# CLINICAL PRESENTATION OF A PATIENT WITH A NOVEL HOMOZYGOUS MUTATION IN THE *TRPM6* GENE

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**Background**

Hereditary hypomagnesemia with secondary hypocalcemia (HSH) is a rare autosomal recessive disease caused by mutations in the Transient Receptor Potential Melastatin 6 (*TRPM6*) gene. It is characterized by severe hypomagnesemia and hypocalcemia which lead to seizures, tetany, and muscle spasms presenting within the first months of life.

The *TRMP6* gene, encoding the epithelial $Mg^{2+}$ channel TRPM6, is mapped to chromosome 9q22. TRMP6 mRNA, which is expressed in intestinal epithelial cells and kidney tubules, has a crucial role for transcellular $Mg^{2+}$ absorption from the intestine and distal convoluted tubules. Existence of a mutant TRMP6 channel leads to impaired intestinal $Mg^{2+}$ reabsorption and enhanced renal loss.

**Aim**

Here, we report the clinical characteristics and genetic analysis of a Turkish inbred girl with HSH due to a novel *TRPM6* gene mutation

**Case report**

She had presented to another clinic with seizures due to hypomagnesemia at the age of 2 months. She was born at term with normal birth weight and length after an uneventful pregnancy. Parents were cousins. Family history was unremarkable regarding hypomagnesemia, hypocalcemia, or seizures (Figure 1).

At the time of first seizure, she had severe hypomagnesemia and hypocalcemia. (Table 1). Intravenous $Mg^{2+}$ sulfate was administered, and she was discharged with subsequent oral magnesium (elemental magnesium oxide 40 mg/kg/day) and calcium gluconate. She had followed-up at another clinic.

At the age of 3.6 years, she admitted to our clinic with complains of chronic diarrhea. She was on magnesium hydroxide theraphy and the daily dose of magnesium was varied due to the severity of diarrhea. Her weight was 14 kg (-0.94 SDS), height was 97.5 cm (-0.69 SDS), BMI was 14.7 (-0.54 SDS). Systemic evaluation was normal and there were no dysmorphic features. Laboratory evaluation revealed normal (Table 1).

Table 1. Laboratory evaluations at presantation and follow-up

| | At presentation | Follow-up (under oral $Mg^{+2}$ therapy) | | |
|---|---|---|---|---|
| **Age** | 2 months | 1 years old | 3,6 years old | 6 years old |
| **Serum Mg** | <0.6 mg/dL | 1.1 | 1 | 1.2 |
| **Serum Ca (mg/dL)** | 6 | 8.5 | 9 | 8.9 |
| **Fe Mg (%)** | NA | 3.9 | 5.5 | NA |
| **PTH (pg/mL)** | 5 | 20 | 43 | 40 |
| **Vitamin -D (ng/mL)** | 32 | NA | NA | 28 |

Molecular genetic analysis of *TRPM6* was performed by direct sequencing of the coding region and the intron/exon boundaries. A homozygous frame-shift mutation (c.3447delT> p.F1149fs) was identified in the *TRPM6* gene. This mutation led to a truncated TRPM6 protein causing a complete loss of function (Figure 2)

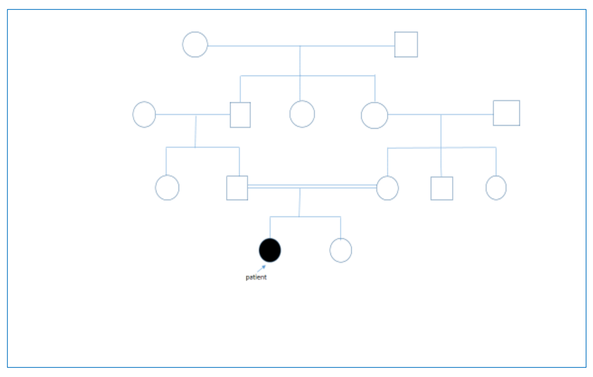


Figure 1. Pedigree of the patient

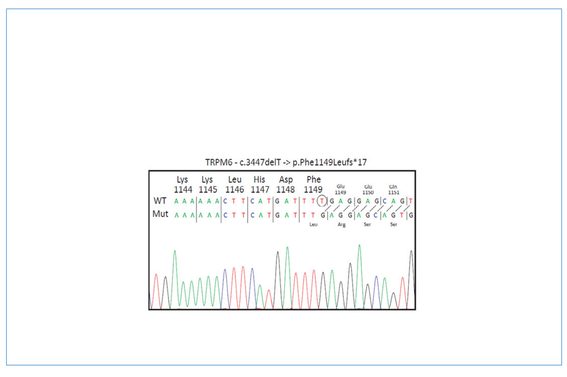


Figure 2. Frame-shift mutation in the *TRPM6 gene*

**Conclusion**

To the best of our knowledge, to date, fewer than 80 cases with *TRPM6* gene mutation and 48 different mutations have been reported world-wide. The identified *TRPM6* mutations were distributed over the whole gene, without clustering in any specific domain, consistent with the allelic heterogeneity. Until now, 10 Turkish patients with 7 different mutations were reported. Six of them had splice site and remaining 4 had non-sense mutations.

Frame-shift mutations has been reported in nine cases with the widespread ethnic distribution including Pakistan, Greece, India and Chinese. These mutations leaded to preterm stop codon and loss of function of TRPM6 protein. Reported patients with frame-shift mutations had classical clinical presentation of HSH with no differencies in phenotypic features.

In summary, we present clinical follow up of a pediatric HSH case due to a novel mutation in the *TRPM6* gene. Furthermore, we aimed to highlight the requirement of molecular genetic analysis in the inbred or familial cases with hypomagnesemia.

ESPE 2015 1077-P3

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DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology