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Do mutations of the Pendred syndrome gene, *SLC26A4*, confer resistance to asthma and hypertension?

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Abstract

Background and aims—Mutations of *SLC26A4* cause Pendred syndrome, an autosomal recessive disorder comprising goiter and deafness with enlarged vestibular aqueducts (EVA). Recent studies in mouse models implicate *Slc26a4* in the pathogenesis of asthma and hypertension. We hypothesize that asthma and hypertension are less prevalent among humans with *SLC26A4* mutations.

Methods—We reviewed medical histories and *SLC26A4* genotypes for 80 individuals with EVA and 130 of their unaffected family members enrolled in a study of EVA. We used Fisher's Exact test to compare the prevalence of asthma and hypertension among groups of subjects with zero, one, or two mutant alleles of *SLC26A4*.

Results—Although none of the 21 subjects with two mutant alleles of *SLC26A4* had asthma or hypertension, there were no statistically significant differences in the prevalence of asthma or hypertension among subjects with zero, one, or two mutant alleles.

Conclusion—There might be a protective effect of *SLC26A4* mutations for asthma and hypertension but our study is statistically underpowered to detect this effect. Study sizes of at least 1125 and 504 individuals will be needed for 80% power to detect an effect at $\alpha = 0.05$ for asthma and hypertension, respectively. Our hypothesis merits a larger study since it has implications for potential strategies to treat hearing loss by manipulating *SLC26A4* expression or function.

INTRODUCTION

Recessive mutations of the *SLC26A4* gene [OMIM 605646] on chromosome 7q31 cause Pendred syndrome [OMIM 274600],¹ an autosomal recessive disorder comprising goiter and deafness with enlarged vestibular aqueducts (EVA; OMIM 600791). *SLC26A4* encodes the pendrin protein, a transmembrane exchanger of I^- , Cl^- and HCO_3^- that is expressed in the inner ear,² thyroid,¹ kidney^{13–5} and lung.⁶

Recent studies in mouse models implicate *Slc26a4* in the pathogenesis of asthma⁷⁸ and hypertension.⁹ Pendrin is expressed in airway epithelial cells⁶ where it mediates mucus

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production,⁸ is induced by stimuli that provoke exacerbations of asthma,⁷ and can contribute to airway inflammation and hyper-reactivity.⁷ Pendrin is also expressed in the apical plasma membrane of renal intercalated cells^{3–5} where it is thought to contribute to blood pressure regulation via Cl[–] absorption⁹ and modulation of the epithelial sodium channel.¹⁰ Since loss of *Slc26a4* function is thought to inhibit the development of asthma and hypertension in mice, we hypothesized that these diseases would be less prevalent among humans with mutation(s) in *SLC26A4*.

METHODS

We reviewed medical histories and *SLC26A4* genotypes for 210 subjects in our IRB-approved study of hearing loss and EVA.¹¹¹² The cohort included 80 subjects with EVA and 130 unaffected family members (2nd degree or closer relatives) who were evaluated at the National Institutes of Health Clinical Center. The evaluations included oral-auditory or sign language interviews of each subject and/or their parent(s) by a physician (A.G. or S.P.). The interviews included queries for past or present conditions requiring medical attention, names and indications for all medications, allergies and sensitivities and their associated symptoms, and an organ-based review of systems that often, but not always, included specific queries about asthma, hypertension, or both. We (A.G. or S.P.) performed physical examinations, including chest auscultation, of all subjects and observed no signs of asthma. We measured blood pressure but did not incorporate this into our phenotype classification since subjects did not return for subsequent independent visits and confirmatory measurements. Asthma and hypertension were classified on the basis of self-report of current or previous diagnoses or medication(s) for either condition.

We previously reported the *SLC26A4* genotypes of the 80 subjects affected with EVA.¹¹¹² The genotype of an unaffected subject was determined by bidirectional sequence analysis of the *SLC26A4* exon(s) known to be mutated in that subject's affected family member. If the affected family member had no mutations, we assumed that the unaffected subject also had no mutations.

We used Fisher's Exact test to compare the prevalence of asthma and hypertension among groups of subjects with zero, one, or two mutant alleles of *SLC26A4*.

RESULTS

None of our 21 subjects with two mutant alleles of *SLC26A4* had hypertension or asthma (Table 1). However, the analysis is statistically underpowered and the association does not reach statistical significance in Fisher's Exact test ($P = .651$, asthma; $P = .134$, hypertension). The observed association is unlikely to reflect differences in ethnicity,¹¹¹² gender (Fisher's Exact test, $P = .728$) or age (one-way ANOVA, $P = .109$). Because hypertension is diagnosed more commonly in adulthood, we repeated the Fisher's Exact test for hypertension among subjects >17 years old. There remained no significant association with number of mutant alleles of *SLC26A4* ($P = .344$).

DISCUSSION

Rare independent mutations in the renal salt handling genes *SLC12A3*, *SLC12A1* and *KCNJ1* were recently shown to contribute to clinically significant blood pressure reduction and protection from development of hypertension in the Framingham Heart Study offspring cohort.¹³ Whereas *SLC12A3*, *SLC12A1* and *KCNJ1* underlie recessive diseases featuring large reductions in blood pressure, our hypothesis about *SLC26A4* mutations may represent a different, pleiotropic, example of balancing natural selection in which primary pathogenic

and protective effects manifest in different organ systems. This is consistent with the observed prevalence of founder mutations of *SLC26A4* among many populations.¹⁴

One potential limitation of our retrospective study design is reliance upon medical history interviews for phenotypic classification. However, previous studies have demonstrated high fidelity of parent¹⁵ or patient¹⁶ recall with the patient's medical record. Nevertheless, more accurate phenotypic classification should be possible with a prospective study design.

Only one mutant allele of *SLC26A4* can be identified in 1/3 of Caucasian EVA patients, and no mutations are detected in another 1/3 of patients.¹² Genotypic misclassification of patients with occult mutations of *SLC26A4* is therefore another potential source of error in our analysis.

Another limitation of our study is the insufficient numbers of subjects. Based on our data (Table 1), we estimated the sample size required to achieve 80% power to detect an association with a chi-square test at $\alpha = 0.05$.¹⁷ Samples of 1,125 and 504 individuals are necessary to detect potential associations of number of mutant alleles of *SLC26A4* with asthma and hypertension, respectively. Adequate statistical power might thus require a collaborative effort among different investigators and institutions, depending upon the recruitment paradigm. Potential confounding effects of co-morbid conditions should be minimized by matching age, gender, ethnicity and body mass index among different genotype groups. A larger, rigorous study is indeed warranted to test our hypothesis because potential therapeutic interventions for deafness that affect *SLC26A4* expression or function may have adverse effects upon cardiovascular or pulmonary function, and vice versa.

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Key points

- We hypothesize that mutations of *SLC26A4* may protect against the development of asthma and hypertension in humans.
- We did not detect a statistically significant difference in the prevalence of asthma or hypertension among subjects with *SLC26A4* mutations, but our analysis lacked adequate statistical power.
- A larger study is warranted to test our hypothesis because it has important implications for potential strategies to treat hearing loss by manipulating *SLC26A4* expression or function.

Table 1

Numbers of individuals with *SLC26A4* mutant alleles and asthma or hypertension.

Disease status	<u>Number of mutant alleles of <i>SLC26A4</i></u>		
	0	1	2
Asthma	11	2	0
No asthma	139	37	21
Hypertension	13	6	0
No hypertension	137	33	21