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Publication Date

2023-12-11

Peer reviewed

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Molecular Vision 2006; 12:324-30 <http://www.molvis.org/molvis/v12/a35/>
Received 12 January 2006 | Accepted 3 April 2006 | Published 10 April 2006

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Proximal renal tubular acidosis and ocular pathology: a novel missense mutation in the gene (*SLC4A4*) for sodium bicarbonate cotransporter protein (NBCe1)

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Purpose: The electrogenic Na^+/HCO_3^- cotransporter (NBCe1) plays a major role in renal bicarbonate absorption via proximal tubules and therefore is crucial for maintaining normal blood pH. The human gene for NBCe1 (*SLC4A4*) produces two major transcripts by alternative promoter usage (kNBCe1, originally cloned from kidney and pNBCe1, pancreatic/general form). Though rare, recessive *SLC4A4* mutations have been reported in patients with proximal renal tubular acidosis, short stature, and ocular pathology. A 27-year-old male presented with these findings. The purpose of this study was to investigate the molecular pathology responsible for this patient's clinical findings.
Methods: A comprehensive ophthalmic examination was performed, detailed ocular and systemic medical histories were taken and past medical records were obtained. Mutation screening was performed by using direct PCR sequencing of *SLC4A4* exons and flanking intronic regions. Functional characterization of the mutation was made by expressing the wild-type and mutant NBCe1 proteins in Xenopus oocytes.
Results: We identified a novel, homozygous, missense *SLC4A4* mutation (Leu522Pro in kNBCe1) in our patient who had pRTA, short stature, enamel hypoplasia, and bilateral ocular disease (cataract, glaucoma, and band keratopathy). The patient also had a medical history of ataxia, migraine with transient hemiparesis attacks, and slight hypothyroidism. The mutant RNA failed to induce electrogenic transport activity. The L522P-protein was not effectively transported to the oocyte membrane and thus was unable to act as a transmembrane transporter.
Conclusions: This novel mutation increases our understanding of the structural/functional aspects of the NBCe1 protein and the molecular basis of the multiorgan pathologies associated with its defects.

Maintenance of blood pH within a narrow range (7.35-7.45) is crucial for essential biochemical and metabolic functions. The kidneys have a key role in homeostasis because of their ability to reabsorb HCO_3^- and excrete acid. The basolateral membrane, electrogenic Na^+/HCO_3^- cotransporter (NBCe1) plays a major role in renal bicarbonate absorption via the proximal tubules [1]. The human gene for NBCe1 protein (*SLC4A4*) is located on chromosome 4q21 and produces two major transcripts with 5'-end variants resulting from alternative promoter usage [2]. The pNBCe1 transcript is generated from the primary promoter and is expressed in most tissues, including the pancreas [1]. The kNBCe1 transcript uses an alternative promoter and transcription initiation site within intron 3 of *SLC4A4* and was originally cloned from kidney [2]. kNBCe1 and pNBCe1 are composed of 1,035 and 1,079 amino acid residues, respectively. kNBCe1 differs from pNBCe1 with its unique NH_2-terminal that harbors 41 amino acids (in lieu of the first 85 amino acids of pNBCe1) [2]. A third isoform, reported in rat but not yet in human, is found in brain and uses the pNBCe1 promoter but a novel C-terminus [3]. NBCe1 expression has also been detected in other tissues such as heart, stomach, intestine, lung, thyroid, salivary glands, and prostate [1,4]. We have adopted the previously used nomenclature for *SLC4A4* mutations based upon their locations in kNBCe1.

The kidney seems to express all NBCe1 variants and their function accounts for 80-90% of renal HCO_3^- absorption [1]. Therefore, the renal findings constitute the major phenotype for *SLC4A4* mutations. Renal tubular acidosis (RTA) is a clinical syndrome characterized by hyperchloremic, metabolic acidosis resulting from defective renal acidification. Proximal RTA (pRTA) is caused by impairment of bicarbonate absorption in proximal tubules with decreased renal HCO_3^- threshold, while the distal tubule acidification remains intact. A rare syndrome was described in patients with *SLC4A4* mutations that was characterized by autosomal recessive (AR) permanent isolated pRTA and hypokalemia (blood pH <7.2, blood HCO_3^-=5-11 mM/L, serum K^+=2.6-3.3 mEq/l), short stature, and ocular pathology (glaucoma, band keratopathy, cataract) [5-8]. Additional features may include enamel defects of permanent teeth and mental retardation [5-7]. Calcification of basal ganglia, hyperamylasemia, and hypothyroidism were also noted in some patients [4]. Eight homozygous *SLC4A4* mutations (6 missense-R298S, S427L, T485S, R510H, A799V, R881C; one nonsense-Q29X; and one frameshift-2311delA) have been published to date [5-9]. One additional mutation (a

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65 bp deletion comprising exon 23 and intron 23) was reported in a meeting abstract [10]. The Q29X mutation is located at unique kNBCe1 NH_2terminal region and predicted to leave the pNBCe1 function intact [6].

We have identified a novel, homozygous, missense *SLC4A4* mutation (Leu522Pro) in a male patient with isolated pRTA associated with ocular and other systemic pathologies. Here, we provide the clinical findings of the patient and functional characterization of the mutated protein.

METHODS

A 27-year-old Caucasian male was referred to our ocular genetics clinic. He had pRTA, short stature, and bilateral ocular disease (cataract, glaucoma, and band keratopathy). A comprehensive ophthalmic examination was performed, detailed ocular and systemic medical histories were taken, and past medical records were obtained in order to understand the full clinical spectrum. Informed consent was obtained prior to participation to this study in accordance with a protocol that was approved by the University of Pittsburgh IRB and in accord with HIPAA regulations.

PCR primers (flanking 22 *SLC4A4* exons; exons 4 through 25 coding for kNBCe1) were designed using the Primer3 software. *SLC4A4* exons and flanking intronic regions were amplified from leukocyte genomic DNA of the patient, purified, and used as templates for sequencing reactions. Direct PCR sequencing was performed using automated DNA analyzers (Applied Biosystems, Foster City, CA). The results were evaluated with Sequencher 4.1 software (Gene Codes Corporation, Ann Arbor, MI).

Functional analysis was performed by expressing the wild-type (wt) and the mutant kNBCe1 proteins in Xenopus oocytes. The site-directed mutagenesis was used to reproduce the mutation in the hkNBCe1 and to create an expression plasmid similar to those generated for other mutations [7]. The hkNBCe1 mutation was verified by direct cDNA sequencing (W. M. Keck, New Haven, CT). The wt- and mutant-hkNBCe1 cRNAs were injected into Xenopus oocytes that were used for voltage clamp experiments. To determine the changes in protein production and localization, the wt-hkNBCe1, mutant-hkNBCe1, and water-injected oocytes were fixed, cryosectioned, and stained with an NBCe1 antibody as previously described [7].

RESULTS

Patient description: systemic findings: The patient, born at full term to a 15-year-old and weighting about 7 lbs, was adopted at age four months. When he was a year old, he began having episodes of dizziness and ataxia and was tentatively diagnosed as having acute cerebellar ataxia. Later, the symptoms were attributed to “benign paroxysmal vertigo” and “episodic ataxia”. He was described as a well-behaved, friendly, and cooperative child with developmental delay in communication, writing/reading, and gross motor skills. He responded well to speech/language therapy from the ages five through seven and his California Achievement Tests indicated a score of 84 in the second grade. At age eight, his height was 114 cm (about tenth percentile for age), his weight was 22.1 kg (about third percentile for age), his hands were short with a full length of 13 cm, and his bone age was 5.5 years. He was noted to have a raspy voice and dental abnormalities consistent with delayed eruption and enamel hypoplasia. G banded chromosome studies revealed mosaicism (46 XY/47 XY+M) for a small amount of chromosomal material (too small to be further characterized). At age nine, his RTA (isolated proximal with low HCO_3^- set point) was recognized. The patient was also noted to have migraines with transient hemiparesis attacks, suspected metabolic encephalopathy episodes, and slight hypothyroidism. CT and MRI brain scans were reportedly normal, but an electrocardiogram showed first degree AV block. Between ages 19-20, he was noted to have nephrocalcinosis and hypercalciuria in addition to pRTA. He was placed on a calcium-restricted diet in addition to his potassium citrate supplementation and potassium-sparing diuretics treatment.

According to recent reports, the patient has been doing well with mildly reduced, but stable renal function. However, he has elevated blood pressure and still shows transiently re-

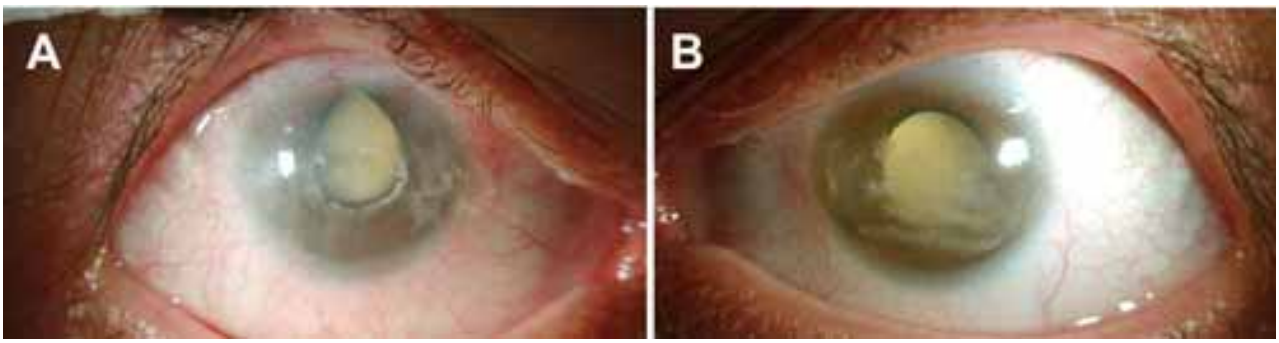


Figure 1. Appearance of the patient’s anterior eye segments at age 27. Anterior segment photographs of the right (**A**) and left (**B**) eye of the patient. Both eyes demonstrate peripheral corneal vascularization and opacification, interpalpebral band keratopathy, and dense, white mature cataract. Note the loss of a distinct corneal-limbal boundary in both eyes, giving an appearance of microcornea. The right eye also shows pupil deformation (superior retraction) that seems to be due to previous glaucoma surgery.

duced serum bicarbonate levels and continuously low CO_2 levels. His current medications include nifedipine SA, phenytoin sodium, propranolol HCL, amiloride HCL, chlorothiazide, and supplements of sodium bicarbonate and potassium citrate.

Patient description: ocular findings: Visual problems were noted in kindergarten, but his initial eye exam at age six revealed no abnormalities. Subsequently, progressive myopia, corneal fine granules, and lenticular minute snowflake-type opacities were noted. His corrected visual acuities were 20/50 in each eye at seven years of age. His corneal diameters were normal (10 mm at age nine) but as corneal opacification progressed, it became difficult to discern the limbal borders of the cornea, giving rise to a false appearance of microcornea as an adult (Figure 1). Cataracts and band keratopathy became more evident with age and bilateral open-angle glaucoma was diagnosed. At age eight, he demonstrated behaviors consistent with markedly constricted visual fields, yet at age nine, his fundus exam reportedly showed only slight shallowing of temporal optic discs with cup/disc ratios of 0.1. Eventually, the lens and corneal opacities limited the fundus examination. At age 11, he had bilaterally abnormal visual evoked responses to both flash and pattern stimuli (left>right). His glaucoma was initially treated with only topical medication (acetazolamide was used for only short periods) but eventually required surgical therapy (trabeculectomy and goniotomy for the right eye). EDTA chelation procedures were performed for his band keratopathy in both eyes.

At his presentation to our service at age 27, he was completely blind (hand motion at immediate face for the right eye and no light perception for the left eye) with nystagmus, introcular pressures fluctuating between 15 and 30 mm Hg, advanced band keratopathy, and mature cataracts in both eyes. No visualization was possible for the posterior eye segments, but his recent ocular ultrasound reported no apparent pathology.

SLC4A4 *mutation screening:* Mutation screening revealed a novel, homozygous, missense *SLC4A4* mutation in this patient (CTC to CCC codon change in exon 14, predicted to result with Leu522Pro in kNBCe1 and Leu566Pro in pNBCe1; Figure 2). Given that this sequence variant abolishes a *Bsm*AI restriction site, the restriction endonuclease analysis was used to screen healthy control individuals (100 chromosomes) and confirmed that this is not a common variant (data not shown). The wild-type leucine residue at position 522 is evolutionary conserved among human, bovine, rat, and mouse species.

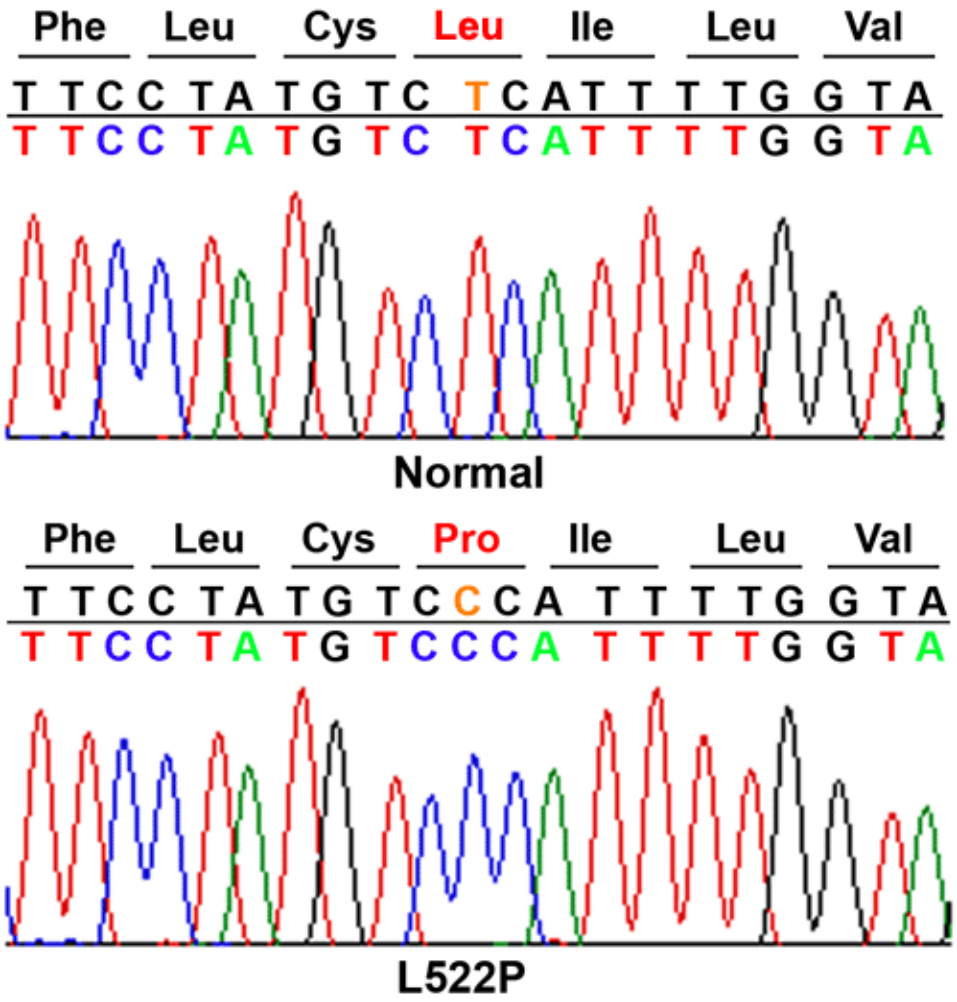


Figure 2. Sequence analysis of *SLC4A4* exon 14. Analysis of the patient's leukocyte DNA revealed a novel, homozygous T to C transition that is predicted to result with the replacement of a leucine residue with proline at codon 522 in hkNBCe1. This sequence variant was not detected in 100 control chromosomes.

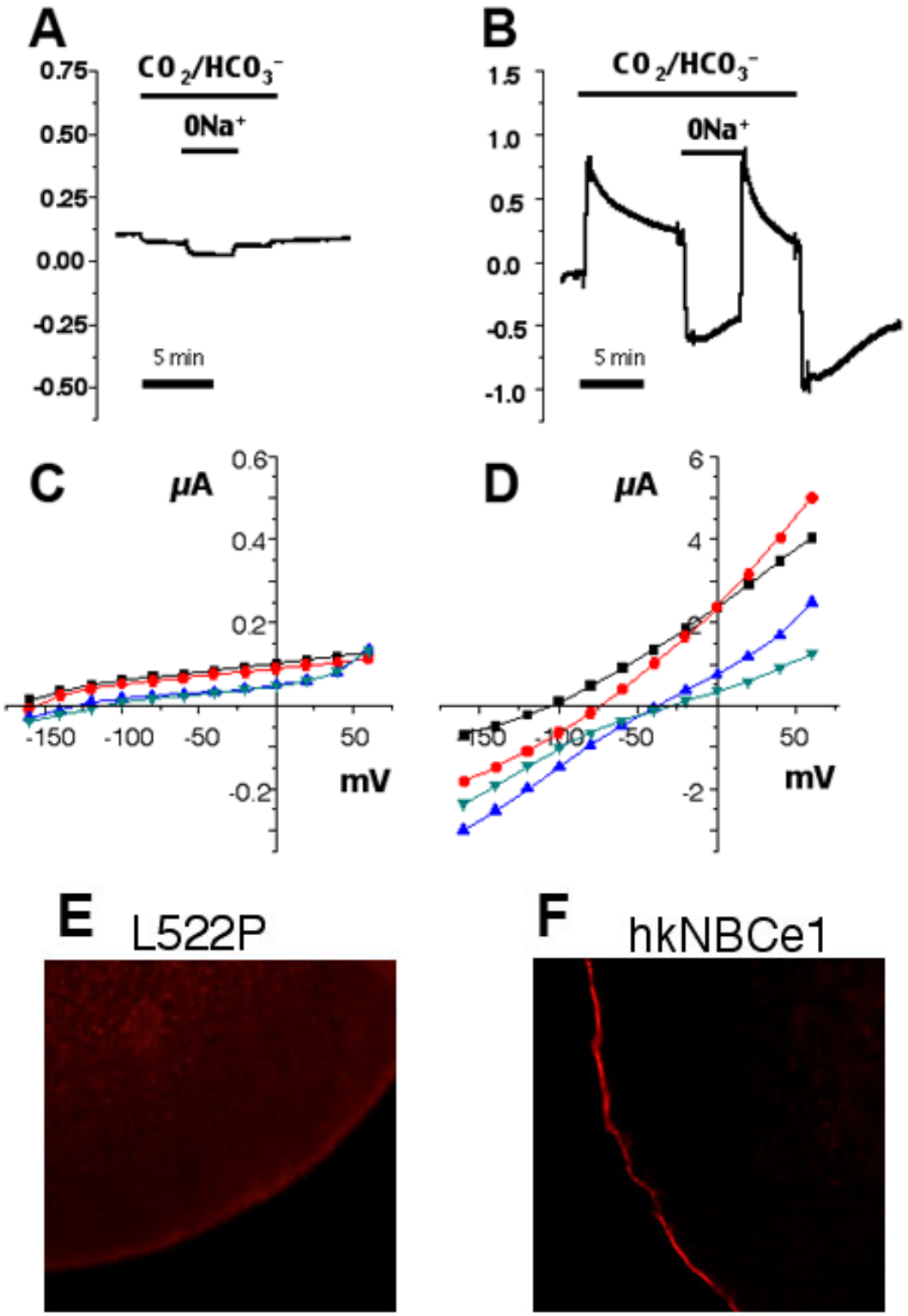


Figure 3. Functional analysis using oocytes. Two electrode voltage clamp experiments were performed on oocytes injected with L522P-hkNBCe1 cRNA (**A**,**C**,**E**) or wt-hkNBCe1 cRNA (**B**,**D**,**F**) as previously reported in the literature [7]. Oocytes were clamped at -60 mV while the bath was continuously perfused with the indicated salt solutions. HCO_3^- solutions were pH 7.5 at room temperature and 5% CO_2 so that [HCO_3^-] is 33 mM. Na^+ was replaced isotonically with choline. Only hkNBCe1 displays currents with HCO_3^- addition or Na^+ removal in HCO_3^- solution. **A**,**B**: Currents at -60 mV. **C**,**D**: The current-voltage (IV) relationships. For IV curves, raw currents were subtracted from the baseline current measured in non-HCO_3^- solution (square, peak HCO_3^- current; circles, steady-state HCO_3^- current; upright triangle, peak $0Na^+/HCO_3^-$ current; inverted triangles, steady-state $0Na^+/HCO_3^-$ current). **E**,**F**: The results of immunostaining with a kNBCe1 specific antibody (α333) as previously described [7]. Membrane staining is obvious for wt-hkNBCe1 (**F**) but not for L522P (**E**). Water controls were negative (not shown).

In addition, as compared to the DNA sequence in GenBank accession number NC_000004, the patient's DNA demonstrated several homozygous intronic *SLC4A4* sequence variants (IVS17+72T>C, IVS19-84T>C, IVS22+22C>T, IVS23-139G>A, IVS23-101A>G, IVS23-77G>A, IVS23-58G>A, IVS24-191A>C) that have been predicted to be nonpathogenic. However, the patient was found to be heterozygous for a single variant affecting a polyadenine repeat region located at the 5' end of intron 10 (alleles carrying 11 compared to 10 repeats of adenine).

Functional analysis using oocytes: The mutation was functionally characterized by expressing the wt-kNBCe1 and L522P-kNBCe1 in Xenopus oocytes. The site directed mutagenesis was used to reproduce the CTC to CCC transition and thereby create L522P in the hkNBCe1 expression plasmid. The wt- and L522P-hkNBCe1 cRNAs were injected into Xenopus oocytes that were used for voltage clamp experiments after five days of incubation (Figure 3). Wt-hkNBCe1 displayed current responses as previously reported [7], while L522P-hkNBCe1 failed to elicit any HCO_3^- or Na^+ dependent currents (Figure 3A,B). The current-voltage relationships also illustrated that wt-hkNBCe1 functioned as expected but it appeared not to be a HCO_3^- elicited current for L522P (Figure 3C,D), though there was a slight current reversal with Na^+ removal perhaps indicating a slight activity (<5% wt). Since L522 was predicted to be in the middle of a transmembrane span, it was likely that protein production and/or membrane trafficking would be greatly reduced by proline, often referred to as a helix breaker. Therefore, the wt-hkNBCe1, L522P-hkNBCe1 and water-injected oocytes were fixed, cryosectioned and stained with an NBCe1 antibody. Figure 3F shows that wt-hkNBCe1 is localized to the oocyte plasma membrane, while the distinct localization of L522P-hkNBCe1 is not apparent (Figure 3E). These experiments demonstrate that the L522P-protein is not effectively made and/or transported to the oocyte membrane and thus is unable to act as a transmembrane transporter.

DISCUSSION

We report a new *SLC4A4* mutation in a male patient with pRTA, short stature, enamel hypoplasia, and bilateral ocular disease (cataract, glaucoma, and band keratopathy). The pa-

Table 1. Molecular and major clinical features of *SLC4A4* mutations

Mutation	Sex	Ocular pathology	MR	ED	Affected NBCe1 variants	Effect on oocyte NBCe1 protein
Q29X	Female	Glc	+	-	kNBCe1	Loss of function due to protein truncation
R298S	Female	Glc, Bk, Cat	+	-	kNBCe1 pNBCe1	About 41% of wild-type activity
S427L	Female	Glc, Bk, Cat	-	+	kNBCe1 pNBCe1	About 10% of wild-type activity
T485S	Male	Glc(nd), Bk, Cat	nd	-	kNBCe1 pNBCe1	About 50% of wild-type activity in ECV304 cells; no activity in oocytes
R510H	Female	Glc, Bk, Cat	nd	-	kNBCe1 pNBCe1	About 57% of wild-type activity in ECV304 cells; 4% of wild-type activity in oocytes
L522P*	Male	Glc, Bk, Cat	-	+	kNBCe1 pNBCe1	Loss of function due to impaired translational processing and membrane trafficking
2311delA	Male	Glc, Bk, Cat	-	+	kNBCe1 pNBCe1	Loss of function due to protein truncation
A799V	Female	Glc, Bk, Cat	+	-	kNBCe1 pNBCe1	About 14% of wild-type activity
R881C	Female	Glc(nd), Bk, Cat	nd	-	kNBCe1 pNBCe1	About 39% of wild-type activity

A summary and comparison of molecular and major clinical features of different SLC4A4 mutations. The features presented affected at least 30% of patients. All patients had proximal renal tubular acidosis and short stature. The table presents additional systemic findings that affected at least 30% of patients, such as mental retardation (MR) and enamel defects (ED). The ocular findings included glaucoma (Glc), band keratopathy (Bk), and cataract (Cat). The asterisk indicates data that originated from this study. Some information from other studies was not clearly determined (nd).

tient also had a medical history of ataxia, migraine with transient hemiparesis attacks, and slight hypothyroidism.

Because the patient was adopted, it was impossible to obtain medical information and DNA samples from his biological parents. The presence of one heterozygous sequence variant (intron 10) in addition to several homozygous variants detected at the 3'-end of the gene (exon 14 through intron 25) suggests that this patient may be the product of a consanguineous mating. However, our data cannot exclude the rare possibilities of hemizygosity (caused by a deletion) or uniparental isodisomy that would have affected the region of *SLC4A4* distal to intron 10. Uniparental disomy (UPD) can result in various AR diseases and may also be associated with small supernumerary marker chromosomes (sSMC), similar to that reported in our patient's mosaic karyotype. sSMC are present in about 0.05% of the population, but the risk for an abnormal phenotype is only about 13% in prenatally ascertained de novo cases [11,12]. Irrespective of the underlying genetic transmission, the conclusion that L522P-kNBCe1 is a pathogenic variant (in either homozygous or hemizygous state) is unambiguously established by our in vitro functional studies. Previous reports of similar phenotypes associated with *SLC4A4* mutations also support the causation of our patient's clinical features by this novel mutation. Because none of the previously reported patients were screened for mutations at the genomic DNA level or were evaluated with karyotypic analysis, it is not clear whether they had any intronic *SLC4A4* variants or evidence of sSMC.

kNBCe1 and pNBCe1 are both expected to be affected by this mutation. Given that the amino acid change is located in the middle of transmembrane span 4 domain, the mutated protein is predicted not to properly fold for membrane insertion. Our functional analysis confirmed that the mutated protein is not efficiently transported to the membrane, resulting in a complete loss of function (<5% wt) due to impairment of translational processing and/or membrane trafficking. This provides a different mutation mechanism than that attributed to the majority of prior mutations (impaired cotransporter activity due to amino acid change or loss of function resulting from protein truncation) [5-8]. The closely located T485S and R510H mutations were also found to cause poor surface expression, though a patchy membrane labeling was still observed [9].

The kidney and eye are the dominant target organs of this clinical pathophysiology as evidenced by the consistent association of pRTA (insufficient renal bicarbonate absorption) and ocular pathology (inappropriate ocular fluid transport) such as bilateral glaucoma, band keratopathy, and cataracts (Table 1). Our patient also demonstrated some infrequent (enamel hypoplasia and mild hypothyroidism) and some distinctive (ataxia and severe migraine symptoms) clinical features.

The corneal endothelium transports fluids, Na^+, and HCO_3^- from the corneal stroma into the aqueous humor to maintain corneal transparency [1,4]. Corneal NBCe1 defects are expected to increase stromal HCO_3^- concentration, which would in turn facilitate calcium deposition and band keratopathy formation [1,4]. A similar mechanism may be essential for lens transparency and may explain cataract formation due to NBCe1 defects. However, little is known about the role of impaired NBCe1 function in the pathogenesis of glaucoma. Previous observations suggest that complete loss of kNBCe1 function alone (Q29X) is sufficient to cause glaucoma, but not band keratopathy or cataract [6]. Since no mutation and associated phenotype were reported to date for the unique pNBCe1 NH_2-terminal region, it is difficult to assess whether the presence of an intact kNBCe1 only or both of the intact pNBCe1 and kNBCe1 are necessary for the proper regulation of intraocular pressure. Future studies are warranted to clarify the roles of NBCe1 variants in ocular tissues.

The brain expression profile of NBCe1 suggests that it may be critical during the late stages of brain development [13]. It is difficult to make a genotype-phenotype correlation given that some mutations affecting both NBCe1 variants (S427L, L522P, 2311delA) were not associated with mental retardation, while the mutation affecting only the kNBCe1 (Q29X) caused mental retardation [6-8]. Our patient had ataxia and migraines with transient hemiparesis attacks. Episodes of paresthesia and headache were previously described in one NBCe1-defective patient with basal ganglia calcification [8], however the CT and MRI scans were normal in our patient.

In summary, we identified a novel homozygous *SLC4A4* mutation, L522P-hkNBCe1, leading to a complete loss of function resulting from an impaired membrane trafficking. In addition to the typical clinical presentation of known *SLC4A4* mutations, some distinct clinical features (ataxia and migraines with transient hemiparesis attacks) and the association of some distinct molecular findings (several homozygous intronic variants and mosaicism for sSMC) were also noted. Identification and characterization of novel mutations increase our understanding of the structural and functional aspects of the NBCe1 and the molecular basis of the multiple organ pathologies associated with its defects.

ACKNOWLEDGEMENTS

We are grateful to the patient who participated in this study. We thank the Genomic Core Laboratories of the Center for Human Genetics at the University of Pittsburgh for helping us with automated sequencing. We appreciate the assistance of Ms. Kira Lathrop in the preparation of the clinical figures. We thank Gerald Babcock for excellent technical assistance. This study was supported in part by NIH Core Grant EY08098, The Eye & Ear Foundation of Pittsburgh, Research to Prevent Blindness, NY, DK-56218 (MFR), and a postdoctoral fellowship from the American Heart Association Ohio Valley Affiliate (M-HC). None of the authors had any proprietary or commercial interests related to this work.

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The print version of this article was created on 10 Apr 2006. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.