IJKD KIDNEY DISEASES

A Novel Mutation Pattern of Kidney Anion Exchanger 1 Gene in Patients With Distal Renal Tubular Acidosis in Iran

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Introduction. Mutations of the anion exchanger 1 (*AE1*) gene encoding the kidney anion exchanger 1 can result in autosomal dominant or autosomal recessive form of distal renal tubular acidosis (DRTA). This study aimed to report deletion mutations of the *AE1* and its impact on Iranian children with DRTA.
Materials and Methods. Twelve children with DRTA referred to Ali Asghar Children Hospital were investigated for all *AE1* gene exons through polymerase chain reaction amplification, DNA sequencing, and bioinformatics analysis.
Results. Eleven of 12 patients (91.7%) showed an alteration in *AE1* gene with a real hot spot in its exons 11 or 15. Homozygote and heterozygote deletions were confirmed in exon 15 in 5 (41.7%) and 3 (25.0%), respectively. Two patients (16.7%) showed homozygote deletions in exon 11 of *AE1* gene, and 1 patient (8.3%) showed point mutation in exon 11. The 3-dimensional structures of the native and these mutant kidney AE1 proteins were determined by the multitemplate method using the Phyre and Hidden Markov Model algorithms.
Conclusions. Parents' consanguinity of these patients reveals that cousins are at a high risk for DRTA. This study is considered as a pilot study showing the importance of *AE1* mutations in Iranian children with DRTA and further studies is recommended in this geographic region of the world. These models suggest that alteration in the structures leads to alteration in function and change in the current role of AE1.

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INTRODUCTION

Hereditary distal renal tubular acidosis (DRTA) syndrome is largely caused by dysfunction of intercalated cells in the collecting tubules of the kidney. Defect in the secretion of hydrogen ion, a process called urine acidification, is the common inability among DRTA syndromes of different mutation types. Acidification of the urine results from a well-orchestrated program, mainly based on the activities of transporters present in apical and basolateral membrane of α-intercalated cells. Mutations in genes encoding these transporters are responsible for autosomal dominant DRTA and autosomal recessive DRTA (ARDRTA).[1]

The α-intercalated cells secrete acid by the cooperative action of apical and basolateral transporters, including proton-adenosine triphosphatase (proton-ATPase) and anion exchanger 1 (AE1), respectively. Proton-ATPase secretes hydrogen ions into the tubular lumen, while AE1 reabsorbs bicarbonate in exchange for the entrance of chloride ion into the α-intercalated

cells, leading to optimal distal acidification of the urine. Dysfunction in each of the partners of this circuit, including *ATP6V1B1* (B1 subunit of proton-ATPase), *ATP6V0A4* (a4 subunit of proton-ATPase), cytosolic carbonic anhydrase II, and *AE1*, can result in failure of acidification that leads to metabolic acidosis, and eventually DRTA.[1-6] Chronic metabolic acidosis in patients with DRTA often coexists with a variety of symptoms, including growth retardation, nephrocalcinosis, nephrolithiasis, hypercalciuria, hypocitraturia, hypokalemia, hemolytic anemia, deafness, and eventually kidney calculi.[7-11]

Mutations in *ATP6V1B1*, *ATP6V0A4*, and cytosolic carbonic anhydrase II lead to the autosomal recessive form of the disease, while *AE1* alterations largely result in autosomal dominant DRTA. The *AE1* gene, however, has also shown to cause ARDRTA. Disease-causing mutations lead to the defect in trafficking of the mutant protein rather than its lack of function as the major occurrence in AE1-associated DRTAs.[1] The *AE1* gene—also known as *SLC4A1* (solute carrier family 4 member 1)—is located on chromosome 17q21-q22, has the length of about 20 kb, and consists of 20 exons. In its upstream region, it contains consensus-binding sites for several transcription factors, including E-boxes, CACCC boxes, GATA (erythroid factor 1), activator protein 1, and activator protein 2, while the TATA and CCAAT boxes are found in intron 3.[12-14] The *AE1* gene is highly expressed in basolateral membrane of α-intercalated cells, as well as erythrocytes plasma membrane. The kidney-AE1 is a truncated isoform of erythrocyte AE1 at the N-terminus by 65 amino acids, which is produced from utilizing different promoters and alternative splicing. The upstream promoter leads to the transcription of erythrocyte-*AE1* mRNA, while kidney-*AE1* mRNA is transcribed by using the promoter in intron 3. The downstream end of exon 20 is defined as the RNA cleavage site or poly A addition site, and a consensus poly A signal (AATAAA) is located 20 nucleotides upstream of the RNA cleavage site.[15] Notably, dysfunction of another member of the solute carrier family, SLC26A7 that is also take part in acidification process, is shown to cause DRTA and impaired gastric acid secretion.[16]

The *AE1* gene encodes a 911-amino acid multispanning membrane protein, with both N-terminal (residues 1-359) and C-terminal (residues 881-911) domains located in the cytoplasm. Both the N and C termini are essential for basolateral trafficking of AE1.[17] Several motifs located within the cytosolic domains of integral membrane proteins are involved in the targeting of basolateral proteins, including tyrosine motifs and di-leucine motifs.[18] A variety of different dominant and recessive mutations in *AE1* cause DRTA, leading to the mistargeting of *AE1* from basolateral membrane.[17,19-22] In the present study we identified a novel pattern of mutations in exons 11 and 15 of *AE1* that caused ARDRTA among Iranian patients.

MATERIALS AND METHODS

Patients

Between 2009 and 2013, a total of 12 patients with a diagnosis of DRTA were requested and accepted to participate in a genetic study. The consent was taken from the patients or their parents. Eight of them (66.7%) had parents' Consanguinity. The diagnosis of DRTA was according to the presence of normal anion gap metabolic acidosis at the time of presentation, impaired urine acidification (persistent alkaline urine documented as urine pH less than 5.6), positive urine anion gap, normal proximal kidney function, and nephrocalcinosis

Table 1. List of Specific Primers Used for Amplification of Exons 11, 15, 17, 19, and 20 of Anion Exchanger 1 Gene in Patients With Distal Renal Tubular Acidosis

Exon	Polymerase Chain Reaction Primer Sequence	Tm (0 C)	Product Size
11	CCTCACCTCCTCCAGCTACTCC CAGAAGTTGGGGCTGAGACAGAG	62	318
15	AAGGCAGGAGGTGGGGAGTGACTG GGAAATGAGGACCTGGGGGGTATC	70	201
17	TGGAGGAGGCAGGGGAGAAC GGGGCAGGAGGATGGTGAAG	70	347
19	GGTACAGGACCCTTTTCTGG GCCTGCCCTAGTTCTGAGAC	60	334
20	TCTCACCCTGTCTCTCTCCTG GAGGTGCCCATGAACTTCTG	65	198

with or without deafness. Children with acidosis at the time of pyelonephritis, obstructive uropathy, cystinosis, drug-induced tubulopathy, and vasculitis were not included. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences.

Mutation Studies

Genomic DNA was isolated from peripheral blood lymphocytes using standard phenol/chloroform DNA extraction method. To amplify *AE1* exons, exon-specific primers including exon/intron junctions were designed, synthesized, and utilized based on their coding sequence. The exon-11- and exon-15-specific primers and their sequences are listed in Table 1.

One microgram per microliter of each DNA sample was subjected to polymerase chain reaction. The samples were first denatured at 95°C for 2 minutes. Polymerase chain reaction reactions were carried out for 30 cycles consisting of denaturation at 94°C for 1 minute, annealing at specific temperature for each primer for 1 minute, and extension at 72°C for 1 minute. The polymerase chain reaction products were run on a 1.5% agarose gel electrophoresis, and the images were analyzed for mutation detections. For mutation screening, sequencing of selective exon polymerase chain reaction product of the human *AE1* gene was performed using the ABI sequencing system.

In Silico and Statistical Analyses

In silico analysis was performed in order to analyze the mutations and their effects on the AE1 protein. Clustal W program (http://www.genome.jp/tools/clustalw/) and Modeller v9.10 were used, as well as Phyre 2 algorithm, HMM algorithm, Kyte-Doolittle scale (R), Needleman-Wunsch, and BLOSUM-62 alignment. All the sequences were derived from the National Center for Biotechnology Information database (http://www.ncbi.nlm.nih.gov/).

RESULTS

Cases Reports and Clinical Follow-up

Demographic information and clinical and paraclinical data of the patients are summarized in Table 2. Some of the patients had been referred while receiving bicarbonate or citrate solution. Most of the patients had suffered from hemolytic anemia (> 87%)

Table 2. Characteristics of Patients With Distal Renal Tubular Acidosis and Mutations in Anion Exchanger 1 Gene

Patient	Age	Sex	Consanguinity	Age of Onset	Urine pH	Bicarbonate, mEq	Carbon Dioxide Pressure, mm Hg	Nephrocalcinosis	Hemoglobin, g/dL	Mean Corpuscular Volume, fL	Hematocrit	Exon Alteration
1	7 mo	Male	Yes	2.5 mo	7.0	12.5	21.2	Yes	10.3	72.5	31.9	15
2	8 mo	Female	Yes	35 d	6.1	15.5	25.9	Yes	10.5	77.5	31.0	15
3	9 y	Male	Yes	4.5 y	6.2	19.4	19.4	Yes	7.8	91.7	25.3	11
4	9 y	Female	Yes	2 y	6.1	18.2	33.3	No	9.8	84.4	32.9	15
5	7.5 y	Male	Yes	40 d	7.5	15	31	Yes	7.5	84.5	23.4	11
6	14 y	Female	Yes	3 mo	7.0	11	22.5	Yes	10.1	73.3	31.4	11, 15
7	9 y	Female	No	8 mo	6.2	14.8	20.9	Yes	13.2	88.8	36.6	15
8	6 y	Female	No	3 mo	6.2	14.8	24.8	Yes	10.7	100.0	32.0	15
9	22 mo	Female	No	1 y	6.4	24	23.4	Yes	11.3	79.7	34.5	15
10	3.5 y	Male	No	27 d	6.2	20.3	27.1	Yes	9.3	76.4	25.3	
11	25 y	Female	Yes	3 y	7.0	19.7	25.4	NO	9.9	81.7	33.1	11

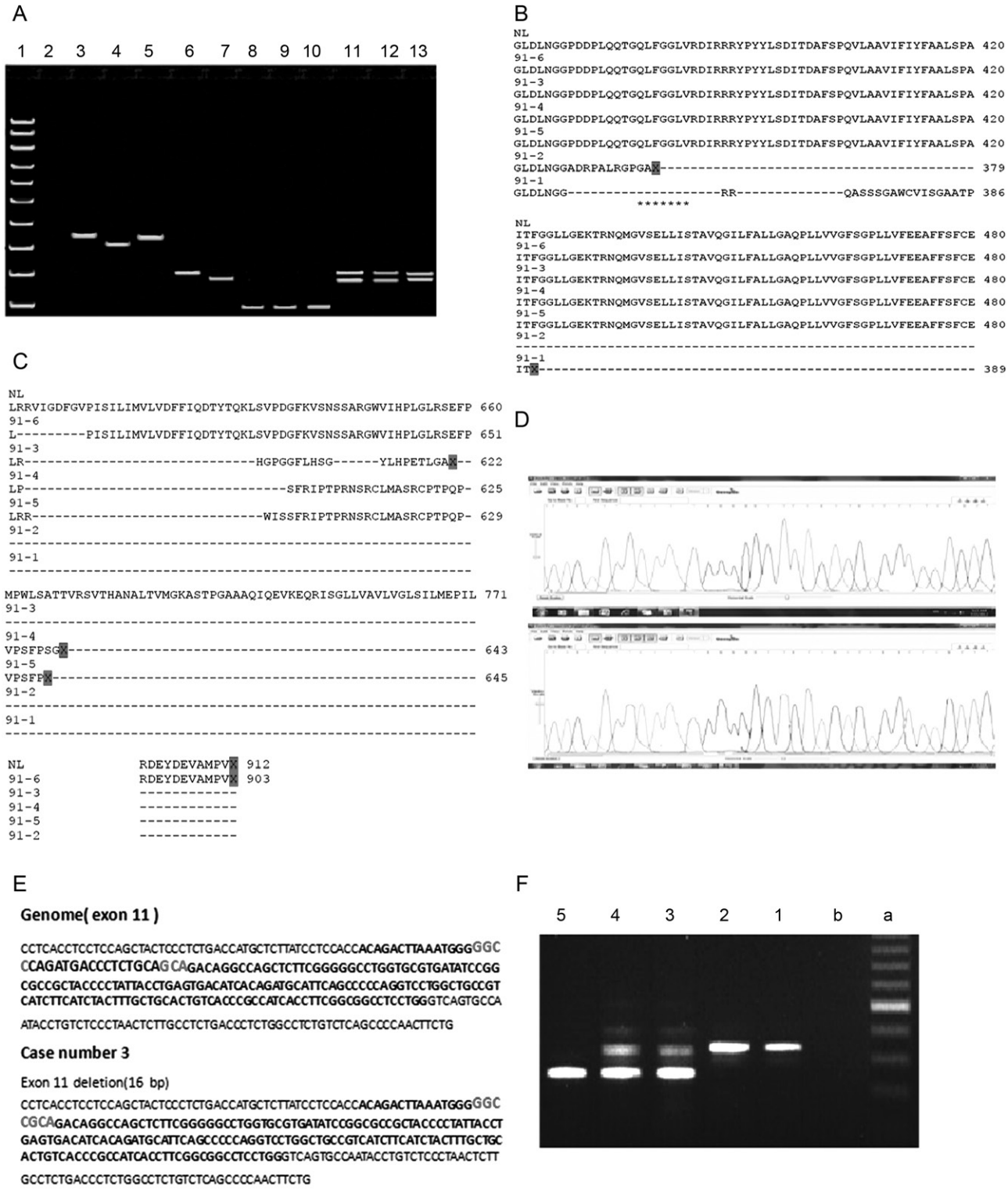

Figure 1. A, Number 1 is 100-bp DNA ladder fermentase; number 2, negative control; number 3, NL-1; number 4, 91-1; number 5, 91-2; number 6, NL-2; number 7, 91-3; number 8, 91-4; number 9, 91-5; number 10, 91-6; number 11, 91-7; number 12, 91-8; and number 13, 91-9. **B,** This alignment shows truncation of the anion exchanger 1 (AE1) proteins in cases 91-2 and 91-1 with deletion in exon 11. **C,** This alignment shows truncation of the AE1 proteins in cases 91-3 and 91-5, but in case 91-6 (that shows no frame shift) with deletion in exon 15. **D,** Deletion chromatography of *AE1* exon 11 in case 91-3. **E,** Deletion sequence of *AE1* exon 11 in case 91-3. **F,** Family analysis of *AE1* exon 11 of patient 91-3. The 'a' is 100-bp DNA ladder; 'b,' negative control; 1, healthy control; 2, patient 91-2; 3, mother; 4, father; and 5, patient 91-3.

accompanying the DRTA criteria (Table 2), which was predictable as the most prevalent manifestation associated with DRTA in *AE1* mutation.[1]

Polymerase Chain Reaction Products With Deletion Mutation

Molecular characterization of the patients with DRTA referred to Ali Asghar Children Hospital was identified. Analysis of gel electrophoresis and sequencing results (Figures 1 and 2) confirmed that there were certain alterations in exons 11 and 15 of the *AE1* among 11 of the 12 cases (91.7%). Eight patients had alterations in exon 15, consisting of homozygote (5 cases) and heterozygote (3 cases) deletion mutations. Three patients showed alterations in exon 11, consisting of homozygote deletion (2 cases) and point mutation (1 case), the latter resulting in substitution of glycine with glutamic acid (c.G1097A). Deletion mutations included c.del 1103-1119 (16 bp), c.del 1165-1181 (16 bp), c.del1807-1848 (41 bp), c.del 1805-1866 (61 bp), c.del 1810-1859 (49 bp), and c.del1805-1832 (27 bp). These alterations likely affected the hydrophobicity of AE1. Table 3 shows DNA and corresponding protein alterations in DRTA patients. The major alterations occurred in the amino acids 368 (prolin) and 602/603 (R/V) which were located in the exons 11 and 15, respectively. Meanwhile, as 2 hotspots, these two exons of the *AE1* could be the most common mutation sites leading to DRTA in our consanguineous Iranian patients.

Table 3. DNA and Protein Change in Some Patients With Distal Renal Tubular Acidosis and Novel Mutations in Anion Exchanger 1 Gene

Patient	DNA Change	Amino Acid Change
91-1	c.del 1103-1119 (16 bp)	p.P368R, fs 20X
91-2	c.del 1165-1181 (16 bp)	p.P368A, fs 10X
91-3	c.del 1807-1848 (41 bp)	p.R603H, fs 19X
92-4	c.del 1805-1866 (61 bp)	p.R602P, fs 40 X
91-5	c.del 1810-1859 (49 bp)	p.V603W, fs 41 X
91-6	c.del 1805-1832 (27 bp)	p.del602-611,non fs
58	c.G1097A	p.G366E

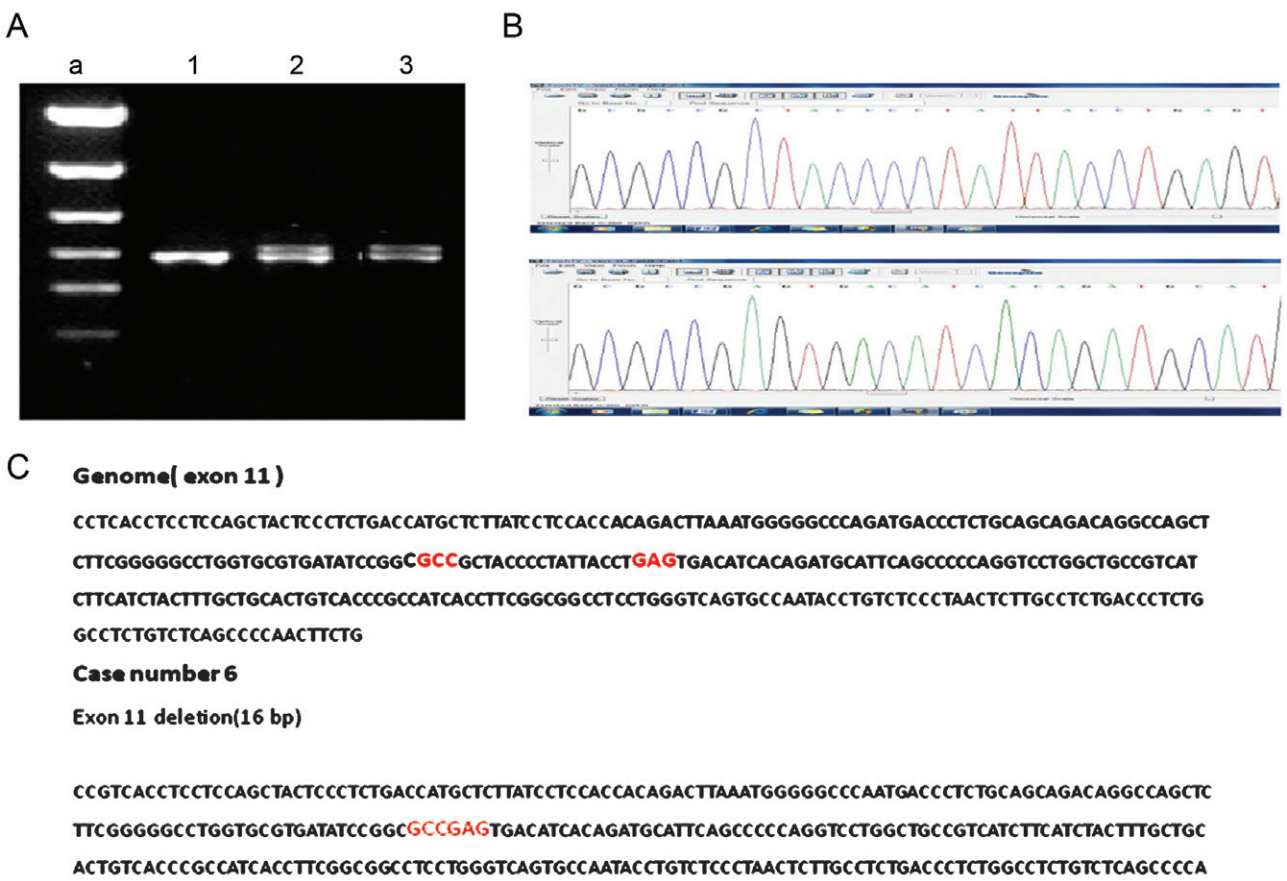

Figure 2. Top Left, Anion exchanger 1 (*AE1*) exon 11. The 'a' is 100-bp DNA ladder; 1, patient 91-6; 2, mother, and 3, father. **Top Right,** Deletion chromatography of *AE1* exon 11 in case 91-6. **Bottom,** Deletion sequence of *AE1* exon 11 in case 91-6.

Protein Alignment, Mutation Detection, and Modeling

Our methods for detecting mutations are based on the alignment with the Clustal W program. To use clinical terminology, samples from the patients were compared to standard reference sequence for *AE1* in the National Center for Biotechnology Information, NM_000342.3 (Figures 1B, 1C, 1E, and 2C). All detected mutations in this study altered the basolateral kidney transporter protein and have been modeled and submitted in protein model database (http://mi.caspur.it/PMDB; Table 4).

Table 4. Mutant Kidney Anion Exchanger 1 Proteins in Iranian Patients With Distal Renal Tubular Acidosis*

Number	Length (Size) aa	Access Number
1	1599	PM0078732
2	1500	PM0078767
3	1532	PM0078768
4	911	PM0078806
5	388	PM0078807
6	378	PM0078808
7	621	PM0078809
8	642	PM0078810
9	1532	PM0078811
10	902	PM0078812

*Protein Model Database available from: http://mi.caspur.it/PMDB

These protein alterations included p. P368R fs 20X, p. P368A fs 10X, p.R603H, fs 19X, p.R602P,fs 40 X, p.V603W, fs 41 X, and p. del602-611, non fs.

The Phyre 2 algorithm which was used in this research project found similar folds. Any of the 20 identical amino acids between query and templates was a hit for this algorithm. After finding similar structures, this server predicted query model based on identical folds. In other words, by using this algorithm, alignment performed between folds instead of the entire template structure. Using this algorithm, we found 58%, 73%, and 62% identical folds for 3 patients (patients 7, 8, and 9). The rest of misaligned residues were modeled by the HMM algorithm. Finally, by using the Modeller v9.10 and multitemplate based prediction method, complete models were generated. The final predicted models minimized regarding energy level by choron algorithm.

Effect of Mutations on Protein Hydrophobicity

Because of frame shift mutations, structures of mutant models versus native one were different in conformation and amino acid type. Since AE1 is a transmembrane protein, any change in hydrophobicity properties may change position of the protein within cell membrane. Any alteration in the protein structure may influence protein function; therefore, to investigate hydrophobicity changes upon mutation the Kyte-Doolittle scale (R) was utilized. This scale is widely used for detecting hydrophobic regions in proteins and can be used for identifying both surface-exposed regions as well as transmembrane regions. Regions with a positive value are hydrophobic. Figure 3 indicates changes in hydrophobicity properties upon some mutations. Based on Figure 4, an increased hydrophobicity in the exon 11 was detected, while cases 91-3, 91-4, and 91-5 show significant decreased hydrophobicity. However, a change in hydrophobicity upon mutation in case 91-6 is not significant. The root-mean-square deviation between mutant structures and wild-type model were calculated by the Needleman-Wunsch alignment algorithm and blocks substitution matrix-62 as alignment matrix. Results indicated that root-mean-square deviation value between wild type and 91-1 was 1.223; for 91-2, it was 0.840; for 91-3 it was 0.472; for 91-4, it was 0.994; for 91-5, it was 0.787; and finally for 91-6, it was 1.088. These scores indicated that most of the changes in protein structure were imposed by mutations in 91-1 and 91-2, while 91-3 had the least influence on protein structure.

DISCUSSION

Our report is the first that identifies relatively large deletions, from 16 bp to 61 bp, in exons 11 and 15 of *AE1* associated with ARDRTA with hemolytic anemia in some Iranian patients. Previously, some proton-ATPase mutations have been reported in DRTA associated with deafness in some other Iranian patients.[11] Deletions mostly cause frame-shift and lead to the intracellular retention of AE1 transporter. We also presented a novel point mutation in exon 11 of *AE1* that affected the hydrophobicity of the protein and likely prevented its placement in the basolateral membrane or trafficking. Our patients were mostly suffering from anemia, which is in line with the previous reports regarding ARDRTA.[1] It should be noted that the recessive diseases are generally defined by clinical phenotypes, which may be variable in expressivity and penetrance and can

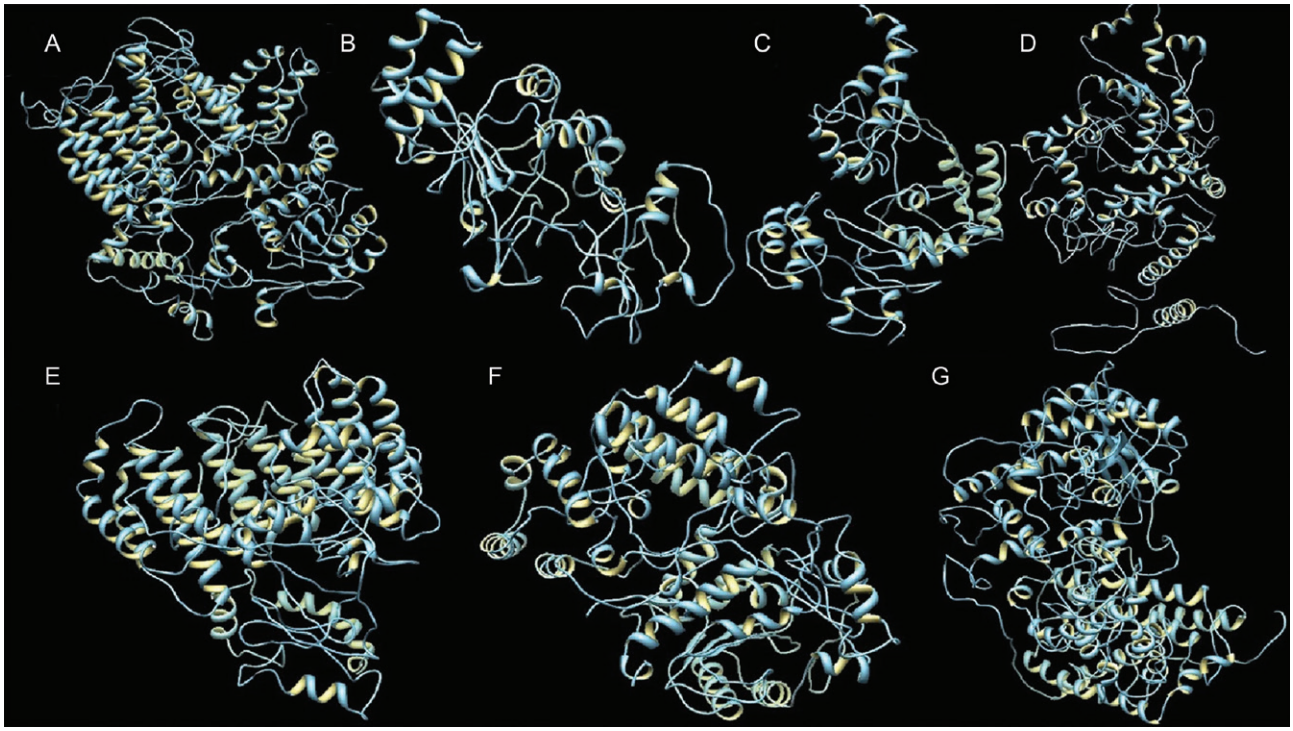

Figure 3. A, Theoretically predicted models of wild type renal tubular acidosis. **B,** Mutant types in exon 11 of case 91-1. **C,** Mutant types in exon 11 of case 96-2. **D to G,** Mutant proteins in exon 15 of cases 91-3, 91-4, 91-5, and 91-6, respectively. Except 91-6, all mutant proteins are truncated.

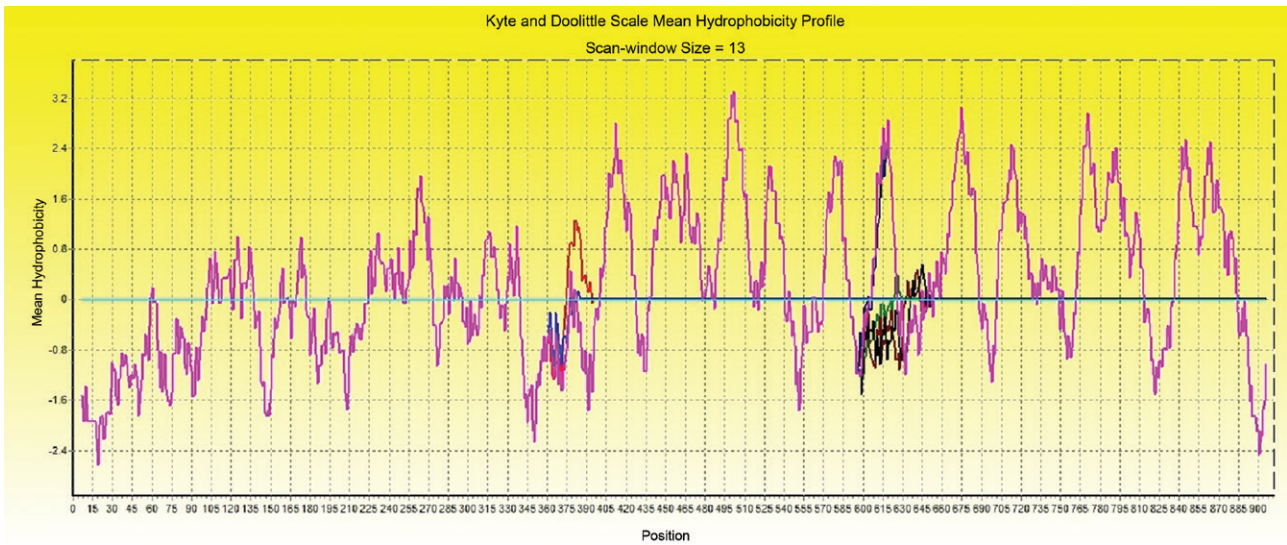

Figure 4. Hydrophobicity plot of renal tubular acidosis protein in Kyte and Doolittle scale. The plot indicates variation in hydrophobicity properties of protein upon mutation.

also be modified by the effect of other genes.

It was first thought that *AE1* mutations always cause autosomal dominant DRTA, although the first *AE1* mutation associated with ARDRTA was reported in 2 Thai siblings.[23] They were found to carry a homozygous *AE1* mutation resulting in a substitution of glycine by aspartic acid at position 701 (exon 17) in the AE1 protein (G701D), namely band 3 Bangkok I, which also links to 2 polymorphisms, M31T and K56E. When expressed in Xenopus oocyte, both erythrocyte-AE1 and kidney-AE1 G701D showed lack of cell surface expression and anion transport activity. Three patients with ARDRTA with compound

heterozygous *AE1* Southeast Asian ovalocytosis (SAO)/G701D mutations were later reported in 2 Malaysian families, and ARDRTA in another patient from a Malaysian family resulted from compound heterozygous *AE1* SAO/A858D mutations (exon 19).[24] In the same study, ARDRTA associated with other genotypes including SAO/ΔV850, ΔV850/ΔV850, and ΔV850/A858D was observed in patients from 6 Papua New Guinean families. Southeast Asian ovalocytosis is a morphological erythrocyte abnormality caused by a mutational deletion of 27 bp in exon 11 of *AE1*, leading to an inframe 9 amino acid deletion involving Ala400-Ala408 of eAE1, at the junction between the N-terminal domain and the first transmembrane span.[25] Additionally, mutations in *AE1* presenting in N-terminal and C-terminal domains, in exons 5 and 9, have shown to be associated in pH-dependent conformational changes.[26] Other reports regarding ARDRTA have shown mutations in exons 5, 11, 13, 14, 15, and 16.[2,10,27,28]

A large proportion of these alterations are point mutations, and notably, some of them are shown to be compound heterozygotes, which result in dysfunctioning of AE1 in different manners, largely trafficking defect.[28-30] However, a small number of deletion mutations are reported, including Human band 3 Walton, which is derived from deletion of 11 amino acids from the C-terminal of AE1. This condition is associated with the autosomal dominant DRTA in which intracellular retention of AE1 prevents its natural function.[31] Another report regarding deletion mutation represents deletion of Valin 850 that showed an autosomal recessive pattern, though in combination with other mutation types (compound heterozygote) led to pseudo-dominant phenotype.[24]

CONCLUSIONS

The results of our study clearly indicate that *AE1* mutations in Iranian patients can cause ARDRTA, occurred in certain pattern of deletion or point mutation in exons 11 and 15. It shows that consanguineous marriage in Iran may put the siblings at high risk for this particular pattern of mutation resulting in DRTA among those with a history of this disease in close family members or relatives. Therefore, all these new findings regarding DRTA should be considered in genetic counseling in Iran. This consideration is recommended in a study of a large sample size of patients involved in DRTA in other Middle East countries. Also functional studies of the AE1 disrupted protein due to the reported mutations of the gene in this report and further translational studies are suggested. Consistent with our results, the most prevalent mutations in DRTA and hemolytic anemia is *AE1* mutations, whereas deafness is an important feature in some proton-ATPase mutations.[1,11] Therefore, we suggest a population-based approach in Iranian DRTA patients with hemolytic anemia to be examined exons 15 and 11, as one of the first actions toward genetic confirmation of the disease.

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CONFLICT OF INTEREST

None declared.

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