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Exome report

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*.

1. 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 4.7 kg (>95th percentile); length and head circumference are unknown.

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 has gynecomastia, a large hydrocele and thickened soles and palms with deep, fleshy creases on hands and feet (Fig. 1A–E; Table 2).

The phenotype also includes 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 (Fig. 1F–K). He underwent gastrostomy and tracheostomy (s/p decannulation) and has oxygen saturation monitoring when asleep.

He has multiple unique vascular abnormalities including 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

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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

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.

2. 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 Axeq Technologies (Seoul, South Korea). All library preparation was performed by Axeq 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 × 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.

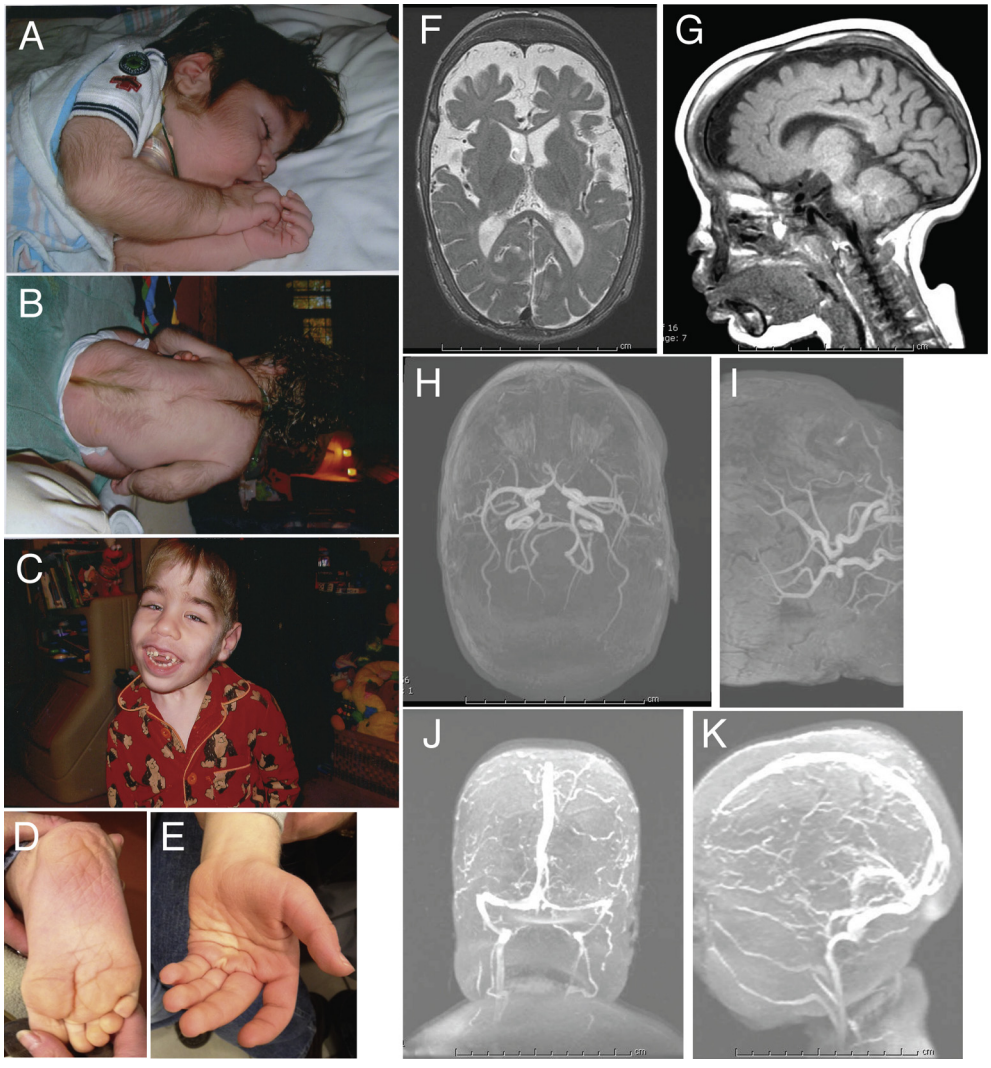

Fig. 1. Clinical phenotype of the patient. Shown are photographs of the patient, (A–B) when an infant, (A) face and right arm, (B) his back, and (C–E) his recent pictures (C) his face, (D) palm and (E) sole. His (F–K) MRI imaging of the brain at 8 months of age is also shown, specifically, (F) axial 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.