Autosomal recessive *SLC30A9* mutations identified with renal dysfunction & developmental delays

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Disclosure Slide

Financial Disclosure for:

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Director, Molecular Diagnostic Lab

I have nothing to disclose

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ASHG American Society of Human Genetics

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Abstract

Background: Mutations in *SLC30A9* were recently reported in consanguineous Bedouin kindred with autosomal recessive cerebro-renal syndrome characterized by early onset intellectual disability and tubulointerstitial nephropathy.

Methods: Whole-exome sequencing of a trio was used to identify the genetic etiology in the affected proband with renal dysfunction and severe developmental delays, progressive dystonia, and learning disabilities.

Results: In this report, we present a 5 year 11-month-old African American female proband who is non-verbal, hypotonic, has feeding difficulties, exhibits hand flapping, and is unable to walk. The child was diagnosed with chronic kidney disease (stage 3), with unknown etiology, and urinalysis contained no blood or protein. An ultrasound of her kidneys reported small kidneys with a relatively normal structure. Exome analysis revealed novel compound heterozygous loss-of-function mutations in *SLC30A9*.

Conclusions: This is the first report of a possible autosomal recessive disorder with two non-consanguineous parents, offering additional support for a link between *SLC30A9* mutations and cerebro-renal pathologies as well as insight into the role of SLC30A9 in human disease.

Introduction

SLC30A9 is located on 4p13 and encodes a highly conserved protein that belongs to the family of zinc transporters. SLC30A9 is highly expressed in the human brain, skeletal muscle and kidney. Subcellular localization studies suggested that it is expressed in the vesicular cytosolic compartment, possibly the endoplasmic reticulum. Recently, mutation in the *SLC30A9* gene has been reported in 6 affected individuals from highly consanguineous Bedouin kindred from Saudi Arabia with cerebro-renal syndrome using a combination of homozygosity mapping and whole-exome sequencing [1]. Here we report a case of bi-allelic mutations in *SLC30A9* in a patient with renal dysfunction & developmental delays.

Methods

Blood specimen was obtained for research-based WES and pre-test counseling was provided. Consent for research participation was obtained with an Institutional Review Board approved protocol. WES sequencing was performed as described previously [2].

Figure 1: (A) The proband (II-1) carried compound heterozygous frameshift mutations as confirmed by Sanger sequencing (B): c.40delA inherited from his father (I-2) and c.86_87dupCC from his mother (I-1).

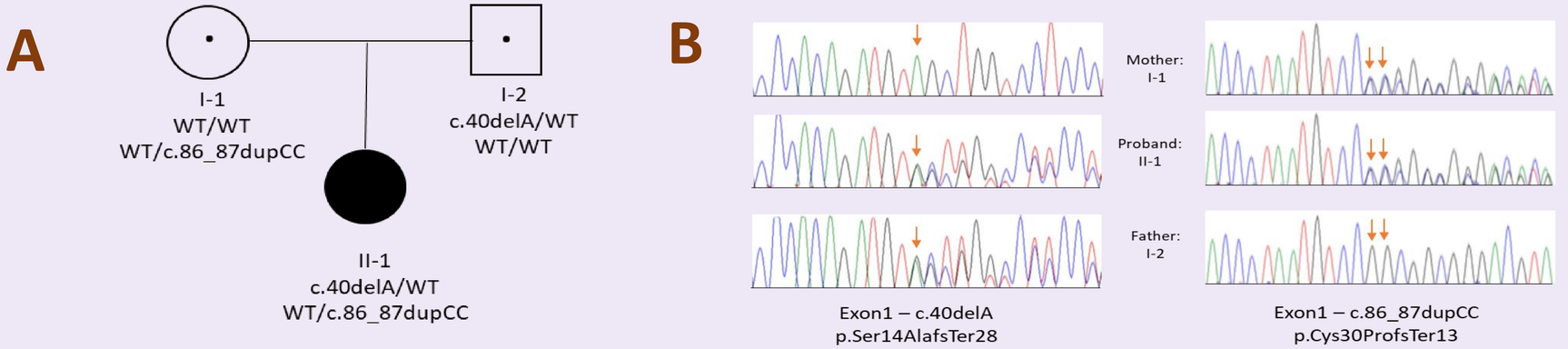

Figure 2: (A) Cross-species alignment showing the predicted truncated *SLC30A9* identified in this proband. Genomic/Exome findings shown in table (B). (C) Alignment of exome sequences to Hg19 using IGV.

B

Gene Transcript	Nomenclature cDNA Protein	Genomic position (hg19)	Zygosity	Classification	dbSNP/dbVar	Inheritance	Parent of origin
SLC30A9 NM_006345.3	c.40delA p.Ser14AlafsTer28	Chr4:41992707	HET	Likely pathogenic	rs767078182	AR	paternal
SLC30A9 NM_006345.3	c.86_87dupCC p.Cys30ProfsTer13	Chr4:41992753	HET	Likely pathogenic	rs752245649	AR	maternal

Results

A novel compound heterozygous mutations, c.40delA, p.Ser14AlafsTer28 and c.86_87dupCC, p.Cys30ProfsTer13 in *SLC30A9* gene has been detected in proband. Both frameshift mutations generate premature stop codon in exon 1 and produce SLC30A9 lacking highly conserved putative cation efflux domain.

Conclusions

- This is the first report of an African American child with bi-allelic loss of function mutations in *SLC30A9* characterized by renal dysfunction & developmental delays.
- It demonstrates the role of SLC30A9 in human disease providing a possible link between *SLC30A9* mutations and cerebro-renal syndrome.

References

1) Perez, Y. Brain, 2017; 140: 928-939
2) Lyon, G.J. Cold Spring Harb Mol Case Stud. 2019; 5:a00371

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