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Identification of Three Novel Mutations in the *GATA3* Gene Responsible for Familial Hypoparathyroidism and Deafness in the Chinese Population

Wei-Yih Chiu, Huan-Wen Chen, Hwei-Wen Chao, Lee-Tzong Yann, and Keh-Sung Tsai

Departments of Laboratory Medicine (W.-Y.C., H.-W.Cha, K.-S.T.) and Internal Medicine (W.-Y.C., L.-T.Y, K.-S.T.), National Taiwan University Hospital, Taipei 100, Taiwan; and Department of Internal Medicine (H.-W.Che), Lo-Tung Pohai Hospital, Ilan 256, Taiwan

Background: Familial hypoparathyroidism may be caused by mutations of several genes. The *CaSR* and *GATA3* genes are the two candidates most commonly responsible for this condition.

Objectives: We collected five unrelated families with familial hypoparathyroidism and examined their *CaSR* and *GATA3* genes.

Methods: Blood samples from these five families and 50 ethnically matched unrelated controls were acquired. Biochemistry screening and formal audiogram were performed to evaluate the affected individuals. All the exons and exon-intron boundaries of the *GATA3* and *CaSR* genes were sequenced.

Results: We identified three novel mutations in the *GATA3* gene responsible for familial hypoparathyroidism and deafness: 1) a frameshift deletion occurring in codon 160 (478delG) was hypothesized to disrupt dual zinc fingers as well as one transactivating domain; 2) a donor splice site mutation at exon 4/intron 4 boundary (IVS4 + 2 *T* to *GCTTACTTCCC*) was predicted to lead to truncated GATA3 proteins that lack both N- and C-terminal zinc-containing fingers; and 3) a missense mutation R353S was predicted to disrupt the helical turn and thus changed the angle between the C-terminal zinc finger and the adjacent C-terminal tail. Except for a previously described polymorphism, G990R, we did not find any genetic variants in the *CaSR* gene.

Conclusions: This is the first article presenting mutations of the *GATA3* gene responsible for familial hypoparathyroidism and deafness in the Chinese population. Our results expand the spectrum of mutations and report the first splice donor site mutation of the *GATA3* gene. In contrast, we do not find causal sequence variants of the *CaSR* gene from our collection of familial hypoparathyroidism. **(*J Clin Endocrinol Metab* 91: 4587–4592, 2006)**

FAMILIAL HYPOPARATHYROIDISM is an unusual condition that may be observed as an isolated defect caused by mutation in the calcium-sensing receptor gene (*CaSR*; MIM 601199), *PTH* gene (MIM 168450), or *GCM2* gene (MIM 603716) (1–8) or as a component of a more widespread disorder, such as autoimmune polyglandular syndrome type I (MIM 240300) (9); DiGeorge's syndrome (MIM 188400) (10); or hypoparathyroidism, sensorineural deafness, and renal anomalies (HDR) syndrome (MIM 146255) (11–16). It can be inherited in an autosomal dominant (2–4, 6, 8, 11–16), autosomal recessive (1, 5, 7), or X-linked recessive (17, 18) pattern. After excluding cases of pseudohypoparathyroidism and any immunological disorder, autosomal dominant inheritance seems to be the most common pattern of familial hypoparathyroidism. In view of reports about autosomal dominant hypoparathyroidism, mutations of the calcium-sensing receptor (*CaSR*) and *GATA3* genes were most common.

In 1994, Finegold *et al.* (19) demonstrated a linkage of autosomal dominant hypocalcemia to chromosome 3q13, which harbors the gene for the CaSR. The CaSR is expressed in tissues involved in calcium homeostasis, including parathyroid gland, thyroid C-cell, kidney, and bone. In parathyroid cells, binding of calcium ion to CaSR decreases PTH secretion by acting as a calcium sensor. In kidney, CaSR activation inhibits the reabsorption of calcium (20). It has been estimated that approximately 40% of cases of idiopathic hypoparathyroidism were harboring activating *CaSR* mutations (21). Recently *GATA3*, a member of the GATA-binding family of transcription factors, was shown to be involved in human HDR syndrome (11–16), which has an autosomal dominant inheritance pattern. GATA3 is a dual zinc finger transcription factor. Human GATA3 expression has been detected in the developing parathyroid gland, inner ear, and kidney, together with thymus and central nervous system (22).

As a candidate gene approach, we investigated patients with familial hypoparathyroidism for the GATA3 and CaSR abnormalities.

Patients and Methods

Patients and controls

The diagnosis of familial hypoparathyroidism was based on the family history and presence of hypocalcemia and hyperphosphatemia in association with low or an inappropriately normal level of serum intact PTH (i-PTH). Patients with postsurgical hypoparathyroidism were excluded. None of the patients had any features, such as mucocutaneous candidiasis or facial abnormalities, that could be suggestive of hypoparathyroidism related to the polyglandular autoimmune syndrome

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Abbreviations: CaSR, Calcium-sensing receptor; HDR, hypoparathyroidism, sensorineural deafness, and renal anomalies; i-PTH, intact PTH.

type I or DiGeorge's syndrome. Blood samples from the patients, their family members, and 50 ethnically matched unrelated controls were acquired after having obtained informed and written consent from each participant according to a protocol reviewed and approved by the local ethical research committee. Genomic DNA was extracted from 0.2 ml of whole blood using a commercial DNA extraction kit (NucleoSpin blood; Macherey-Nagel Gmbh & Co. KG, Düren, Germany) according to the manufacturer's protocol.

Clinical laboratory investigations

All patients and their family members were evaluated both clinically and biochemically. Plasma creatinine, albumin, total calcium, and phosphorus concentrations were measured using commercially available diagnostic kits according to the manufacturer's instructions. Specifically, serum i-PTH concentrations (biologically active molecule, 1–84 amino acids full length) were measured using a two-site immunochemiluminometric assay on an Immulite 2000 machine (Diagnostics Product Corp., Los Angeles, CA). Urinalysis, nephrosonography, and formal audiogram were performed to evaluate renal and hearing impairment of all the probands and some of the family members.

Mutation detection and analysis

All the coding exons and exon-intron boundaries of the *GATA3* and *CaSR* genes were amplified by PCR as described (12, 23). Subsequently, the PCR products were purified and subjected to cycle sequencing reaction by a BigDye terminator cycle sequencing kit (version 3.1; Applied Biosystems, Foster City, CA). All the genetic variants detected in the probands, which were confirmed by repeat DNA sequence analysis on independently obtained PCR products, were demonstrated to cosegregate with the disorder and to be absent in the DNA obtained from 50 unrelated individuals. Restriction enzyme genotyping using *Bsm*F I was performed to determine the disease segregation pattern of A1059T (amino acid R353S) gene variant within the family as well as the frequency in 100 normal chromosomes.

To examine gene features, like intron/exon boundaries, the HMM-based gene structure predictor is useful. We used the *FGENESH* program (www.softberry.com) based on the consensus sequence of exon-intron junctions (ag . . . gt rule of intronic sequence) as well as on the codon usage within ORF to predict the effect of the splice donor mutation.

Based on the determined NMR structure of C-terminal DNA binding domain of GATA1 (24), this homologous domain of GATA3 consists of a core that contains a zinc coordinated by four cysteines and a carboxyl-terminal tail. The core interacts with the major groove of the DNA, and the carboxyl-terminal tail wraps around into the minor groove. The residue 353 of human GATA3 is located in the long loop that connects the core and the carboxyl-terminal tail. We used the NNPredict software (http://www.cmpharm.ucsf.edu/~nomi/nnpredict.html) to determine the effect of R353S on human GATA3 structure. Besides, key amino-acid positions that are important for maintaining the three-dimensional structure of a protein and/or its functions are often under strong evolutionary constrains. Thus, the biological importance of a residue often correlates with its level of evolutionary conservation within the protein family. ConSurf (http://consurf.tau.ac.il/) (25, 26) is a web-based tool that automatically calculates evolutionary conservation scores and maps them on protein structures. The run was carried out using default parameters and a PDB file that was acquired from CPHmodels 2.0 server (http://www.cbs.dtu.dk/services/CPHmodels/) (27).

Results

Clinical findings

Twelve patients with familial hypoparathyroidism from five unrelated families were ascertained (Table 1). In these 12 cases, age at onset of hypoparathyroidism varied from 7 to 50 yr; six were female. Unexplained hypocalcemia (median 1.58 mM) and hyperphosphatemia (median 1.74 mM) were present in eight patients. This was associated with tetany in six patients and seizure in two patients. Computerized tomography of the head performed in those two patients (C/II.3 and D/II.1) with grand mal seizure showed calcification at bilateral cerebrum, basal ganglia, and frontal white matter. Bilateral sensorineural hearing loss was identified in three probands and their family members (families A, B, and C). In addition, renal lesion was radiologically confirmed in one case (patient B/III.2). When she was 5 yr old, renal insufficiency was noted (creatinine clearance 39 ml/min, normal range 120–140 ml/min). Nephrosonography disclosed small size of the kidneys (Table 1). Intravenous py-

TABLE 1. Clinical and biochemical presentation in patients with familial hypoparathyroidism

Patients	Hypoparathyroidism						Renal findings			Deafness (age[b])
	Symptoms	Ca[a]	P[a]	i-PTH[a]	Cre[a]	Age, yr[b]	Proteinuria	Hematuria	Length (right/left)[a]	
A										
II.2	Tetany	1.6	1.58	4.3	1.4	50	−	−	10.6/9.8	SNHL (childhood)[c]
III.1	Asymptomatic	2.26	1.29	23.2	1.1	23[d]	−	−	10.9/9.9	SNHL (10)[c]
III.2	Asymptomatic	2.14	1.55	7.17	1.0	18	−	−	10.7/10.3	SNHL (17)
B										
II.2	Tetany	1.55	1.71	17.1	0.8	33	−	−	9.0/9.2[e]	SNHL (childhood)[c]
III.2	Tetany	1.78	1.58	13.0	2.7	16	+	+	6.5/6.7	SNHL (2)[c]
C										
II.3	Seizure, CBG	1.18	2.03	<3.0	1.0	32	−	−	10.1/9.9	SNHL (childhood)[c]
III.1	Asymptomatic	2.21	1.55	26.4	0.7	10[d]	−	−	N/A	SNHL (5)[c]
III.2	Asymptomatic	2.09	1.81	14.6	0.5	7	−	−	N/A	SNHL (4)[c]
D										
II.1	Seizure, CBG	1.89	1.52	<3.0	1.3	37	−	−	N/A	None
III.2	Tetany	1.88	1.91	5.08	1.0	18	−	−	N/A	None
E										
II.2	Tetany	1.54	1.78	5.1	1.0	27	−	−	N/A	None
II.3	Tetany	1.51	1.84	3.2	0.7	30	−	−	N/A	None

CBG, Calcification of basal ganglia; Cre, creatinine; N/A, not available; SNHL, sensorineural hearing loss; +, positive; −, negative.

[a] Reference value: Ca, 2.02–2.60 mmol/liter; P, 0.87–1.45 mmol/liter; i-PTH, 12–72 ng/liter; creatinine, 0.8–1.2 mg/dl in men and 0.6–0.9 mg/dl in women; and renal length in our population, 10.52 ± 0.95 cm.

[b] Age at diagnosis of hypoparathyroidism or deafness.

[c] Using hearing aids.

[d] Present age.

[e] The values are regarded as normal in terms of her body height and weight.

elography showed vesicoureteral reflux at both sides. Abdominal magnetic resonance imaging revealed renal hypoplasia with lobulated contour in kidney shape. On the last examination at age 16 yr, bilateral contracted kidneys (right/left side = 5.9/6.5 cm) with chronic renal failure were noticed.

Mutation analysis

Direct sequencing of the *CaSR* gene revealed the sequences in coding exons, and splice junctions were well conserved except one gene variant: an A-to-G transition at nucleotide 2968 (starting from ATG) in exon 7. This change resulted in a substitution of arginine for glycine (G990R) and was present in one or both alleles in nine of the 12 cases. The frequencies of A/A, A/G, and G/G genotypes in the patients were 8.3, 66.7, and 25%, respectively. It was noted that neither the 990G allele nor 990R allele cosegregated with the hypocalcemia/hypoparathyroidism within the families we studied. This variant, G990R, was previously reported as a benign polymorphism without contribution to hypocalcemia (23, 28).

Sequence analysis of the GATA3 gene disclosed three heterozygous genetic variants. The first, in family A, was a single-base deletion at nucleotide 478 of the cDNA sequence (478delG) located in exon 3 (Fig. 1A). This variant is predicted to result in a frameshift from codon 160 and a premature termination at codon 194. This mutation was present only in the affected family members and was not identified in any of the unaffected relatives or ethnically matched controls. The second sequence variant, found in family B, involved a *t* to *gcttacttccc* substitution of the invariant *gt* in junction of exon-intron 4 (IVS 4 + 2 $T \rightarrow GCTTACTTCCC$ mutation) (Fig. 1B). This mutation occurred in the affected family members and not in the unaffected relatives and control samples. The *FGENESH* correctly predicted the gene structures, including coding regions through exon 2 to exon 5, of the reference *GATA3* gene sequence. In contrast, exon 4 was skipped and the fusion of exons 3 and 5 leads to a reading frameshift at position V260 in this splice donor mutant (Fig. 2). Family C contained a heterozygous A to T transversion at nucleotide 1059 (1059A > T) of the GATA3 cDNA sequence (Fig. 1C). This mutation resided in exon 6 and was predicted to result in the substitution of serine for an arginine residue at position 353 of the GATA3 amino-acid sequence. This mutation was not seen in sequences from unaffected relatives. The base change created a *Bsm*F I restriction site that facilitated screening of control samples. All affected family members demonstrated the presence of the *Bsm*F I restriction site; however, no digestion was observed in unaffected family members or an additional 50 unrelated control samples. Using the ConSurf server (25, 26), we found that R353 is extremely well conserved among various homologous proteins in humans and across species (score = 9; range 1–9; calculation performed on 50 unique sequences) (Fig. 3). The three-dimensional structure of the carboxyl-terminal DNA binding domain of human GATA3 and the position of R353 were shown in Fig. 3. This mutant, R353S, was predicted to disrupt the helix turn composed of residue 355 to 358 by using the NNPredict software with alpha/beta tertiary structure class for prediction.

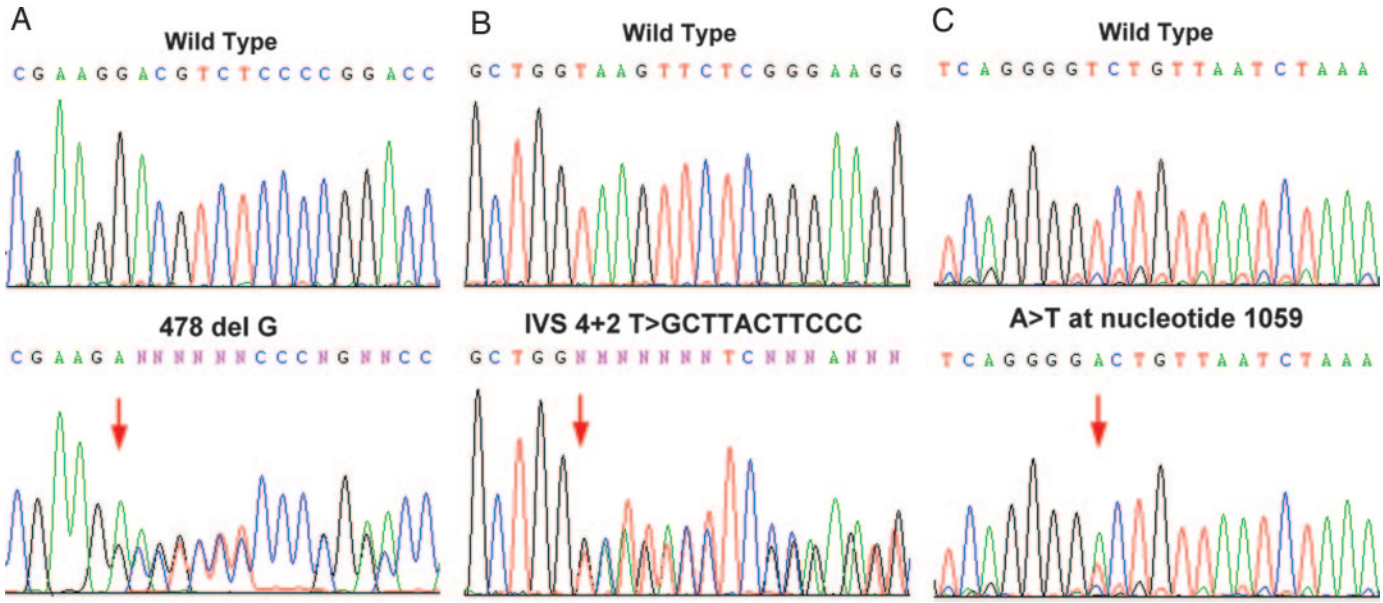

FIG. 1. Results of mutation analysis. The wild-type sequences are given for comparison (*upper panels*). *Arrow* denotes mutation site. A, Direct sequencing reveals a heterozygous G deletion at position 478 of the *GATA3* cDNA sequence. This mutation was identified in case II.2, III.1, and III.2 of family A. B, Sequence analysis disclosed heterozygous mutant sequence in case II.2, III.2 of family B. This splice donor mutation, IVS4 + 2 *T>GCTTACTTCCC*, in the *GATA3* gene cosegregated with the hypoparathyroidism and hearing loss phenotypes in family B. C, Sequence of antisense strand in exon 6 in family C, *Arrow* denotes heterozygous A to T transversion at nucleotide 1059 of the cDNA sequence. The variant is predicted to result in the substitution of serine for an arginine residue at position 353 of the GATA3 amino-acid sequence. Cosegregation of this R353S mutation and its heterozygosity in the affected members (II.3, III.1, and III.2) were demonstrated. This mutation was not detected in 100 chromosomes from 50 unrelated normal individuals.

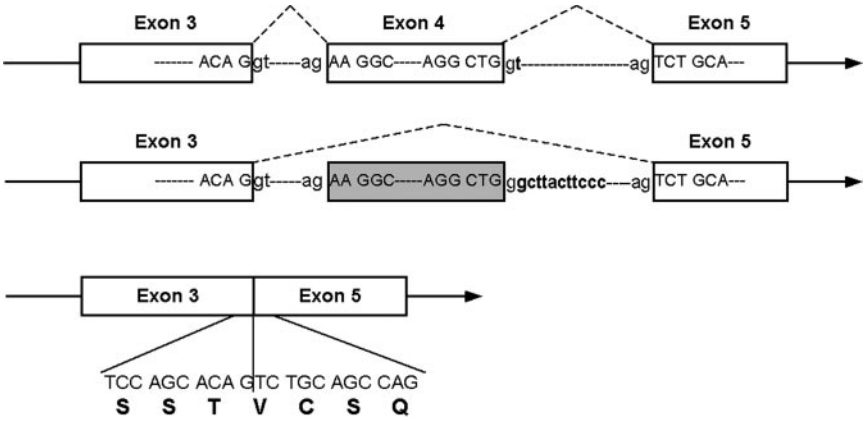

FIG. 2. Ideogram of putative splicing consequence of the IVS 4 + 2 *T* → *GCTTACTTCCC* mutation. Introns and exon 2 of the GATA3 gene are not drawn to scale. The *FGENESH* correctly predicts gene structure, including coding regions in exons 3–5, of the reference *GATA3* sequence (*upper panel*). By contrast, the novel *t* to *gcttacttccc* substitution at the splice donor site of intron 4 results in exon 4 skipping (*middle panel*) and shifting of the open reading frame (*bottom panel*).

Discussion

The combination of hypoparathyroidism, sensorineural deafness, and renal anomalies was termed the HDR syndrome. Recently deletion-mapping studies and subsequent mutation analysis revealed that haploinsufficiency for GATA3 due to various mutations is the underlying mechanism of this syndrome (12–16, 29, 30). In the present study, we examined five families with familial hypoparathyroidism and found that in the three families (A–C) with hearing problems, there were three different kinds of mutations of the *GATA3* gene. We found that even within families with patients harboring identical GATA3 mutations, there appears to be a variable penetrance of renal abnormalities as illustrated by family B, and that of parathyroid disorder as illustrated by families A and C (Table 1 and Fig. 4). This provided further evidence that haploinsufficiency of genes involved in human development frequently shows a wide range of penetrance and expressivity, depending on other genetic and environment factors (31). The clinical feature of early-onset deafness is the most completely penetrant part of the HDR syndrome so that the diagnosis can be made by identifying the invariant hearing problem and the accompanying hypoparathyroidism, not by a genetic screen.

GATA3 encodes a 444-amino-acid transcription factor that contains two transactivating and two zinc finger DNA-binding domains. The N-terminal finger (ZnF1) is encoded by residues 264–288 located in exon 4, and the C-terminal finger (ZnF2) is encoded by residues 318–342 located in exon 5. Functional study had shown that the ZnF2 is essential for DNA binding, whereas the ZnF1 appears to stabilize this binding and interact with other zinc finger protein, such as the Friends of GATA (13). Up to now, 18 causal mutations of the *GATA3* gene have been reported (12–16, 30). All of this evidence established the role of GATA3 haploinsufficiency in the etiology of this developmental disorder. Mutations that disrupt either ZnF2 or the adjacent C-terminal tail lead to a loss of DNA binding, whereas those that disrupt ZnF1 do not result in loss of DNA binding but instead alter DNA binding affinity (13). In our present study, the 478delG mutation in family A represented a frameshift from codon 160 with a premature termination at codon 194. The deletion was hypothesized to disrupt dual zinc fingers as well as one trans-

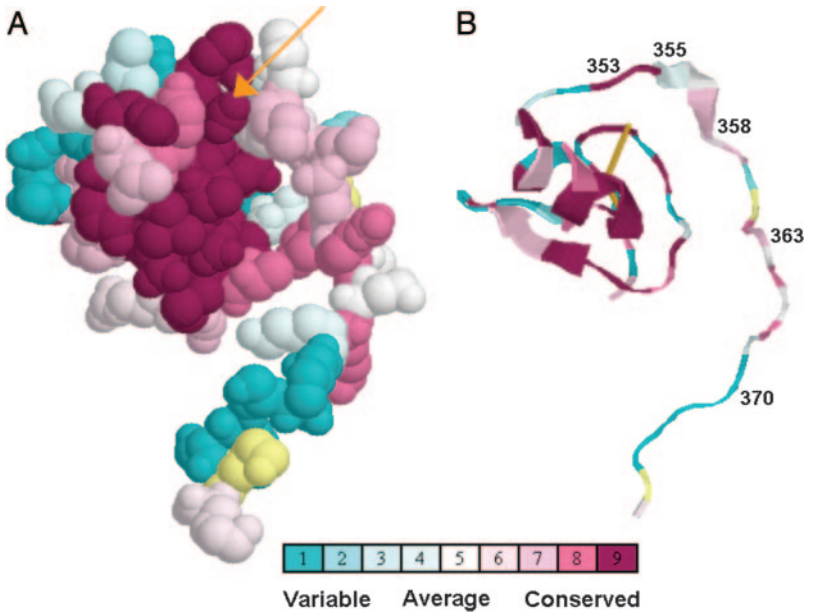

FIG. 3. Surface mapping of phylogenetic information of the C-terminal zinc-containing DNA binding domain (residues 312–375 of cDNA) of human GATA-3. It is presented using a space-filling (A) and cartoon model (B). The amino acids are colored by their conservation grades using the color-coding bar, with *turquoise* through *maroon* indicating variable through conserved. Amino-acid positions, for which the inferred conservation level was assigned with low confidence, are marked with *light yellow*. The residual 353 of the human GATA3 is colored *maroon*. The three-dimensional structure of the C-terminal DNA binding domain of human GATA3 was based on the NMR structure of that of chicken GATA1 (protein code: 2gatA). *Arrow* indicates R353. The helical turn (composed of residues 355–358) and carboxyl-terminal tail (composed of residues 363–370) of this DNA binding domain of human GATA3 are shown in the cartoon model.

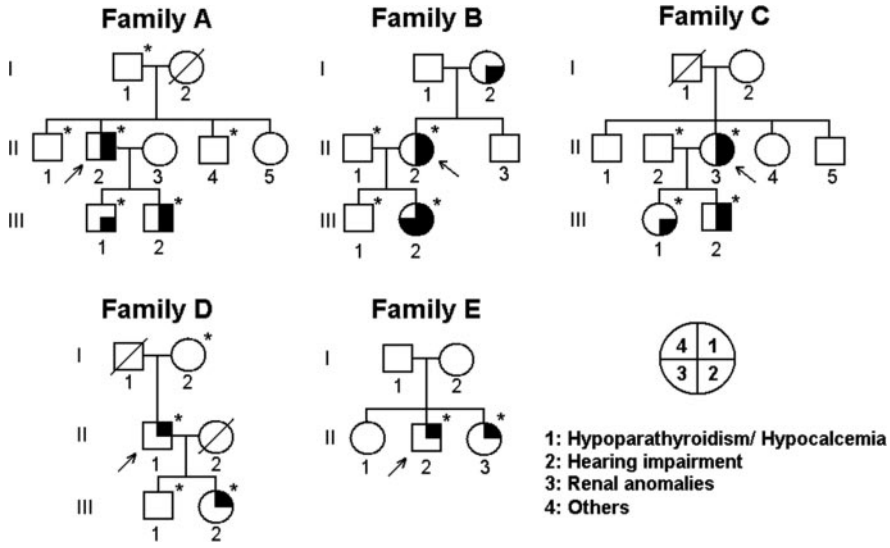

FIG. 4. Familial hypoparathyroidism pedigrees. *Arrow* denotes the proband in each family, *asterisks* indicate subjects who underwent blood sampling, and *filled symbols* in each quartered area represent the features in affected family members.

activating domain. The splice donor mutation at exon 4/intron 4 boundary (IVS 4 + 2 *T* → *GCTTACTTCCC*) in family B was predicted to lead to exon 4 skipping and a reading frameshift at position V260. This mutant produced truncated GATA3 proteins that lack both zinc finger DNA-binding domains.

The possibility that the R353S substitution found in family C might be a rare polymorphism cannot be excluded formally, despite the absence of this polymorphism in 100 chromosomes from unaffected controls because functional studies have not been performed. However, the arginine at codon 353 is located within the C-terminal zinc-containing DNA binding domain and is extremely conserved among various homologous proteins in humans and across species, suggesting the biological importance of this residue. Thus, the R353S substitution is considered to be a causative mutation rather than a rare polymorphism. This mutant, R353S, was predicted to disrupt the helix turn composed of residues 355–358. This would lead to a change of directionality of the carboxyl-terminal tail, which is composed of residues 363–370 and is an essential determinant of specific DNA binding in the minor groove (24). The complex of zinc-containing DNA binding domain resembles a hand holding a rope with the palm and fingers representing the protein core, and the thumb, the carboxyl-terminal tail. The long axis of the protein core lies at an angle of approximately 40° to the base planes of the DNA, whereas the carboxyl-terminal tail is approximately parallel to the base planes (24). Thus, change of the angle between the core and carboxyl-terminal tail would be expected to have a significant impact on the specific function of this transcription factor.

In conclusion, the present study, presenting three newly found mutations, is the first article presenting mutations of the GATA3 gene responsible for familial hypoparathyroidism and deafness in the Chinese population. Our results expand the spectrum of disease-causing mutations, provide further evidence that HDR is caused by the haploinsufficiency of GATA3, and report the first splice donor mutation. The commonly described polymorphism, G990R, and mutations in the *CaSR* gene are not linked to familial hypoparathyroidism in the group of patients we studied. To our knowledge, literatures about mutations in the *CaSR* gene leading to hypoparathyroidism were absent in our population. Neither the *GATA3* nor the *CaSR* abnormalities were identified in the remaining two families. Additional studies are required to determine the involvement of other regions including intronic and regulatory sequences, or other candidate genes, in the pathogenesis of familial hypoparathyroidism. In our opinion, mutations of the GATA3 gene should be considered in patients with a coexistence of family hypoparathyroidism and sensorineural hearing loss, despite of absence of renal involvement. Besides, it is crucial to evaluate the auditory and renal functions in all patients with familial hypoparathyroidism.

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Address all correspondence and requests for reprints to: Keh-Sung Tsai, M.D., Ph.D., Department of Laboratory Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan. E-mail: kstsaimd@ha.mc.ntu.edu.tw.

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