A Novel *De novo* GATA-binding Protein 3 Mutation in a Patient with Hypoparathyroidism, Sensorineural Deafness, and Renal Dysplasia Syndrome

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Introduction

Hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome, also called Barakat syndrome, is an autosomal dominant genetic disease caused by haploinsufficiency of the GATA-binding protein 3 (*GATA3*) gene located on the 10p15 chromosome.[1]

GATA3 belongs to a family of dual zinc finger transcription factors. There are six GATA proteins (GATA 1–6) that share a zinc finger DNA-binding domain Cys-X2-Cys-X17-Cys-X2-Cys, where X represents any amino acid residue. This domain binds to the consensus motif 5'-(A/T)GATA(A/G)-3'. GATA proteins are widely expressed during the development processes of the human cardiovascular, digestive, urogenital, and hematopoietic systems. More specifically, GATA3 is expressed in the parathyroids, inner ears, and kidneys during development.[2] More than 50 mutations in *GATA3* gene have been reported till now.[3] In this study, we reported a novel *GATA3* gene mutation in a patient with HDR syndrome.

Case Report

A 14-year-old female presented to Peking Union Medical College Hospital in 2014 with frequent episodes of febrile seizures since she was 6 months old. At age 6, her seizure attacks became more frequent. A computed tomography scan detected bilateral basal ganglia calcification. She was diagnosed with epilepsy and given oxcarbazepine for seizure management; her seizure episodes decreased. At age 11, the patient had hypocalcemia (1.62 mmol/L, normal range: 2.13–2.70 mmol/L), hyperphosphatemia (3.70 mmol/L, normal range: 0.81–1.45 mmol/L), and an inappropriately low parathyroid hormone (PTH) level (22 pg/ml, normal range 12–65 pg/ml). Her serum calcium was still low one year later. She was given calcium (600 mg/d) and calcitriol (0.25 μg/day) supplements and her tetany relieved. At age 11, the patient also started complaining of bilateral hearing loss, which gradually deteriorated. When she presented at age 14, she had some difficulty communicating without a hearing aid but was still able to manage daily life.

The patient was born through normal vaginal delivery. Her parents were nonconsanguineous and had no family history of HDR syndrome. She had normal developmental milestones and had an average grade at school. The patient was 147 cm (–2 standard deviations [SDs]) tall and weighed 38 kg –1 SD to –2 SD). There were no facial or other skeletal deformities present. Both Trousseau and Chvostek signs were negative.

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The results of laboratory tests on the patient's first presentation to our hospital were serum calcium 1.87 mmol/L, serum phosphorus 2.35 mmol/L, serum magnesium 0.99 mmol/L (normal range: 0.70–1.10 mmol/L), and 25-hydroxy-vitamin D (27.1 ng/ml, normal range: 8.0–50.0 ng/ml). Serum albumin, glucose, electrolytes, creatinine, complete blood count, and urinalysis were normal. Blood cortisol, adrenocorticotropic hormone, thyroid hormone, and thyrotropin were also normal. Renal ultrasound revealed no anomalies. Bone mineral density (BMD) was 0.84 g/cm^2 in the femoral neck and 1.20 g/cm^2 in the lumbar spine (L1–L4). Ophthalmologic examination was normal. The patient was diagnosed with idiopathic hypoparathyroidism. Calcitriol 0.25 μg/d, cholecalciferol 300,000 U/week, and calcium 1200 mg/d were prescribed, and the doses of oxcarbazepine were gradually reduced. She had symptomatic relief with only mild residual limb numbness. One year after initial presentation, the patient had bilateral mixed deafness of both low and high frequencies; thus HDR syndrome was considered, and genetic testing was performed for definitive diagnosis.

Blood samples were collected from the patient and her parents. Genomic DNA was isolated from peripheral blood leukocytes using a DNA extraction kit (Omega, D3494-03 Blood DNA Midi Kit). Six pairs of DNA primers designed by Oligo Primer Analysis software v. 7 (Molecular Biology Insights, Inc., Colorado Springs, Colorado, USA) were used to sequence the *GATA3* gene in blood samples. The primers used for amplification are displayed in Table 1. Sequencing was performed using the chain termination method on an automatic sequencer (Applied Biosystems 3730 Genetic Analyzer).

A single *de novo* nucleotide deletion in exon 2 of the *GATA3* gene (c.286delT) was detected in this patient. This mutation was not found in the patient's parents and 100 unrelated healthy individuals. Functional assessment of this mutation was assessed using mutation taser (http://www.mutationtaster.org/). The mutation was predicted to cause the 96th amino acid of the GATA3, tryptophan, to be substituted by glycine, resulting in a frameshift (p. W96Gfs*99) mutation that yielded a truncated 193 amino acids protein with the last 97 amino acids being different from the normal GATA3. Nonsense-mediated mRNA decay of the mutated protein was likely. This variant was not found in the Database of Short Genetic Variation (http://www.ncbi.nlm.nih.gov/snp/), Exome Variant Server (http://evs.gs.washington.edu/EVS/), or the Ensemble Genome Browser Database (asia.ensembl.org/index.html). The sequencing results of the proband and her parents are shown in Figure 1.

Discussion

There are six exons in the human *GATA3* gene, encoding a 444 amino acid protein. The GATA3 has two transactivating domains (TA1 and TA2) and two zinc finger DNA-binding domains (ZnF_1 and ZnF_2). The C-terminal zinc finger ZnF_2

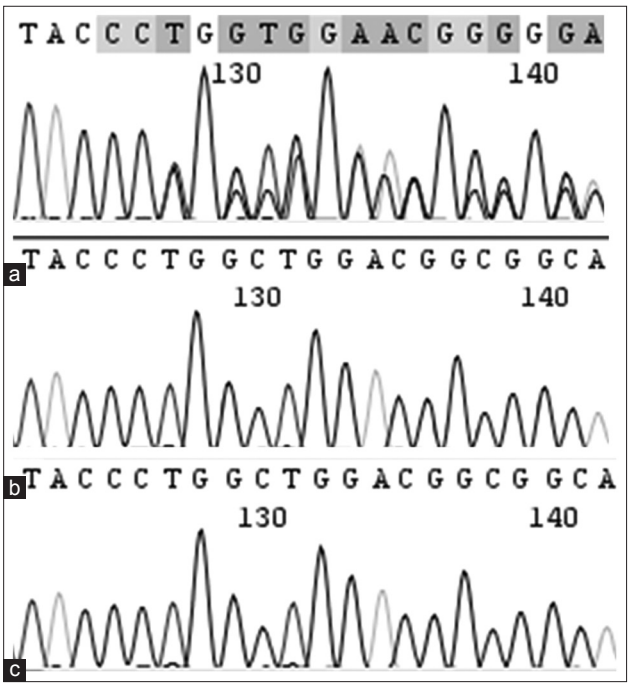

Figure 1: Direct sequencings of the GATA-binding protein 3 gene in the patient and her parents. Sequence analysis revealed the novel c.286delT frameshift mutation in the patient (a); and no *GATA3* mutation could be found from the proband's mother (b) and father (c), respectively. *GATA3*: GATA-binding protein 3.

Table 1: Primer sequences used for amplification of GATA-binding protein 3 gene

Exons	Primer sequence	Length (bp)	Annealing temperature (°C)
1 and 2	Forward: 5'-TCTTTGCTAAACGACCCCT-3' Reverse: 5'-GCGACTCTTTCAAAACACACTCT-3'	659	61.8
3 (part 1)	Forward: 5'-AGCTGTACTCGGGCACGTAG-3' Reverse: 5'-AGCTGTACTCGGGCACGTAG-3'	561	63.0
3 (part 2)	Forward: 5'-CCGCCTCTGCTTCATGGAT' Reverse: 5'-TCTCAACTTTGGAGCATCTTG-3'	651	62.0
4	Forward: 5'-CAAGCCAGCTGACACGATT-3' Reverse: 5'-TTTTGGGGATCTGTATTACTTT-3'	438	56.7
5	Forward: 5'-TTTTGGGGATCTGTATTACTTT-3' Reverse: 5'-CATCGGATTGCTGCATGGTA-3'	547	55.9
6	Forward: 5'-ACCCTTCTTGGTGTGCGAGA-3' Reverse: 5'-AGTCAGAATGGCTTATTCACAG-3'	588	56.3

(residues 318–342) is encoded by exon 5 and is essential for DNA binding, whereas the N-terminal zinc finger ZnF_1 (residues 264–288) is encoded by exon 4 and helps to stabilize this binding through interactions with other proteins, such as the Friends of GATA (FOG).[4]

In our patient, the c.286delT mutation caused a premature stop at codon 193, with 97 new amino acids from codon 96 through 193. Consequently, the resultant protein lost both ZnF_1 and ZnF_2 domains, and the protein lost its DNA-binding potential and ability to interact with FOGs.

In 2016, Belge *et al*.[5] summarized the presentations of 115 patients with HDR syndrome and demonstrated that 106/112 (95%) had hypoparathyroidism, 106/110 (96%) had various degrees of sensorineural deafness, and 74/115 (64%) had renal anomalies. Similar to our patient, the sensorineural hearing loss in patients with HDR syndrome is often moderate to severe and is slightly worse at the higher end of the frequency spectrum. Sensorineural hearing loss in HDR syndrome may be progressive with age.[5] Renal abnormalities can be multiform. Structural changes, such as cystic kidneys, renal dysplasia, and vesicoureteric reflux can either be bilateral or unilateral.[2] Functional renal conditions, such as nephrotic syndrome, hematuria, or proximal and distal renal tubular acidosis, can also exist.[5]

In this case, the combination of seizures resulting from hypocalcemia and hyperphosphatemia in the setting of a low PTH level led to a diagnosis of hypoparathyroidism. This diagnosis was supported by bilateral basal ganglia calcification and increased BMD in both the femur and lumbar spine. Her bilateral sensorineural deafness developed gradually and presented in adolescence. However, some patients with HDR syndrome present with hearing loss since childhood or even infancy that becomes more prominent in adolescence. Our patient had neither renal structural nor functional abnormalities, indicating that *GATA3* haploinsufficiency in this patient did not reach the threshold that can lead to obvious renal dysplasia.

In conclusion, screening for *GATA3* mutations is warranted in a young patient with hypoparathyroidism without other obvious causes. Assessment and monitoring of auditory acuity and renal function are necessary in these patients due to their tendency to have mild symptoms at the onset that gradually deteriorate over time.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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