Cantu Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK246980/

SummaryClinical characteristics.Cantú syndrome is characterized by congenital hypertrichosis; distinctive coarse facial features (including broad nasal bridge, wide mouth with full lips and macroglossia); enlarged heart with enhanced systolic function or pericardial effusion and in many, a large patent ductus arteriosus (PDA) requiring repair; and skeletal abnormalities (thickening of the calvaria, broad ribs, scoliosis, and flaring of the metaphyses). Other cardiovascular abnormalities may include dilated aortic root and ascending aorta with rare aortic aneurysm, tortuous vascularity involving brain and retinal vasculature, and pulmonary arteriovenous communications. Generalized edema (which may be present at birth) spontaneously resolves; peripheral edema of the lower extremities (and sometimes arms and hands) may develop at adolescence. Developmental delays are common, but intellect is typically normal; behavioral problems can include attention-deficit/hyperactivity disorder, autism spectrum disorder, obsessive-compulsive disorder, anxiety, and depression.Diagnosis/testing.The diagnosis of Cantú syndrome is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in ABCC9 or KCNJ8 identified by molecular genetic testing. Some individuals with a clinical diagnosis of Cantú syndrome have not had a pathogenic variant identified in either gene, suggesting the existence of another as-yet unidentified causative gene.Management.Treatment of manifestations: Surgical or device closure of PDA in infancy or early childhood as needed. Pericardiocentesis and pericardial stripping as needed to treat pericardial effusion. Compression stockings for peripheral edema; shaving and (in teenagers and adults) use of depilatories or laser hair removal for hypertrichosis; bracing and/or surgery as needed for scoliosis; individualized management for migraine headaches and developmental delays if present.Surveillance: Yearly echocardiogram and electrocardiogram to monitor cardiac size and function, as well as for evidence of pericardial effusion. Clinical evaluation and cardiac biomarkers to monitor late development of high-output cardiac failure. Monitor for evidence of peripheral edema

annually starting in adolescence and for scoliosis with physical examination, followed by spine radiographs as needed. Monitor for a history of persistent headaches or other neurologic symptoms, which may require brain imaging for cerebral vasculature abnormality and evaluation by a neurologist.Evaluation of relatives at risk: If the pathogenic variant in an affected family member is known, relatives at risk who are suspected of having Cantú syndrome can be offered molecular genetic testing to clarify their genetic status. Family members who are affected should be evaluated and monitored for cardiac manifestations, scoliosis, and peripheral edema.Genetic counseling.Cantú syndrome is inherited in an autosomal dominant manner. Each child of an individual with Cantú syndrome has a 50% chance of inheriting the pathogenic variant and being affected. Prenatal and preimplantation genetic testing are possible if the pathogenic variant has been identified in an affected family member.

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DiagnosisNo formal diagnostic criteria for Cantú syndrome have been established.Suggestive FindingsCantú syndrome should be suspected in individuals with a combination of the

following:Congenital hypertrichosis: excess hair growth on scalp, forehead, face, back, and limbs (See Figure 1 and Figure 2.)Craniofacial dysmorphic features: coarse facial features, epicanthal folds, broad nasal bridge, anteverted nares, long philtrum, macroglossia, wide mouth, and full lips (See Figure 1.)Enlarged heart with enhanced systolic function or pericardial effusion (See Figure 3 and Figure 4.)Large patent ductus arteriosus (PDA) requiring repairCharacteristic skeletal abnormalities: thickening of the calvaria (see Figure 3), broad ribs, platyspondyly, ovoid vertebral bodies, scoliosis, narrow thorax and shoulders, pectus carinatum, hypoplastic ischium and pubic bones, Erlenmeyer-flask-like long bones with metaphyseal flaring (see Figure 3 and Figure 4), narrow obturator foramen, and coxa varaFigure 1. Woman age 40 years (A, D), girl age 16 years (B, E), and girl age 11 years (C, F) with Cantù syndrome A, B, C. Facial appearance showing hirsutism of the forehead with low frontal hairline and coarse featuresFigure 2. Girl age 11 years (A, B) and girl age 16 years (C) with Cantù syndrome A. Narrow thorax and pectus carinatum deformityFigure 3. Woman age 40 years with Cantù syndrome A. Chest x-ray showing marked cardiomegalyFigure 4. Girl age 16 years with Cantù syndrome A. Chest x-ray showing cardiomegalyEstablishing the DiagnosisThe diagnosis of Cantú syndrome is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in ABCC9 or KCNJ8 identified by molecular genetic testing (see Table 1).Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, exome array, genome sequencing) depending on the phenotype.Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Cantú syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).Option 1When the phenotypic findings suggest the diagnosis of Cantú syndrome, molecular genetic testing approaches can include use of a multigene panel.A multigene panel that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while

limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.Option 2When the diagnosis of Cantú syndrome is unclear because an individual has atypical phenotypic features, comprehensive

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Suggestive FindingsCantú syndrome should be suspected in individuals with a combination of the following:Congenital hypertrichosis: excess hair growth on scalp, forehead, face, back, and limbs (See Figure 1 and Figure 2.)Craniofacial dysmorphic features: coarse facial features, epicanthal folds, broad nasal bridge, anteverted nares, long philtrum, macroglossia, wide mouth, and full lips (See Figure 1.)Enlarged heart with enhanced systolic function or pericardial effusion (See Figure 3 and Figure 4.)Large patent ductus arteriosus (PDA) requiring repairCharacteristic skeletal abnormalities: thickening of the calvaria (see Figure 3), broad ribs, platyspondyly, ovoid vertebral bodies, scoliosis, narrow thorax and shoulders, pectus carinatum, hypoplastic ischium and pubic bones, Erlenmeyer-flask-like long bones with metaphyseal flaring (see Figure 3 and Figure 4), narrow obturator foramen, and coxa varaFigure 1. Woman age 40 years (A, D), girl age 16 years (B, E), and girl age 11 years (C, F) with Cantù syndrome A, B, C. Facial appearance showing

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Congenital hypertrichosis: excess hair growth on scalp, forehead, face, back, and limbs (See Figure 1 and Figure 2.)

Craniofacial dysmorphic features: coarse facial features, epicanthal folds, broad nasal bridge, anteverted nares, long philtrum, macroglossia, wide mouth, and full lips (See Figure 1.)

Enlarged heart with enhanced systolic function or pericardial effusion (See Figure 3 and Figure 4.)

Large patent ductus arteriosus (PDA) requiring repair

Characteristic skeletal abnormalities: thickening of the calvaria (see Figure 3), broad ribs, platyspondyly, ovoid vertebral bodies, scoliosis, narrow thorax and shoulders, pectus carinatum, hypoplastic ischium and pubic bones, Erlenmeyer-flask-like long bones with metaphyseal flaring (see Figure 3 and Figure 4), narrow obturator foramen, and coxa vara

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Establishing the DiagnosisThe diagnosis of Cantú syndrome is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in ABCC9 or KCNJ8 identified by molecular genetic testing (see Table 1).Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, exome array, genome sequencing) depending on the phenotype.Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Cantú syndrome has not been considered are more likely to

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Clinical CharacteristicsClinical DescriptionTo date, approximately 150 individuals with a clinical diagnosis of Cantú syndrome have been identified; a pathogenic variant in ABCC9 or KCNJ8 has been identified in 107 individuals [Grange et al 2019]. The following description of the phenotypic features associated with this condition is based on this report.Table 2. Cantú Syndrome: Frequency of Select FeaturesView in own windowFeature% of Personsw/FeatureCommentPolyhydramnios57%Prematurity (<37 weeks)58%Neonatal hypertrichosis99%Macrosomia38%Birth weight >4,000 gGeneralized edema at birth43%Macrocephaly48% of adultsstudiedSkeletal abnormalities19%Usually asymptomatic so detection dependent on imaging; not all persons had full skeletal surveyGastroesophageal reflux42%Cardiovascular findingsPDA58%Valvular defects18%Bicuspid aortic valve, mitral valve regurgitation, aortic valve stenosisCardiac enlargement64%Dilated aortic root32%Pericardial effusion25%Tortuous vascularity100% (10/10) on neurovascular imagingTrue number is unknown in entire population; neuroimaging at Washington University in St Louis showed that all tested persons have this finding in head & neck.Pulmonary hypertension24%Seen in infancy; typically resolves w/agePeripheral edema51%Usually develops in teenagers & young adultsDevelopmental delays63%Present in infants & young children related to hypotonia, but improve over time; most have normal intellect.Hypotonia65%Headaches40%Often migraine-type headache w/assoc symptomsSeizures24%Various typesBehavioral issues 1ADHD19%ASD16%OCD13%Anxiety13%Depression19%ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OCD = obsessive-compulsive disorder; PDA = patent ductus arteriosus1. Self-reported in many individualsPrenatal. Many pregnancies with a fetus with Cantú syndrome are complicated by

polyhydramnios, leading in some instances to repeated amniotic fluid reductions as well as preterm labor and delivery.Newborns. All newborns with Cantú syndrome have hypertrichosis with thick scalp hair and excessive hair growth on the forehead, face, back, and extremities. Some have thick and/or curly eyelashes. The hypertrichosis usually persists over time.Many newborns have macrosomia (large birth weight and birth length) and macrocephaly.Generalized edema at birth (observed on occasion) usually resolves spontaneously.Growth. Ultimate adult height is usually within the normal range; however, short stature has been seen in a few individuals.Macrocephaly, often present at birth, typically persists throughout life. Some individuals who do not have macrocephaly at birth have developed progressive macrocephaly in childhood.Skeletal abnormalities are usually asymptomatic and identified on radiographs. Characteristic skeletal abnormalities have included thickening of the calvaria, broad ribs, platyspondyly, ovoid vertebral bodies, scoliosis, narrow thorax and shoulders, pectus carinatum, hypoplastic ischium and pubic bones, Erlenmeyer-flask-like long bones with metaphyseal flaring, narrow obturator foramen, and coxa vara.Gastroesophageal reflux is reported by just under half of individuals. A smaller percentage report intestinal dysfunction characterized by chronic constipation or slow intestinal motility.Cardiac findings include the following:Cardiac enlargement, with increased ventricular mass but normal chamber wall thickness and enlarged chambers of the heart, often present at birth. Despite the enlarged cardiac chambers, cardiac function is typically normal and ventricular contractility is increased on imaging studies [Grange et al 2006, Grange et al 2019]. Some patients note exercise intolerance, but others have been able to participate in organized sports without difficulty.Patent ductus arteriosus (PDA) in 58% (and described as extremely large in some), often requiring surgical closure in infancy or early childhoodBicuspid aortic valve with and without stenosisPericardial effusion in about 25% of affected individuals. Small pericardial effusions may be asymptomatic; large fluid accumulations result in symptoms such as exercise intolerance and require intervention.Dilated aortic root and ascending aorta are present in about two thirds of individuals. The natural history is poorly understood. However, development of an aortic aneurysm is rare. Aortic aneurysm requiring surgical intervention was reported in one individual with an

ABCC9 pathogenic variant [Hiraki et al 2014].Tortuous vascularity including tortuous retinal vessels and multiple tortuous pulmonary arteriovenous communications have been reported [Scurr et al 2011, Grange et al 2019]. Abnormal tortuous vasculature in the brain is present in essentially all individuals who have been imaged specifically [Leon Guerrero et al 2016, Grange et al 2019].Pulmonary hypertension has been reported in infants and young children, although the natural history is not well understood [Cantú et al 1982, Robertson et al 1999, Lazalde et al 2000, Kobayashi et al 2010, Scurr et al 2011]. In one child, pulmonary hypertension secondary to partial pulmonary venous obstruction was associated with severe mitral valve regurgitation that spontaneously resolved by age eight years [Kobayashi et al 2010]. In another individual, progressive (and ultimately fatal) pulmonary hypertension was reported [Park et al 2014]. In the majority of cases, pulmonary hypertension is mild and improves with age [Grange et al 2019].Generalized edema, which may be present at birth, spontaneously resolves. Subsequently, edema involving the lower extremities and occasionally the arms and hands may develop over time, usually in adolescence or early adulthood. Puffiness of the eyelids is often observed. In one individual, lymphangiography demonstrated dilated lymphatic vessels in the legs with delayed lymphatic drainage [García-Cruz et al 2011]. In contrast, lymphatic studies were normal in another individual [Scurr et al 2011]. Therefore, it is unclear at this time whether the observed swelling is edema or lymphedema.Intellect. Although the majority of affected individuals have normal intellect, mild learning disabilities and/or developmental delays have been observed, including delay in acquisition of early motor milestones (most likely related to decreased muscle tone) and delay in speech development. Ultimately, most affected individuals attend regular schools, and some are described as having a high IQ [Scurr et al 2011, Grange et al 2019].Seizures are reported in about one quarter of individuals. Febrile, tonic-clonic, and absence seizure types have been observed as well as temporal lobe epilepsy.Headaches are reported by many individuals, especially migraine-type headaches with associated aura, photophobia, and phonophobia, and occasionally with transient hemiparesis.Behavioral problems have been reported in some individuals, including anxiety, mood swings, obsessive-compulsive disorder, and tics [Scurr et al 2011, Grange et al

2019]. Attention-deficit/hyperactivity disorder, autism spectrum disorder, and depression may also be present. Many individuals have self-reported these issues.Features of a connective tissue abnormality are observed in many individuals with Cantú syndrome, including wrinkled or loose skin especially at birth, deep palmar and plantar creases, and joint hyperextensibility. Some have decreased subcutaneous fat with the appearance of a muscular build in childhood.

Less frequent features

Umbilical herniaPyloric stenosisPoor intestinal motility [Grange et al 2019]PtosisCraniosynostosis involving the sagittal and coronal sutures in one individual [Hiraki et al 2014]Increased frequency of infections, raising the possibility of immune dysfunction [Scurr et al 2011, Grange et al 2019]Growth hormone deficiency in a few individuals [Cooper et al 2014, Grange et al 2019]Panhypopituitarism [Grange et al 2019, Theis et al 2019] and pituitary adenoma [Marques et al 2018] in a few individualsThe three individuals reported thus far with a pathogenic variant in KCNJ8 had typical clinical features seen in Cantú syndrome [Brownstein et al 2013, Cooper et al 2014, Chihara et al 2020]. The individual reported by Brownstein et al [2013] had the following additional abnormalities:Brain MRI: cerebral atrophy and thin corpus callosumMultiple tortuous venous collaterals and lack of flow in the inferior sagittal sinusSystemic vasculature: dilated hepatic and celiac arteries, dilated and tortuous intrahepatic arteries and veinsGenotype-Phenotype CorrelationsCurrent information about genotype-phenotype correlation in Cantú syndrome is limited.No significant genotype-phenotype correlations for ABCC9 or KCNJ8 have been identified.PenetrancePenetrance for Cantú syndrome in familial cases reported thus far appears to be complete although with variable expression [Grange et al 2019]. In a few families, somatic mosaicism for an ABCC9 variant has been identified in one of the parents, resulting in much milder phenotypic manifestations [Grange et al 2019; DK Grange, unpublished].NomenclatureCantú syndrome may also be referred to as hypertrichotic osteochondrodysplasia.PrevalenceThe prevalence of Cantú syndrome is unknown. To date, about 150 individuals have been reported with Cantú syndrome. Two previously reported conditions, acromegaloid facial appearance (AFA) syndrome and hypertrichosis with acromegaloid

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Ptosis

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Increased frequency of infections, raising the possibility of immune dysfunction [Scurr et al 2011, Grange et al 2019]

Growth hormone deficiency in a few individuals [Cooper et al 2014, Grange et al 2019]

Panhypopituitarism [Grange et al 2019, Theis et al 2019] and pituitary adenoma [Marques et al 2018] in a few individuals

Brain MRI: cerebral atrophy and thin corpus callosum

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Systemic vasculature: dilated hepatic and celiac arteries, dilated and tortuous intrahepatic arteries and veins

Genotype-Phenotype CorrelationsCurrent information about genotype-phenotype correlation in Cantú syndrome is limited.No significant genotype-phenotype correlations for ABCC9 or KCNJ8 have been identified.

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Genetically Related (Allelic) DisordersOther phenotypes associated with germline pathogenic variants in ABCC9 and KCNJ8 are summarized in Table 3.Table 3. Allelic DisordersView in own windowGeneDisorderReference

ABCC9

Atrial fibrillation reported in 1 person w/loss-of-function pathogenic variant NM_005691.2: c.4640C>T; p.Thr1547Ile

Olson et al [2007]

Isolated idiopathic dilated cardiomyopathy reported in 2 persons 1 (NM_005691.2:

c.4570_4572delTTAinsAAAT; p.Leu1524LysfsTer5 & c.4537G>A; p.Ala1513Thr)

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Early repolarization syndrome

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c.1265C>T (p.Ser422Leu) has been reported in assoc w/J-wave abnormalities on electrocardiogram; however, assoc remains controversial.Antzelevitch & Yan [2010], Veeramah et al [2014]1. This diagnosis is in question because the reported persons did not meet the WHO definition of dilated cardiomyopathy [Author, personal observation].

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Differential DiagnosisTable 4. Genes of Interest in the Differential Diagnosis of Cantú SyndromeView in own windowGene(s) / Genetic MechanismDisorderMOIFeatures of This DisorderOverlapping w/Cantú SyndromeDistinguishing from Cantú SyndromeAbnormal methylation at 11p15.5CDKN1C 1

Beckwith-Wiedemann syndrome

Variable 2Neonatal macrosomia; coarse facial features w/macroglossia; umbilical herniaNeonatal hypoglycemia, & hyperinsulinism; ear pits & creases; omphalocele; hemihypertrophy; abdominal tumors in childhood (Wilms tumor, hepatoblastoma)

ATP6V1B2

KCNH1

KCNN3

Zimmermann-Laband syndrome (OMIM PS135500)ADHypertrichosis; coarse facial features; full lips; macrosomia at birth; PDA; aortic root dilatation; scoliosis; hypotoniaGingival hyperplasia or fibromatosis; bulbous nose; distal phalangeal hypoplasia; hypo/aplastic nails; hepatosplenomegaly; seizures; severe ID/DD in some persons

AGPAT2

BSCL2

Berardinelli-Seip congenital lipodystrophy

ARMuscular build w/↓ subcutaneous fat in assoc w/cardiomegalyInsulin resistance; diabetes mellitus; hepatomegaly & hepatic steatosis; hypertrophy of skeletal muscles; hypertrophic cardiomyopathy different from cardiac involvement in Cantú syndromeANKRD1BAG3LMNAMYBPC3MYH6MYH7SCN5ATNNT2TTN(~30 genes) 3

Dilated cardiomyopathy

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Hypertrophic cardiomyopathy

AD

KCNK4

FHEIG syndrome (Bauer-Tartaglia syndrome) (OMIM 618381)ADHypertrichosis; coarse facial features; thick scalp hair; large mouth; hypotoniaOcular abnormalities (e.g. nystagmus & optic nerve

hypoplasia); severe gingival hyperplasia; brachydactyly; ID/DD; epilepsy; lack of cardiac manifestations

GALNS

MPS IVA (Morquio syndrome type A)ARCoarse facial features & hirsutism; some skeletal radiologic features (e.g., thickening of ribs)Flexion contractures; progressively worsening skeletal changes over time; progressive ID & neurologic deterioration in some persons; hepatomegaly & splenomegaly

GNPTAB

Mucolipidosis III α/β (See GNPTAB Disorders.)AR

GNPTG

Mucolipidosis III gamma

AR

IDS

MPS II (Hunter syndrome)XL

IDUA

Severe MPS IAR

MAN2B1

Alpha-mannosidosis

ARAD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; FHEIG syndrome = facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome; ID = intellectual disability; MOI = mode of inheritance; MPS = mucopolysaccharidosis; PDA = patent ductus arteriosus; XL = X-linked1. Beckwith-Wiedemann syndrome (BWS) is caused by an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS-causing pathogenic variant in CDKN1C.2. The risk to the sibs of a child with BWS depends on the genetic basis for BWS in the proband.3. Pathogenic variants in

ANKRD1, BAG3, LMNA, MYBPC3, MYH6, MYH7, SCN5A, TNNT2, and TTN account for about one third of nonsyndromic dilated cardiomyopathy (DCM); about 30 genes are known to be associated with nonsyndromic DCM (see Dilated Cardiomyopathy Overview).4. Pathogenic variants in MYBPC3, MYH7, TNNI3, and TNNT2 account for more than 90% of nonsyndromic hypertrophic cardiomyopathy (HCM); about 30 genes are known to be associated with nonsyndromic HCM (see Hypertrophic Cardiomyopathy Overview).Other ConditionsCongenital hypothyroidism. The macroglossia and hirsutism that can be seen in congenital hypothyroidism may overlap with features of Cantú syndrome.Acromegaly. The macrocephaly, coarse facial features, and tall stature in some adults with Cantú syndrome have been confused with acromegaly due to excess human growth hormone.Minoxidil treatment may lead to coarsening of facial features and hirsutism that has been called "pseudoacromegaly" [Ohko et al 2020]. Minoxidil has long been associated with hair growth and is used topically to treat scalp hair loss. When taken orally, it may cause generalized hirsutism, progressive coarsening of the facial features, and pericardial effusions, all of which can resemble the clinical features of Cantú syndrome.Diazoxide treatment for hyperinsulinism may lead to hypertrichosis especially on the forehead, back, arms and legs, edema, and rarely pericardial effusion or pulmonary hypertension, which can resemble clinical features of Cantú syndrome [Herrera et al 2018].Note: Both minoxidil and diazoxide can activate the same ATP-sensitive potassium (KATP) channels that are overactive in Cantú syndrome due to pathogenic variants in ABCC9 or KCNJ8.

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Mucolipidosis III α/β (See GNPTAB Disorders.)AR

GNPTG

Mucolipidosis III gamma

AR

IDS

MPS II (Hunter syndrome)XL

IDUA

Severe MPS IAR

MAN2B1

Alpha-mannosidosis

ARAD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; FHEIG syndrome = facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome; ID = intellectual disability; MOI = mode of inheritance; MPS = mucopolysaccharidosis; PDA = patent ductus arteriosus; XL = X-linked1. Beckwith-Wiedemann syndrome (BWS) is caused by an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS-causing pathogenic variant in CDKN1C.2. The risk to the sibs of

a child with BWS depends on the genetic basis for BWS in the proband.3. Pathogenic variants in ANKRD1, BAG3, LMNA, MYBPC3, MYH6, MYH7, SCN5A, TNNT2, and TTN account for about one third of nonsyndromic dilated cardiomyopathy (DCM); about 30 genes are known to be associated with nonsyndromic DCM (see Dilated Cardiomyopathy Overview).4. Pathogenic variants in MYBPC3, MYH7, TNNI3, and TNNT2 account for more than 90% of nonsyndromic hypertrophic cardiomyopathy (HCM); about 30 genes are known to be associated with nonsyndromic HCM (see Hypertrophic Cardiomyopathy Overview).

Genes of Interest in the Differential Diagnosis of Cantú Syndrome

Gene(s) / Genetic MechanismDisorderMOIFeatures of This DisorderOverlapping w/Cantú SyndromeDistinguishing from Cantú SyndromeAbnormal methylation at 11p15.5CDKN1C 1
Beckwith-Wiedemann syndrome
Variable 2Neonatal macrosomia; coarse facial features w/macroglossia; umbilical herniaNeonatal hypoglycemia, & hyperinsulinism; ear pits & creases; omphalocele; hemihypertrophy; abdominal tumors in childhood (Wilms tumor, hepatoblastoma)
ATP6V1B2

KCNH1

KCNN3
Zimmermann-Laband syndrome (OMIM PS135500)ADHypertrichosis; coarse facial features; full lips; macrosomia at birth; PDA; aortic root dilatation; scoliosis; hypotoniaGingival hyperplasia or fibromatosis; bulbous nose; distal phalangeal hypoplasia; hypo/aplastic nails; hepatosplenomegaly; seizures; severe ID/DD in some persons
AGPAT2

BSCL2

Berardinelli-Seip congenital lipodystrophy

ARMuscular build w/↓ subcutaneous fat in assoc w/cardiomegalyInsulin resistance; diabetes mellitus; hepatomegaly & hepatic steatosis; hypertrophy of skeletal muscles; hypertrophic cardiomyopathy different from cardiac involvement in Cantú syndromeANKRD1BAG3LMNAMYBPC3MYH6MYH7SCN5ATNNT2TTN(~30 genes) 3

Dilated cardiomyopathy

ADCardiomegalyAbsence of noncardiac findings(Note: Persons w/Cantú syndrome have normal ventricular wall thickness & normal or enhanced myocardial function [despite enlargement of cardiac chambers] & high cardiac output.)MYBPC3MYH7TNNI3TNNT2(~30 genes) 4

Hypertrophic cardiomyopathy

AD

KCNK4

FHEIG syndrome (Bauer-Tartaglia syndrome) (OMIM 618381)ADHypertrichosis; coarse facial features; thick scalp hair; large mouth; hypotoniaOcular abnormalities (e.g. nystagmus & optic nerve hypoplasia); severe gingival hyperplasia; brachydactyly; ID/DD; epilepsy; lack of cardiac manifestations

GALNS

MPS IVA (Morquio syndrome type A)ARCoarse facial features & hirsutism; some skeletal radiologic features (e.g., thickening of ribs)Flexion contractures; progressively worsening skeletal changes over time; progressive ID & neurologic deterioration in some persons; hepatomegaly & splenomegaly

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AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; FHEIG syndrome

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Beckwith-Wiedemann syndrome (BWS) is caused by an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS-causing pathogenic variant in CDKN1C.

The risk to the sibs of a child with BWS depends on the genetic basis for BWS in the proband.

Pathogenic variants in ANKRD1, BAG3, LMNA, MYBPC3, MYH6, MYH7, SCN5A, TNNT2, and TTN account for about one third of nonsyndromic dilated cardiomyopathy (DCM); about 30 genes are known to be associated with nonsyndromic DCM (see Dilated Cardiomyopathy Overview).

Pathogenic variants in MYBPC3, MYH7, TNNI3, and TNNT2 account for more than 90% of nonsyndromic hypertrophic cardiomyopathy (HCM); about 30 genes are known to be associated with nonsyndromic HCM (see Hypertrophic Cardiomyopathy Overview).

Other ConditionsCongenital hypothyroidism. The macroglossia and hirsutism that can be seen in congenital hypothyroidism may overlap with features of Cantú syndrome.Acromegaly. The macrocephaly, coarse facial features, and tall stature in some adults with Cantú syndrome have been confused with acromegaly due to excess human growth hormone.Minoxidil treatment may lead to coarsening of facial features and hirsutism that has been called "pseudoacromegaly" [Ohko et al 2020]. Minoxidil has long been associated with hair growth and is used topically to treat scalp hair loss. When taken orally, it may cause generalized hirsutism, progressive coarsening of the facial features, and pericardial effusions, all of which can resemble the clinical features of Cantú syndrome.Diazoxide treatment for hyperinsulinism may lead to hypertrichosis especially on the forehead, back, arms and legs, edema, and rarely pericardial effusion or pulmonary hypertension, which can resemble clinical features of Cantú syndrome [Herrera et al 2018].Note: Both minoxidil and diazoxide can activate the same ATP-sensitive potassium (KATP) channels that are overactive in Cantú syndrome due to pathogenic variants in ABCC9 or KCNJ8.

ManagementEvaluations Following Initial DiagnosisTo establish the extent of disease and needs in an individual diagnosed with Cantú syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Cantú SyndromeView in own windowSystem/ConcernEvaluationComment

Cardiac

Cardiology assessment to incl echocardiogram & electrocardiogram

Brain imaging

Brain MRI w/MRA & MRVShould be considered for all persons, but esp if history of headaches, migraine headaches, or hemiparesis

Skeletal

Radiographic skeletal survey to assess for bone abnormalitiesEval for scoliosis

Development

Developmental eval for infants & young childrenNeuropsychological eval for older personsEspecially for those w/concern for ASD, ADHD, OCD, or depression

Genetic

counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of Cantú syndrome to facilitate medical & personal decision making

Family support/

resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; MOI = mode of inheritance; MRA = magnetic resonance angiogram; MRV = magnetic resonance venography; OCD = obsessive-compulsive disorder1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurseTreatment of ManifestationsTable 6. Treatment of Manifestations in Individuals with Cantú SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Cardiac issues

PDA, if present, often requires surgical or device closure in infancy or early childhood.Pericardial

effusion, if present, sometimes requires pericardiocentesis.Pericardial stripping may be required to prevent recurrent & hemodynamically significant pericardial effusion.

Peripheral edema

Compression stockings & other standard mgmt

Hypertrichosis

Referral to dermatologist for treatment optionsPossible treatments: shaving & (in teenagers & adults) use of depilatories or laser hair removal

Scoliosis

Bracing or surgical correction

Migraines or other

types of headaches

Referral to neurologist for consideration of medication

Developmental delay

See Developmental Delay Management Issues.PDA = patent ductus arteriosusDevelopmental Delay Management IssuesThe following information represents typical management recommendations for individuals with developmental delay in the United States; standard recommendations may vary from country to country.Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition.All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational

agencies (US) and to support parents in maximizing quality of life.Motor DelayGross motor delay. Physical therapy may be recommended if there are gross motor delays in infancy or early childhood due to hypotonia.Fine motor delay. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.Oral motor dysfunction should be assessed in infants and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) may be needed to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.Social/Behavioral ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.SurveillanceTable 7. Recommended Surveillance for Individuals with Cantú SyndromeView in own windowSystem/ConcernEvaluationFrequency

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Headaches/

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Eval by neurologistPer neurologist

Scoliosis

Spine radiographsOrthopedic eval if scoliosis is present

If concern based on physical examBNP = brain natriuretic peptide; EKG = electrocardiogram; MRA = magnetic resonance angiogram; MRV = magnetic resonance venographyAgents/Circumstances to AvoidAvoid the following:MinoxidilDiazoxideAngiotensin-converting enzyme inhibitorsEvaluation of Relatives at RiskIt is appropriate to clarify the genetic/clinical status of older and younger relatives of an affected individual in order to identify as early as possible those who should be evaluated and monitored for cardiac manifestations of Cantú syndrome, as well as peripheral edema and scoliosis (see Evaluations Following Initial Diagnosis and Surveillance).Evaluations can include:Molecular genetic testing if the causative pathogenic variant in the family is known;Complete physical examination to assess for the characteristic clinical features, as well as an echocardiogram, electrocardiogram, and skeletal survey, should be performed if the pathogenic variant in the family is not known. Additional studies such as brain MRI with magnetic resonance angiogram and magnetic resonance venography may be indicated.See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Pregnancy ManagementWomen affected by Cantú syndrome should be referred to a maternal-fetal medicine specialist for evaluation and

management.Therapies Under InvestigationSearch ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Evaluations Following Initial DiagnosisTo establish the extent of disease and needs in an individual diagnosed with Cantú syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Cantú SyndromeView in own windowSystem/ConcernEvaluationComment

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Skeletal

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Development

Developmental eval for infants & young childrenNeuropsychological eval for older personsEspecially for those w/concern for ASD, ADHD, OCD, or depression

Genetic

counseling

By genetics professionals 1To inform affected persons & their families re nature, MOI, & implications of Cantú syndrome to facilitate medical & personal decision making

Family support/

resources

Assess need for:

Community or online resources such as Parent to Parent;Social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; MOI = mode of inheritance; MRA = magnetic resonance angiogram; MRV = magnetic resonance venography; OCD = obsessive-compulsive disorder1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Cantú

SyndromeView in own windowSystem/ConcernEvaluationComment

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Skeletal

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Recommended Evaluations Following Initial Diagnosis in Individuals with Cantú Syndrome

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Treatment of ManifestationsTable 6. Treatment of Manifestations in Individuals with Cantú SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Cardiac issues

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Peripheral edema

Compression stockings & other standard mgmt

Hypertrichosis

Referral to dermatologist for treatment optionsPossible treatments: shaving & (in teenagers & adults) use of depilatories or laser hair removal

Scoliosis

Bracing or surgical correction

Migraines or other

types of headaches

Referral to neurologist for consideration of medication

Developmental delay

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SurveillanceTable 7. Recommended Surveillance for Individuals with Cantú SyndromeView in own windowSystem/ConcernEvaluationFrequency

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Per cardiologist or annually

Peripheral

edema

Monitor w/history & examAnnually starting in adolescence

Cerebral

vasculature

abnormality

Brain MRI w/MRA & MRVIf persistent headaches or other neurologic symptoms develop

Headaches/

Migraines

Eval by neurologistPer neurologist

Scoliosis

Spine radiographsOrthopedic eval if scoliosis is present

If concern based on physical examBNP = brain natriuretic peptide; EKG = electrocardiogram; MRA = magnetic resonance angiogram; MRV = magnetic resonance venography

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Agents/Circumstances to AvoidAvoid the following:MinoxidilDiazoxideAngiotensin-converting enzyme inhibitors

Minoxidil

Diazoxide

Angiotensin-converting enzyme inhibitors

Evaluation of Relatives at RiskIt is appropriate to clarify the genetic/clinical status of older and

younger relatives of an affected individual in order to identify as early as possible those who should be evaluated and monitored for cardiac manifestations of Cantú syndrome, as well as peripheral edema and scoliosis (see Evaluations Following Initial Diagnosis and Surveillance).Evaluations can include:Molecular genetic testing if the causative pathogenic variant in the family is known;Complete physical examination to assess for the characteristic clinical features, as well as an echocardiogram, electrocardiogram, and skeletal survey, should be performed if the pathogenic variant in the family is not known. Additional studies such as brain MRI with magnetic resonance angiogram and magnetic resonance venography may be indicated.See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

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Pregnancy ManagementWomen affected by Cantú syndrome should be referred to a maternal-fetal medicine specialist for evaluation and management.

Therapies Under InvestigationSearch ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them

make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.Mode of InheritanceCantú syndrome is inherited in an autosomal dominant manner.Risk to Family Members

Parents of a proband

In one study, 22% of individuals diagnosed with Cantú syndrome had an affected parent [Grange et al 2019].Approximately 75% to 80% of individuals diagnosed with Cantú syndrome have the disorder as the result of a de novo pathogenic variant.If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.If the causative ABCC9 or KCNJ8 pathogenic variant found in the proband is not identified in either parent, the following possibilities should be considered:The proband has a de novo pathogenic variant. Note: A pathogenic variant is reported as "de novo" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed de novo" [Richards et al 2015].The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Parental germline (or somatic and germline) mosaicism has been reported [Grange et al 2019]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.* A parent with somatic and germline mosaicism for an ABCC9 or KCNJ8 pathogenic variant may be mildly/minimally affected.The family history of some individuals diagnosed with Cantú syndrome may appear to be negative because of failure to recognize the disorder in family members with a milder phenotype. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.Sibs of a proband. The risk to the

sibs of the proband depends on the clinical/genetic status of the proband's parents.If a parent of the proband is affected and/or has the ABCC9 or KCNJ8 pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because Cantú syndrome is associated with intrafamilial clinical variability, the phenotype, age of onset, and severity in sibs who inherit a pathogenic variant are not predictable [Grange et al 2019].If the proband has a known Cantú syndrome-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Grange et al 2019].If the parents are clinically unaffected but their genetic status is unknown, risk to sibs of a proband is presumed to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.Offspring of a proband. Each child of an individual with Cantú syndrome has a 50% chance of inheriting the pathogenic variant; the phenotype, age of onset, and severity in offspring who inherit a causative pathogenic variant are not predictable.Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a causative pathogenic variant, his or her family members may be at risk.Related Genetic Counseling IssuesSee Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).Prenatal Testing and Preimplantation Genetic TestingIf the Cantú syndrome-causing pathogenic variant has been

identified in an affected family member, prenatal and preimplantation genetic testing are possible. The phenotype, age of onset, and severity are not predictable based on results of prenatal molecular genetic testing.If the Cantú syndrome-causing pathogenic variant has not been identified in an affected family member, evaluation of a pregnancy at increased risk is recommended using ultrasound to look for fetal macrosomia and polyhydramnios and a fetal echocardiogram to evaluate for cardiovascular abnormalities.In a fetus not known to be at increased risk for Cantú syndrome based on family history, the combination of fetal macrosomia and polyhydramnios should lead to consideration of Cantú syndrome. (Note: The etiology of polyhydramnios is diverse.)Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

National Library of Medicine Genetics Home Reference

Cantú syndrome

Cantu Syndrome Interest Group and Registry

Phone: 314-454-6093Email: cantu-group@wustl.edu

cantu.wustl.edu/registry

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Molecular GeneticsInformation in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.Table A.Cantú syndrome: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

ABCC9

12p12.1

ATP-binding cassette sub-family C member 9

ABCC9 database

ABCC9

ABCC9

KCNJ8

12p12.1

ATP-sensitive inward rectifier potassium channel 8

KCNJ8

KCNJ8

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Data are compiled from the following standard references: gene from

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For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.Table B.OMIM Entries for Cantú syndrome (View All in OMIM) View in own window

239850CANTU SYNDROME

600935POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 8; KCNJ8

601439ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9; ABCC9Molecular PathogenesisABCC9 and KCNJ8 encode the regulatory (SUR2) and pore-forming (Kir6.1) subunits of ATP-sensitive potassium (KATP) channels, respectively. KATP channels are prominent in cardiac, skeletal, and smooth muscle, as well as endothelial and other tissues. KATP channels are inhibited by nonhydrolytic binding of ATP, whereas MgADP has the opposite effect, activating channels through interaction with SUR subunits. Physiologic activity is thus effectively dependent on the [ADP]:[ATP] ratio. KATP activation results in membrane hyperpolarization and decrease in voltage-dependent Ca2+ entry, leading to inhibition of muscle contraction. All identified Cantú syndrome pathogenic variants result in increased SUR2/Kir6.2-dependent KATP channel activity. Primary reduction of smooth muscle activity is a major consequence, underlying at least the cardiovascular features.Mechanism of disease causation. Cantú syndrome is caused by gain-of-function variants in either ABCC9 or KCNJ8.Table 8. Notable ABCC9 Pathogenic VariantsView in own windowReference SequencesDNA Nucleotide ChangePredicted Protein ChangeComment [Reference]

NM_005691.4

NP_005682.2

c.3461G>Ap.Arg1154GlnRecurrent variants [Grange et al 2019]c.3460C>Tp.Arg1154Trpc.3346C>Tp.Arg1116Cysc.3347G>Ap.Arg1116HisVariants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.GeneReviews follows the standard naming conventions of the Human

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Chapter NotesAuthor Notes

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Dr Nichols's research is focused on the biology of ion channels, with emphasis on the molecular basis of potassium channel activity and the role of potassium channels in physiology and disease. Using various molecular biological and biophysical approaches, his laboratory is developing detailed understanding of the structural basis of channel activity, and animal models to understand the role of potassium channels in disease processes including diabetes, cardiovascular pathology and arrhythmias, and epilepsy.

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