Hypomagnesemia with Secondary Hypoparathyroidism and Hypocalcemia due to Novel Variants in the Transient Receptor Potential Cation Channel Subfamily M Member 6 (*TRPM6*) Gene

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Abstract

HOMG1 (hypomagnesemia 1, intestinal) or hypomagnesemia with secondary hypocalcemia is a rare autosomal recessive disorder of magnesium metabolism, characterized by impaired magnesium absorption. This disorder may mimic other conditions presenting with neonatal seizures. Here, we report an infant diagnosed to have hypomagnesemia with secondary hypocalcemia due to novel variants in *TRPM6* gene.

Keywords
- hypomagnesemia
- hypocalcemia
- hypoparathyroidism
- *TRPM6*

Introduction

HOMG1 or hypomagnesemia with secondary hypocalcemia (HSH; OMIM no.: 602014) is a rare autosomal recessive disorder. The condition was originally defined by Paunier et al.[1,2] Mutations in the *TRPM6* gene which codes for TRPM6, a member of the transient receptor potential (TRP) family of cation channels, involved in magnesium absorption in the intestine and distal convoluted tubule of the kidney is responsible for this disorder. Here, we report an infant with history of recurrent hypocalcemic seizures since early neonatal life, and on further evaluation was confirmed to have HOMG1 or HSH due to novel variants in *TRPM6* gene.

Background

HOMG1 or HSH (OMIM no.: 602014) is a rare autosomal recessive disorder in early infancy with generalized convulsions or with the signs of increased neuromuscular excitability. The primary etiology of HOMG1 is abnormal intestinal uptake of magnesium leading to hypomagnesemia. Changes in serum calcium or production of parathormone (PTH) are secondary to hypomagnesemia.[3,4] Life-threatening complications related to this condition can be certainly avoided by early and timely diagnosis in majority of the cases.[5] Mutations in the *TRPM6* gene which codes for TRPM6, a member of the transient receptor potential (TRP) family of cation channels, involved in magnesium absorption in the intestine and distal

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convoluted tubule of the kidney is responsible for this disorder. Several loss-of-function variants in TRPM6 (nonsense, frameshift termination, splice variants, and exon deletions) have been identified.[2,6,7]

Clinical Manifestations

Low levels of magnesium and calcium can cause neurological problems, such as tetany and seizures, that begin in infancy. If left untreated, it can lead to developmental delay, intellectual disability, failure to thrive, cardiac arrhythmias, and heart failure.

Diagnosis

HSH is characterized by low levels of serum magnesium and calcium. Parathormone levels may be normal or low. The diagnosis is confirmed by the identification of homozygous or compound heterozygous pathogenic variants in *TRPM6* gene.

Management

Magnesium supplementation remains the main stay of treatment. Doses of magnesium differs from patient to patient. Acute conditions require intravenous magnesium followed by life-long oral magnesium supplements. Patient should be monitored regularly for serum magnesium and calcium levels.

Prognosis

Prognosis depends on early recognition of the condition and institution of treatment in the form of magnesium supplements. Delay in diagnosis may cause permanent neurological sequelae. Secondary hypocalcemia may cause life-threatening cardiac arrhythmias and early mortality.

Case Report

An 11-month-old male infant, who is the second child of a nonconsanguineous marriage, presented with history of recurrent generalized tonic–clonic seizures beginning in the early neonatal period. His female sibling was similarly affected and died at 1 year of age. He was born by full-term normal vaginal delivery to a 29-year-old mother with birth weight of 2.9 kg. The perinatal period was uneventful. On day of life 15, he was noted to have generalized tonic–clonic seizures. Evaluation revealed hypocalcemia. He was managed with parenteral calcium and antiepileptic drugs and discharged on oral calcium supplements and antiepileptic drugs. He remained seizure free from the second to eighth month of life; this was followed by recurrent seizures beginning at 9 months of age. There was no history suggestive of failure to thrive/polyuria/tone abnormalities/vision or hearing impairment or recurrent infections. He attained all milestones on time until 9 months of age, with stagnation noted over the last 2 months. The infant was exclusively breastfed till 6 months of age and complimentary feeding was started after 6 months of age. On examination, his weight was 10 kg (0 to +2, Z score), length was 76 cm (0 to +1, *Z* score), weight for height was between 0 and +1 *Z* score, head circumference was 48.5 cm (0 to + 2, *Z* score), and middle-upper arm circumference was 12.5 cm. Vital parameters were within normal limits. Pallor was present, but there was no icterus, cyanosis, pedal edema, or lymphadenopathy. There was no obvious dysmorphism. Mental status, cranial nerves, and motor system examinations were within normal limits. There were no cerebellar signs or signs of meningeal irritation. Other systemic examinations were normal. Laboratory investigations during admission are shown in the ►**Table 1**. Our patient had seizures since neonatal period, persistent hypocalcemia, hypomagnesemia, decreased parathormone levels, and a significant family

Table 1 Timeline of investigations

Investigations	Results (at 15 days of life)	Results (at presentation to us)	Reference range
Hemoglobin (gm/dL)	–	8.6	10.5–14.0
Total leucocyte count (per mm^3)	–	5,740	4,000–11,000
Differential leucocyte count	–	P52L40	–
Platelet count (per mm^3)	–	3,80,000	1.5–4.5
BUN/serum creatinine (mg/dL)	–	21/0.6	0.4–0.8
Serum sodium (mEq/L)	–	138	134–144
Serum potassium (mEq/L)	–	4.8	3.5–6.1
Serum calcium (mg/dL)	6.3	5.5	8.8–10.8
Serum phosphorus (mg/dL)	–	6.3	4.5–6.5
Serum magnesium (mg/dL)	–	1.0	1.7–2.3
Serum 25 hydroxy vitamin D3 (ng/mL)	–	104	40–80 is sufficient
Serum parathormone (pg/mL)	–	8	12–92
Serum pH, HCO3 (mEq/L)	–	7.4/20	7.35–7.45/21–28

Abbreviation: BUN, blood urea nitrogen.

history of a female sibling succumbing to similar illness. Considering the metabolic derangements, positive family history and presentation in neonatal period, a differential diagnosis of familial hypoparathyroidism and inborn errors of magnesium metabolism were considered.

Library preparation was performed from DNA isolated from the peripheral venous blood. Targeted capture probes were used to selectively amplify the coding regions of 4,100 genes of known clinical significance. Illumina platform (Illumina Inc., San Diego, California, United States) was used to sequence the libraries at a mean depth of 80–100X. Base calling and data analysis were performed according to the Genome Analysis Toolkit (GATK) best practice framework. Obtained reads were mapped to the human reference genome (GRCh37/hg19) using burrow wheels alignment (BWA) algorithm BWA-mem aligner. Inbuilt modules were used for the detection and elimination of duplicates, as well as recalibration and realignment of reads based on indels. The Haplotype caller module (Sentieon Inc., San Jose, California, United States) was used to identify the variants. The deep variant analysis pipeline on Google cloud platform was used as a secondary pipeline to call genetic variants. Detected variants were annotated using Varseq variant analysis software (GoldenHelix Inc., Bozeman, MT). This software provided access to published genomic databases including the Online Mendelian Inheritance in Man (OMIM), Genome

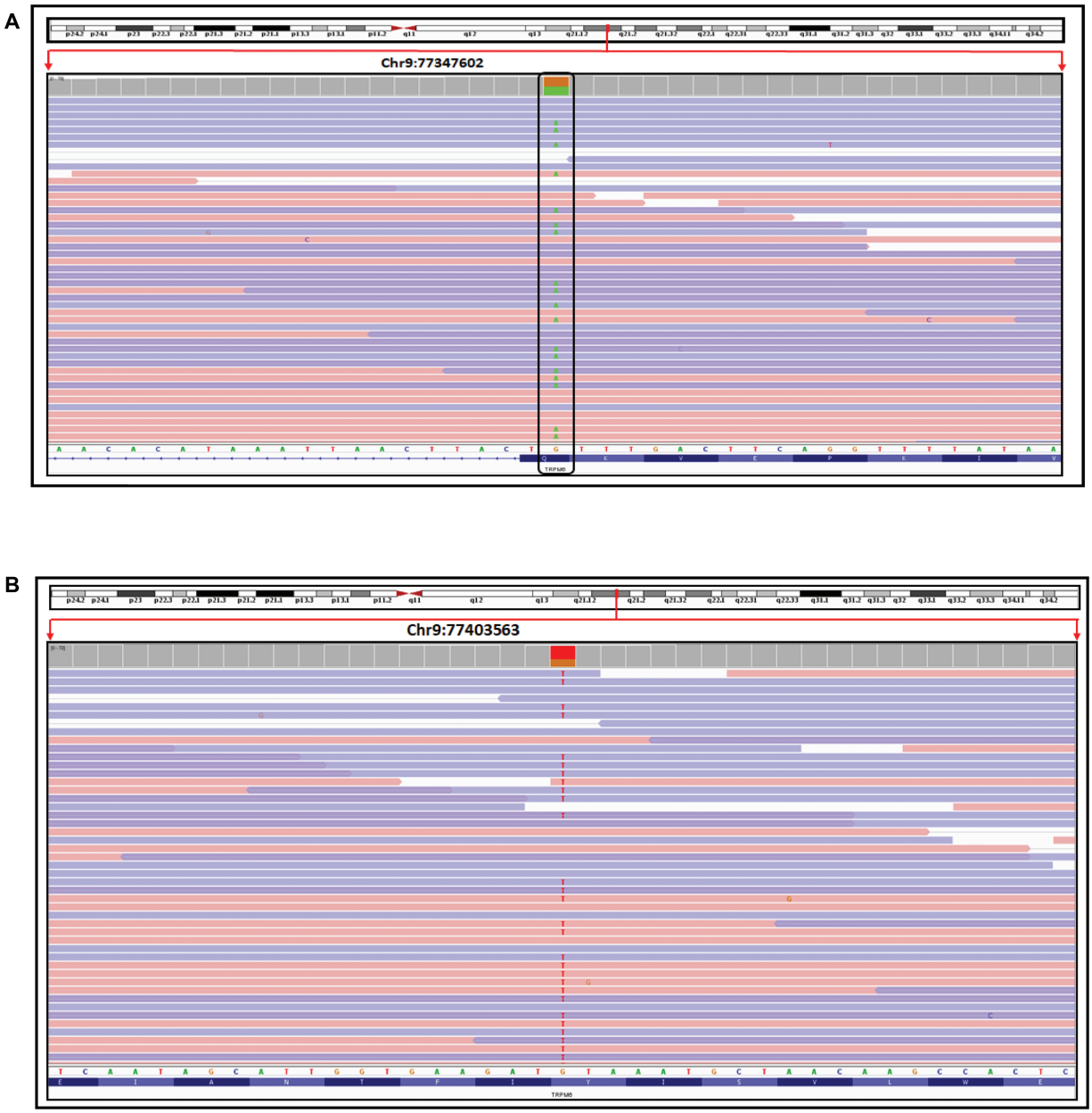

Fig. 1 (**A and B**) Integrative genomic viewer (IGV) snapshot depicting the heterozygous variant in the *TRPM6* gene. (**A**) Gene and transcript: *TRPM6*, NM_017662.4, variant: c.5827C > T (p.Gln1943Ter), location: exon 37, zygosity: heterozygous. (**B**) Gene and transcript: *TRPM6*, NM_017662.4, variant: c.2634C > A (p.Tyr878Ter), location: exon 20, zygosity: heterozygous.

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Fig. 2 TRPM6 conserved domains and functionally important regions found in NCBI CDD database. Query sequences 1, 2, and 3 represent the hypothetical truncated proteins of lengths 877 and 1942 aa and the complete one, respectively. CDD, Conserved Domain Database; NCBI, National Center for Biotechnology Information.

Table 2 Predicted posttranslational modification sites in TRPM6 protein searched on September 29, 2020

No.	Database	Web site	Posttranslational modification sites				
1	qPTM	*http://qphos.cancerbio.info/*	893, 1000, 1074, 1304, 1306, 1322, 1339, 1676, 1678, 1679, 1699, 1922				
2	EPSD	*http://epsd.biocuckoo.cn/*	968, 1000, 1089, 1091, 1094, 1095, 1181, 1184, 1195, 1244, 1245, 1281, 1304, 1322, 1324, 1325, 1339, 1430, 1435, 1560, 1562, 1563, 1685, 1699, 1747, 1756, 1851, 1986, 2011				
3	PHOSPHONET	*http://www.phosphonet.ca/*	893, 909, 936, 1000, 1006, 1008, 1022, 1034, 1035, 1038, 1043, 1095, 1137, 1139, 1157, 1176, 1177, 1181, 1184, 1195, 1200, 1203, 1206, 1230, 1244, 1245, 1273, 1275, 1277, 1281, 1285, 1304, 1306, 1311, 1322, 1324, 1325, 1329, 1332, 1341, 1360, 1395, 1399, 1426, 1428, 1430, 1435, 1437, 1438, 1441, 1452, 1458, 1463, 1478, 1479, 1482, 1484, 1498, 1500, 1503, 1504, 1506, 1509, 1510, 1513, 1533, 1539, 1541, 1560, 1562, 1577, 1583, 1603, 1616, 1618, 1622, 1623, 1628, 1660, 1664, 1669, 1672, 1676, 1678, 1679, 1685, 1689, 1697, 1699, 1702, 1722, 1739, 1741, 1747, 1754, 1756, 1759, 1771, 1787, 1813, 1843, 1851, 1854, 1855, 1878, 1880, 1886, 1895, 1897, 1912, 1914, 1932, 1935, 1985, 1986, 1992, 1993, 2011, 2015				
4	GPS v5.0	*http://gps.biocuckoo.cn/*	913, 974, 990, 1000, 1006, 1008, 1034, 1035, 1038, 1046, 1094, 1139, 1168, 1177, 1200, 1206, 1221, 1226, 1230, 1244, 1245, 1254, 1281, 1285, 1311, 1322, 1324, 1325, 1332, 1349, 1357, 1365, 1368, 1375, 1388, 1391, 1395, 1399, 1428, 1430, 1435, 1438, 1441, 1458, 1463, 1467, 1474, 1478, 1482, 1484, 1485, 1487, 1497, 1498, 1500, 1503, 1504, 1506, 1510, 1513, 1523, 1524, 1539, 1541, 1560, 1562, 1563, 1577, 1583, 1589, 1598, 1603, 1605, 1616, 1618, 1630, 1633, 1635, 1647, 1658, 1664, 1669, 1672, 1676, 1678, 1679, 1685, 1689, 1690, 1697, 1699, 1702, 1711, 1724, 1728, 1739, 1746, 1747, 1754, 1756, 1757, 1759, 1771, 1787, 1790, 1805, 1821, 1843, 1851, 1868, 1880, 1895, 1899, 1911, 1915, 1935, 1986, 1992, 1993, 2002, 2011, 2015				

Wide Association Studies (GWAS) catalog, 1000 Genomes, and ClinVar. The Mastermind database (Genomenon Inc., Ann Arbor, Michigan, United States) was used to ascertain the relevant literatures related to the prioritized genetic variants of interest.

Exome sequencing in this case revealed two heterozygous nonsense variants in compound heterozygous state in *TRPM6* (NM_017662.4) gene (c.2634C > A; p.Tyr878Ter [exon 20; ►**Fig. 1A**] and c.5827C > T; p.Gln1943Ter [exon 37; ►**Fig. 1B**]). The variant detected was not present in the 1000 Genomes (*http://www.internationalgenome.org/*) and gnomAD (*https://gnomad.broadinstitute.org/*) databases. The reference base is conserved across the vertebrates and in-silico prediction of both variants are damaging by Mutationtaster2 (*www.mutationtaster.org*) and computer aided design and drafting (CADD). Variants are classified likely pathogenic as per the American College of Medical Genetics (ACMG) guidelines of sequence interpretation.[8] Sanger's sequencing was done to further confirm the variant presence in the proband. Further segregation analysis revealed that the parents were both carriers for the (asymptomatic heterozygote; father is carrier of c.2634C > A, while mother is carrier of c.5827C > T). The deceased female sibling of the proband had similar clinical presentation notably hypomagnesemia and hypocalcemia; however, genetic testing was not performed on her. After the diagnosis was confirmation in proband, couple planned another pregnancy and prenatal diagnosis was performed after adequate counseling. The fetus was found to have same compound heterozygous variants, and the couple decided to continue the pregnancy. A male child was born, he was found to have hypomagnesemia and was placed on prophylactic magnesium supplements.

To predict the effect of these termination codons on protein function, comparative analysis of sequences and structure of these hypothetical truncated protein sequences of lengths 877 (query sequence 1) and 1,942 (query sequence 2) amino acids (aa) with wild type of length 2,022 aa (query sequence 3) were performed. Functional domains were analyzed using the National Center for Biotechnology Information (NCBI) Conserved Domain Database (CDD v3.18)[9] and the Batch Web CD-search tool (*https://www.ncbi.nlm.nih.gov/Structure/bwrpsb/*; ►**Fig. 2**). Three functionally important regions were identified using the comparative analysis of query sequences of TRPM6 protein while searching the CDD database. The LSDAT superfamily (SLOG domain) located at N-terminal and responsible for the regulation of flux across membranes was first identified.[10] Next identified were two important regions TRP channel and α-kinase domain of serine/threonine-specific protein kinase type.[11] Posttranslation modification (PTM) sites have been mined from the existing databases like QPhos,[12] GPS v5.0,[13] and others. These sites are mainly important for the modulation of channel activities like gating, protein–protein interactions (PPIs), trafficking, and others, and their deletion might affect channel protein function.[14] The PTM sites which are absent in query-1 and -2 sequences were mined from various databases and presented in ►**Table 2**.

Due to nonavailability of a previously known structure for TRPM6, its paralog, TRMP7 (PDB ID: 5ZX5), was taken as a template to partially model TRPM6 protein using Swiss model webserver. The validated output model, depicted in ►**Fig. 3A** contains four chains A, B, C, and D (~1201 AA/chain [►**Fig. 3B**]) including an ion channel domain (841–1081 AA, golden

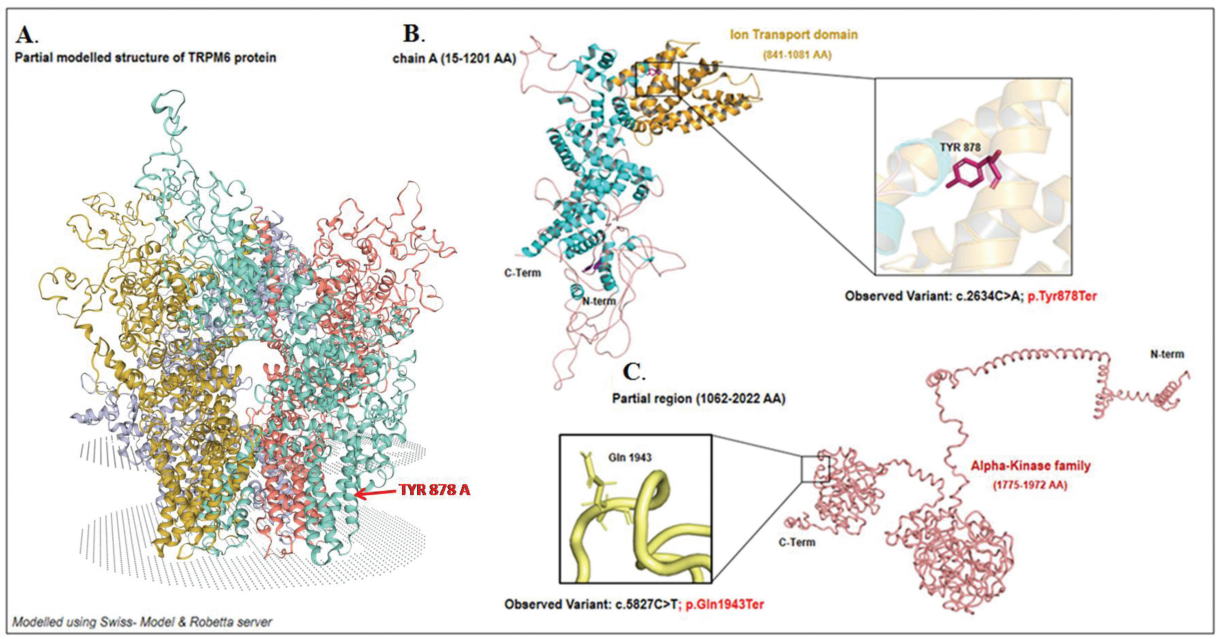

Fig. 3 Structural modeling of TRPM6 protein (Uniprot ID: Q9BX84) using Swiss model and Robetta servers. (**A**) Using TRPM7 protein (PDB ID: 5ZX5) as reference, a partially modeled structure (16-1205 AA) was predicted by Swiss model web server. All the chains (A, B, C, and D) were shown in blue, golden, purple, and red, respectively. Mutation points were marked by red arrows. (**B**) Chain A (15-1201 AA) was shown in blue and Ion transport domain (841-1081 AA) was shown in golden. (**C**) Another model for the partial region (1062-2022 AA) was predicted using Robetta server including alpha kinase domain (1775-1972 AA) in dark pink.

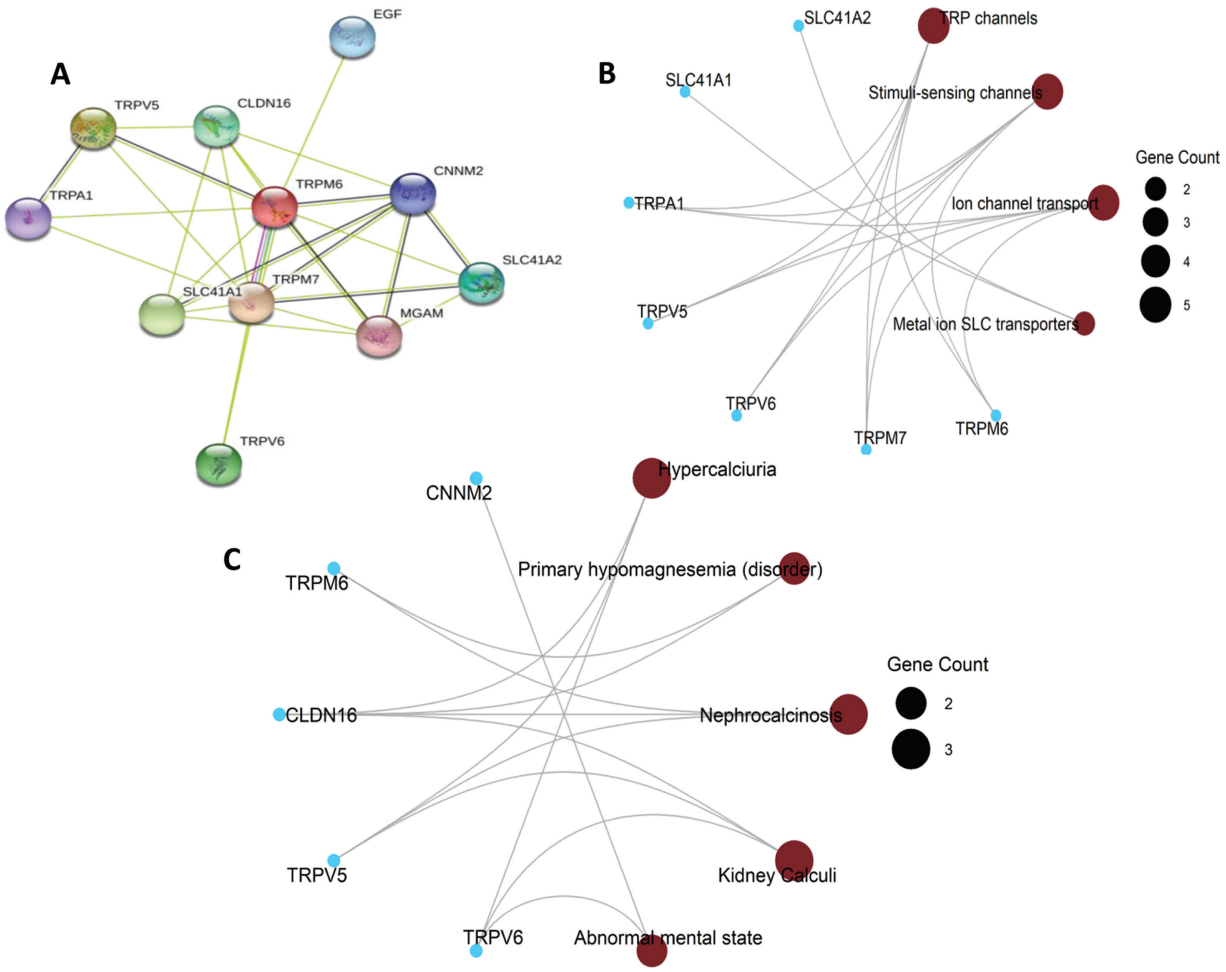

Fig. 4 Network analysis for possibly influenced interacting proteins, pathways due to TRPM6 mutations and disease overview. (**A**) Patient–patient interaction (PPI) network for TRPM6 predicted from STRING database. Different color indicates different proteins; (**B**) Reactome pathway enrichment analysis; (**C**) TRPM6 and interacting proteins and associated disease network. Blue nodes represent genes/proteins and maroon nodes pathways/disease terms.

yellow). Another model was produced using Robetta server (1062–2022 regions) that encompassed the α-kinase domain (1775–1972 AA, dark pink; ►**Fig. 3C**). Two novel termination variants: c.2634C > A; p.Tyr878Ter and c.5827C > T; p. Gln1943Ter have been observed in the ion transport domain and the α-kinase domain respectively, that could lead to HSH.

Interacting proteins and PPI network were fetched from STRING database (v11.0) and associated pathways and diseases were explored with R package clusterProfiler.[15] TRPM6 forms heteromeric complex with TRPM7 to build the essential ion channel for Mg2+ intake.[16] while mutations in the TRPM6 protein might affect its interacting partners like TRPM7. The list of interacting proteins was fetched from STRING database with PPI enrichment, *p*-value of 8.49e-06. A total of 11 proteins have been found to interact with TRPM6 (►**Fig. 4A**) with average node degree of 5.09 and average local clustering coefficient of 0.842. The Reactome[17] pathway enrichment analysis on interacting protein associates from STRING[18] network resulted in the identification of four-ion channel transportation-related pathways. Integrated protein-pathway network has been shown in ►**Fig. 4B**. Similarly, to explore hypomagnesemia-related disorders, HSH disease term enrichment analysis has been performed using DisGeNET,[19] leading to the integrated network of five-gene and five-disease term nodes including HSH (►**Fig. 4C**).

Postidentification of this variant, the child was managed with parenteral calcium and magnesium for acute symptomatic seizures. After stabilization, oral magnesium (50 mg/kg/day) and calcium were prescribed, and the child has been seizure free for the past 1 year and is tolerating the therapy well. He is gaining milestones and serum magnesium levels are stable between 1.1 to 1.4 mg/dL (normal range is 1.7–2.3 mg/dL) but serum calcium levels have been normal.

Discussion

We described a rare case of HOMG1 or HSH due to novel compound heterozygous nonsense variants in *TRPM6* gene. The clinical presentation of our patient was very similar to the previously described cases in literature. In a study done by Schlingmann et al, on a cohort of 21 families with HOMG1 or HSH, the age of initial presentation ranged from 2 weeks to

7 months. All patients presented with generalized seizures except for one patient who presented with tetany. In their study, two patients also had cognitive delays, four had failure to thrive, and one had cardiac arrhythmia; none of these were present in our patient. They found 23 different pathogenic mutations in *TRPM6* gene and these were distributed across the gene without clustering.[2] The *TRPM6* gene consists of 39 exons coding for an amino acid protein. The TRPM6 protein has SLOG-like domain (109–372aa), ion transport protein domain (846–1077aa), tetramerization domain of TRPM (1170–1225aa), and alpha-kinase family domain (1776–1972aa). The TRPM6 protein also has a transmembrane domain which is responsible for ion transportation across the membrane (DECIPHER: Database).[20] The protein plays a crucial role in magnesium homeostasis and has a vital role in epithelial magnesium transport and in the active magnesium absorption in the gut and kidney. Isoforms of the type M6-kinase lack the ion channel region. Thus, patients suffering from HSH can compensate for their genetic defect by high oral magnesium intake (as passive paracellular transport mechanism is intact).[21] Our patient had mutations in ion transport protein domain (exon 20) and alpha-kinase family domain (exon 37), creating a premature stop codon which is predicted to result in a truncated TRPM6 protein as depicted by in silico analysis. The patients with HSH have hypoparathyroidism and resultant hypocalcemia, in addition to hypomagnesemia, as was present in our case. The exact mechanism by which hypomagnesemia causes hypoparathyroidism is not known. In a case series by Astor et al, five patients in four families with clinical features of HOMG1 or HSH were studied; one patient had low PTH level (0.1 pmol/L) at the time of initial diagnosis and the others were not tested at initial presentation. However, PTH values during oral magnesium supplementation were within the normal reference range in all the other patients, in subsequent visits. Also, in HSH/HOMG1 cases reported by Astor et al, and Zhao et al, serum magnesium levels remained low (0.5–0.6 and 0.62 mmol/L, respectively) despite treatment, as was in our case.[22,23]

Our patient stayed asymptomatic with magnesium replacement at a dose of 50 mg/kg/day and low-dose calcium supplementation (25 mg/kg/day). Daily oral doses differ from patient to patient. In HOMG1 or HSH case reported by Lal et al, very high doses of magnesium had to be used both for initial stabilization (up to 12 g/day) and maintenance (8.5 g/kg/day).[24]

Conclusion

The key to favorable outcome of this rare disorder was clinical suspicion in a patient presenting with seizures and hypocalcemia and early diagnosis. Magnesium levels should be checked in all cases of hypocalcemia to determine its potential contribution to the same. Genetic cause should be suspected if any of family members is suffering from/succumbed to similar illness and genetic testing should be performed in suspected patients for management of the disease, genetic counseling, and prognostication.

Authors' Contributions

G.J., S.R., R.M., and A.D. managed the patient and drafted the manuscript. N.M.P., G.A., U.S., and G.D. edited the manuscript and performed computational analysis.

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None.

Conflict of Interest

None declared.

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