.Asn561Asn homozygote silence mutation
4. c.172-86G>C; p. intron splice site mutations

Ala404Val and Asn561Asn missense mutations have already been reported and phenotypic expression of these was not known. Proserin mutation which is located the end of the protein was first found, and function of the mutation was not known. P112Q mutations, which were found in the same location of the protein, lead to both increased amplitude and duration of calcium influx. We thought that the mutations which thought to lead TRPC6 dysfunction have role in nephrocalcinosis in our patient.