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Mutation of *KCNJ8* in a patient with Cantú syndrome with unique vascular abnormalities - support for the role of K(ATP) channels in this condition

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Abstract

KCNJ8 (NM_004982) encodes the pore forming subunit of one of the ATP-sensitive inwardly rectifying potassium (K_{ATP}) channels. *KCNJ8* sequence variations are traditionally associated with J-wave syndromes, involving ventricular fibrillation and sudden cardiac death. Recently, the K_{ATP} gene *ABCC9* (SUR2, NM_020297) has been associated with the multi-organ disorder Cantú syndrome or hypertrichotic osteochondrodysplasia (MIM 239850) (hypertrichosis, macrosomia, osteochondrodysplasia, and cardiomegaly). Here, we report on a patient with a *de novo* nonsynonymous *KCNJ8* SNV (p.V65M) and Cantú syndrome, who tested negative for mutations in *ABCC9*. The genotype and multi-organ abnormalities of this patient are reviewed. A careful screening of the K_{ATP} genes should be performed in all individuals diagnosed with Cantú syndrome and no mutation in *ABCC9*.

Clinical Description

The proband is a Caucasian male child of healthy unrelated parents with ancestry from Wales, Sicily, Germany and the Czech Republic (mother: 36 years, father: 42 years). He was an induced vaginal delivery at 37 3/7 weeks gestation due to large size for gestational age. His birth weight was 4.7kg (>95th percentile); length and head circumference are unknown.

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Supplementary Tables. Fully annotated, unfiltered, variant call files from single-sample genotyping are provided for the proband and each of his parents. Note that the reference and alternate depths reported here may differ slightly from the depths reported in the Variants Table. Homozygous reference genotypes are typically not reported by genotyping algorithms. To provide this information for calculation of frequencies in the Variant Table, those 3 loci were resequenced using GATK's multi-sample genotyper (UnifiedGenotyper). The genotypes fully agree with the initial calls and information for homozygous reference loci is available, but due to different read filtration criteria, the depths sometimes disagree by a small amount.

Developmental history includes mild developmental delay with cognitive development more significantly delayed than motor development (see Table 1). The patient has a good vocabulary at 6 years of age, but has difficulties with articulation. He is in an individualized educational program (IEP) and receives speech, occupational, and physical therapies. His dysmorphic features include plagiocephaly, midfacial hypoplasia, epicanthal folds and nystagmus, hypertrichosis as well as coarse facial features including bulbous nose with anteverted nostrils and prominent mouth, macroglossia, thick alveolar ridges and high arched palate. In addition, he had gynecomastia, a large hydrocele and thickened soles and palms with deep, fleshy creases on hands and feet (Figure 1A-E; Table 2).

The phenotype also included findings of hepatomegaly, gallstones, cholestatic jaundice, enlarged heart with dilated left heart and aorta, systemic hypertension, pulmonary hemorrhage, mild pulmonary hypertension, severe tracheomalacia, seizures (well controlled on medication) and diffuse cerebral and cerebellar parenchymal loss with white matter gliosis and thinning of corpus callosum (Figure 1F-K). He underwent gastrostomy and tracheostomy (s/p decannulation) and had oxygen saturation monitoring when asleep.

He had multiple unique vascular abnormalities including multiple major aorto-pulmonary and bronchial collaterals, dilated aortic root, hepatic and celiac arteries, dilated and tortuous intrahepatic arteries and veins suggestive of intrahepatic shunting, tortuous major cerebral arteries including internal carotids, anterior cerebral and middle cerebral arteries, circle of Willis and multiple venous defects in the brain including absent flow in inferior sagittal and straight sinuses, markedly diminutive internal cerebral veins and multiple tortuous venous collaterals of intracranial extracerebral vessels suggestive of past thrombotic event.

Cytogenetic evaluation and array-CGH testing were both normal, with no evidence for chromosomal aneuploidies, rearrangements, or internal deletions/duplications reported.

At last examination at the age of 6 years, his weight was 27.3 kg (95th percentile), height 120.2 cm (78th percentile) and head circumference 55.6 cm (95th percentile). He has had extensive evaluation by cardiology and so far has not had ECG abnormalities.

Methods

DNA and medical records of the proband and his family were collected by The Manton Center for Orphan Disease Research, Gene Discovery Core under informed consent governed by the Institutional Review Board of Boston Children's Hospital. Whole exome sequencing was performed by Axseq Technologies (Seoul, South Korea). All library preparation was performed by Axseq using the Illumina TruSeq Exome Enrichment kits (62 Mb) with 16 sample indexing for the Illumina HiSeq platform with no alterations to the protocol. Libraries were quantified and multiplexed into pools. Completed, indexed library pools were run on the Illumina HiSeq platform as paired-end 2 x 100 bp runs. FASTQ files were mapped against UCSC hg19 using BWA, and SNPs and Indels were detected by SAMTOOLS. The product was a comprehensive report listing variants of phenotypic significance. Further analysis was performed by the Boston Children's Hospital genomic analytic pipeline. Databases, NHLBI Exome Variant Server (EVS), 1000 Genomes (1000G), and the Complete Genomics Public Genome Data Repository [1] were checked on July 1, 2013.

NGS summary

WES Parameters*	Proband	Father	Mother
Captured target size	62 Mb	62 Mb	62 Mb
% target covered by 10+ reads	90.5%	89.1%	89.3%
Mean read depth of target region	77.1X	63.9X	72.4X
Total number of SNPs	46,049	46,063	45,521
Total number of INDELs	4,590	4,541	4,414
N rare variants	1,951	1,986	1,809
N compound heterozygous variants	29	N/A	N/A
N X linked	158	137	154
N <i>de novo</i> events	383	N/A	N/A

* Values are limited to variants mapping to the TruSeq target region. Rare variants and X-linked variants are defined as having allele frequencies <1% in ESP5000 (from NHLBI EVS), 1000G and CG52. Compound heterozygous variants are restricted to non-synonymous variants shared heterozygous with each parent and with allele frequencies of <1% in each reference database. *De novo* events are defined as all variants in the TruSeq target region which are seen in neither parent and are absent from dbSNP, EVS5000, 1000G and 52 unrelated control individuals

Variations of interest

All variants presented in this section have predicted pathogenicity by at least one prediction program and occur in genes that are hypothesized to be associated with the phenotype based on current knowledge of gene function, pathway, expression pattern, etc. All listed variants have been checked by Sanger sequencing in the trio. Other variants are available online (see Supplementary data). Secondary findings unrelated to the phenotype have not been reported.

Chromosome	12	3	3
Position	21926358	27763350	27763770
Gene Name	<i>KCNJ8</i>	<i>EOMES</i>	<i>EOMES</i>
Reference	C	G	G
Number of reads with reference PROBAND	25	29	2
Alternative PROBAND	T	A	C
Number of reads with alternative PROBAND	20	21	3
Number of reads with reference MOTHER	50	46	4
Alternative MOTHER	None	none	C
Number of reads with alternative MOTHER	None	none	2
Number of reads with reference FATHER	46	17	7
Alternative FATHER	None	A	none
Number of reads with alternative FATHER	None		none
Mutation type	Nonsynonymous SNV	Nonsynonymous SNV	Nonsynonymous SNV

Refseq ID	NM_004982	NM_005442	NM_005442
Mutation DNA (HGVS nomenclature _c)	c.193G>A	c.436C>T	c.16C>G
Mutation DNA (HGVS nomenclature _p)	p.V65M	p.L146F	p.Q6E
Prediction from SIFT, Polyphen2	SIFT 0.00, Polyphen2 0.998	SIFT 0.01, Polyphen2 0.16	SIFT 0.1, Polyphen2 0.929
Sanger Verification	YES	YES	YES

* SIFT and PolyPhen2 scores are derived from Liu et al. 2011 [2]. SIFT scores ≤ 0.05 are predicted “damaging” and >0.05 are predicted to be “tolerated”. Polyphen2 scores ≥ 0.2 and <0.85 are considered “possibly damaging” and ≥ 0.85 are predicted to be “probably damaging”.

Discussion

Here we present evidence for a *de novo* *KCNJ8* mutation, c.193G>A (p.V65M), as being causative for Cantú syndrome (MIM 239850). The *KCNJ8* gene encodes the Kir6.1 pore forming inwardly rectifying potassium channel. Kir6.1 channels complex at 4:4 stoichiometry with the sulfonylurea receptor SUR1 and SUR2 proteins to form ATP-sensitive potassium channels (K_{ATP}) [3-5]. K_{ATP} channels are broadly expressed and serve diverse physiological functions in different tissues, including control of hormone secretion, cardioprotection under ischemic conditions, control of vasodilation, neuroprotection from hypoxia, and more [5-7]. SUR1 is encoded by the *ABCC9* gene of the ATP-binding cassette superfamily and heterozygous *ABCC9* mutations have recently been reported in patients with Cantú syndrome [8-10]. Given the tight functional relationship between Kir6.1 and SUR2 in K_{ATP} channels, we find it reasonable to propose that mutations of either gene should be causative of Cantú syndrome.

Mutation analysis of *KCNJ8* gene in our proband revealed the presence of a novel *de novo* missense mutation, NM_004982: c.193G>A, in exon 1. This single nucleotide transition is predicted to have pathogenic consequences by both SIFT and PolyPhen2 by creating a methionine codon at amino acid position 65, resulting potentially in a new start codon or a disturbed topological domain. The residue is within the amino terminus of Kir6.1 that contains a single beta-strand. This beta-strand forms a beta-sheet with two beta-strands in the carboxy terminus. The amino and carboxy termini of four Kir6 subunits form the cytoplasmic domain of the channel. Interaction between amino and carboxy termini contributes to the stability of the whole cytoplasmic region. The modulation of the conformation of NH_2 and $COOH$ termini and their interaction clearly play pivotal roles in the regulation of Kir channel gating [6]. The valine residue itself, as well as the surrounding region, is highly conserved across mammals, amphibians, and teleost fishes (Figure 2).

In mice, loss of function (knock-out) mutations of *KCNJ8* have been associated with an immune deficiency phenotype and sudden death [11]; there is also a report of two loss of function mutations (p.E332del and p.V346I) found in two infants with sudden infant death syndrome [12]. Another mutation in *KCNJ8* (p.S422L) has been reported in association with J-wave phenomenon of the ECG. That mutation, located in the carboxy-terminal cytoplasmic domain, has now been reported in nine individuals with Brugada syndrome as well as in both atrial and ventricular fibrillation [10].

Our case shows a neurological phenotype and most of the major clinical features present in other individuals with Cantú syndrome reported in the literature (Table 2) [8]. Most notably, the proband has facial dysmorphism, hypertrichosis, macrosomia and cardiomegaly typical

of Cantú syndrome or high-dose minoxidil, which, as a potassium channel opener, replicates the effects of Cantú syndrome at elevated doses [13-15].

However, this patient had unique vascular abnormalities, including a dilated aortic root, hepatic and celiac arteries, dilated and tortuous intrahepatic arteries and veins, tortuous cerebral arteries and multiple venous defects in the brain that have not been reported in Cantú syndrome. In addition, the osteodysplastic findings often described in Cantú syndrome are not demonstrated in this patient, however a DEXA scan and full body x-rays have not been performed although broadening of the ribs is visible in later chest x-rays.

The patient also has compound heterozygous mutations in *EOMES*. We do not believe them to be causal to the multi-organ disorder in the patient. The patient's brain MRI does not greatly resemble what is reported in the literature for *EOMES* mutations, since the published family with four affected individuals shows bilateral polymicrogyria, agenesis of the corpus callosum and myelination delay, with large ventricles and extreme microcephaly [16]. None of those features are present in our patient. Instead, his significant brain MRI findings include tortuosity and ectasia of the major arteries and venous defects potentially leading to cerebral and cerebellar atrophy and thinning of corpus callosum. These findings were not described in the family members with *EOMES* mutations. Further, both the missense changes in *EOMES* (rs200789175 and rs200215171) are present in the NHLBI EVS, with the former found in 54/11962 alleles, which also makes it seem less likely to be pathogenic.

The unique vascular abnormalities in our proband have not been previously associated with *KCNJ8* mutations or in patients with Cantú syndrome, however, two cases of Cantú syndrome described by Scurr et al. [17] did exhibit various other vascular anomalies including tortuous retinal vessels in patient 5 and multiple tortuous pulmonary arteriovenous communications in both lungs of Patient 10. Patient 10 was later found to carry an *ABCC9* mutation [9]. Taken together with the present case, these observations support the suggestion that Cantú syndrome may be characterized by an underlying vascular pathology [17] that we postulate is a primary defect as KATP channels are expressed in vascular smooth muscle and control basal vascular tone [18].

In conclusion, based on our observations, we propose that the *KCNJ8* mutation p.V65M constitutes a new cause of Cantú syndrome, characterized by neonatal macrosomia, hypotonia, dysmorphic features, and intellectual disability and it may be responsible for the abnormal vascular state in our patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Clinical phenotype of the patient. Shown are photographs of the patient, (A-B) when an infant, (A) face and right arm, (B) his back, and (C-E) his recent pictures (C) his face, (D) palm and (E) sole. His (F-K) MRI imaging of the brain at 8 months of age is also shown, specifically, (F) axial T-2 weighted, (G) sagittal T-1 weighted, (H-I), MR angiography, and (J-K) MR venography. Note the hypertrichosis, short neck (A-B) and coarse facial features including bulbous nose, prominent mouth, thick lips and gingival hyperplasia with irregular teeth (C). Deep palmar and plantar creases with wrinkled skin and thickened pads on palms and soles are also seen (D-E). MRI findings include cerebral atrophy (F-G), thick calvarium (G), thin corpus callosum (G), tortuous circle of Willis (H) and internal carotids (I), multiple tortuous venous collaterals and no flow in the inferior sagittal sinus.

Figure 2.
KCNJ8 p.V65M mutation in the proband with Cantú syndrome. A) Sanger DNA sequencing of genomic PCR products confirms a *de novo* c.193G>A transition mutation in the proband (P), that is absent in the mother (M) and father (F) below. B) Schematic of a single Kir6.1 subunit oriented in the plasma membrane illustrating the cytoplasmic amino (N) and carboxy (C) terminal domains responsible for subunit association. The two transmembrane domains encoded by residues 70-94 and 155-176 are shown as cylinders with the selectivity filter (residues 140-145) in between. Location of the p.V65M mutation is indicated with a red arrow and asterisk. C) Pileup of Kir6.1 amino acid sequences illustrating high degree of evolutionary conservation of p.V65 through mammalian, avian, amphibian and telost fish orthologues (species and Genbank sequence IDs indicated at left). The proband's mutated sequence is shown at top.

Table 1

Age at selected developmental milestones

Milestone	Age in months
Lifted head	6
Roll over	6
Crawl	6
Walk	12
2 word sentences	48
Follow 2 step commands	48

Table 2

Comparison to literature on Cantú features (adapted from van Bon et al. (2012)[6])

	Patient has	% Cantu patients
Coarse face	Yes	100%
Epicanthal folds	Yes	100%
Abundant and/or curly eyelashes	Yes	80%
Broad and/or flat nasal bridge	Broad nasal rout; bulbous nose	90%
Small nose and/or anteverted nostrils	Anteverted nares	100%
Prominent mouth and/or thick lips	Prominent mouth	100%
Long philtrum	Yes	100%
High and/or narrow palate	High arched palate	60%
Macroglossy	Yes	60%
Anterior open bite	Yes	30%
Gingival hyperplasia	Yes	70%
Short neck	No- normal neck	50%
Cardiac Features		
Structural cardiac anomalies	Abnormal connection from aorta to pulmonary artery (caused pulmonary hemorrhage)	40%
Pulmonary hypertension	Yes	20%
Pericardial effusion	No	30%
Cardiomegaly	Yes	60%
Hypertrophic and/or dilated cardiomyopathy	Yes- left ventricular hypertrophy	40%
Radiological Findings		
Generalized osteopenia	N/A	10%
Thick calvarium	Yes	50%
Delayed bone age	N/A	30%
Enlarged sella turcica, vertical skull base	N/A	10%
Narrow shoulders	N/A	0%
Narrow thorax	“small thorax”	30%
Broad ribs	Yes	70%
Vertebral endplate irregularities	N/A	20%
Platyspondyly	N/A	40%
Ovoid vertebral bodies	N/A	30%
Hypoplastic ischium and pubic bones	N/A	0%
Narrow obturator foramen	N/A	20%
Erlenmeyer-flask-like long bones	N/A	50%
Bilateral coxa valga	N/A	20%
Metaphyseal flare with enlarged medullary canal	n/a	70%
Transverse metaphyseal bands	N/A	0%
Other Features		

	Patient has	% Cantu patients
Preaxial distal phalangeal hypoplasia	N/A	10%
Short, broad first toe	Yes	30%
Umbilical hernia	Yes	40%
Pyloric stenosis	N/A	10%
Immune deficiency	N/A	20%
Wrinkled and/or loose skin	Yes	30%
Deep palmar creases	Yes	30%
Finger pads	Thickened pads on palms and soles	30%
Hyperextensibility interphalangeal joints	Yes	50%
Pectus carinatum	N/A	20%
Genital anomalies	Large hydrocele	30%
Scoliosis	No	40%
Lymphedema	N/A	40%
Increased tendency for upper GI bleeding	N/A	0%
Renal anomalies	Yes	0%