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Cantú Syndrome

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Summary

Clinical 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

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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.

Diagnosis

No formal diagnostic criteria for Cantú syndrome have been established.

Suggestive Findings

Cantú 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 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

Establishing the Diagnosis

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 (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

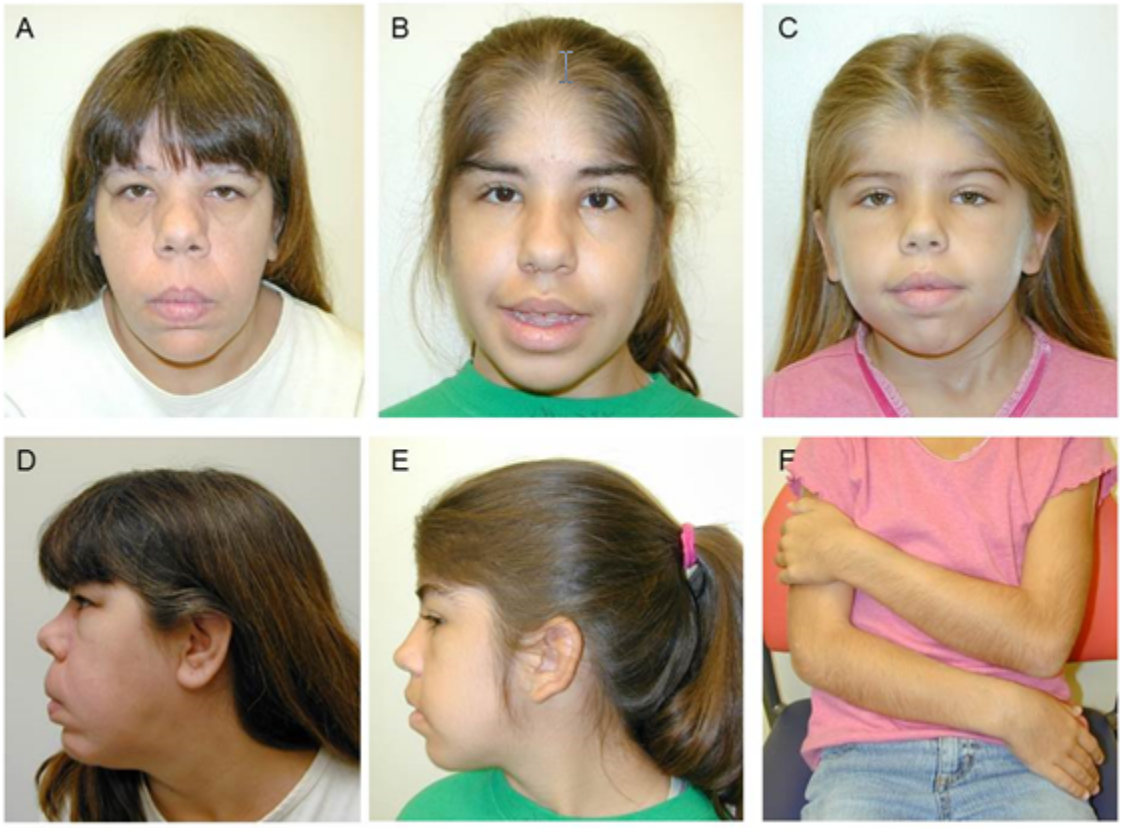

Figure 1. Woman age 40 years (A, D), girl age 16 years (B, E), and girl age 11 years (C, F) with Cantù syndrome

A, B, C. Facial appearance showing hirsutism of the forehead with low frontal hairline and coarse features

D, E. Lateral views showing excess hair on the cheeks

F. Hirsutism of the arms

From Grange et al [2006]; used with permission from *Am J Med Genet*

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 1

When 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.

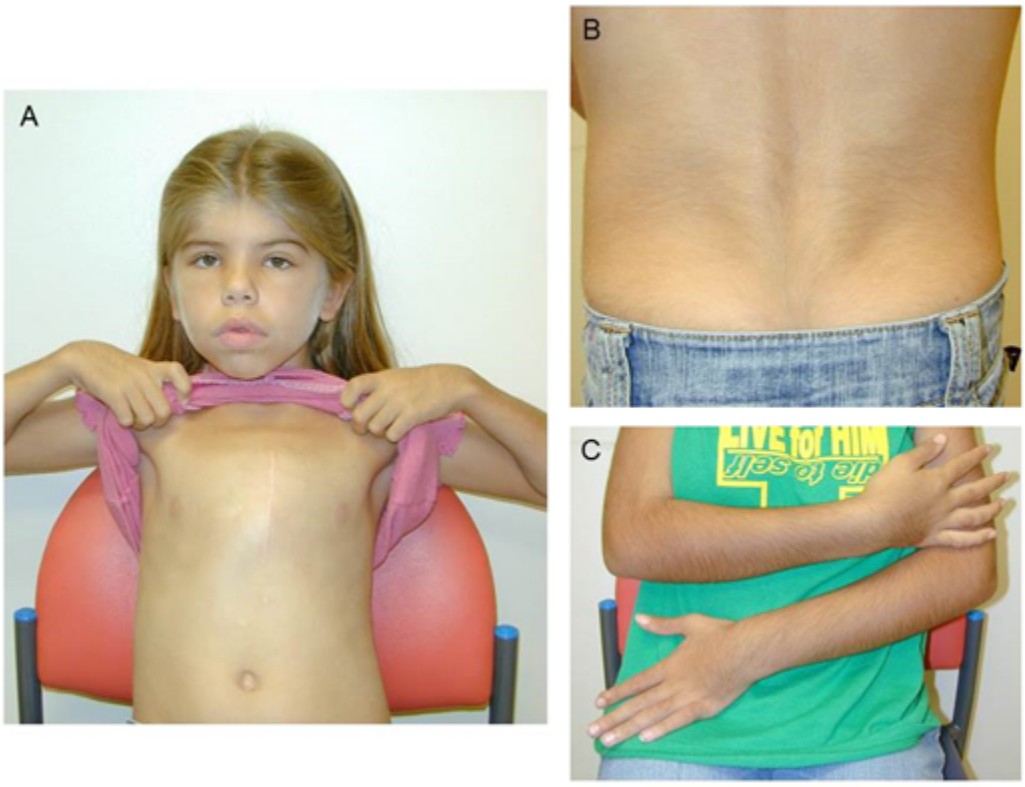

Figure 2. Girl age 11 years (A, B) and girl age 16 years (C) with Cantù syndrome

A. Narrow thorax and pectus carinatum deformity

B, C. Hirsutism of the lower back (B) and forearms(C)

From Grange et al [2006]; used with permission from *Am J Med Genet*

Option 2

When the diagnosis of Cantú syndrome is unclear because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: All pathogenic variants reported to date are gain-of-function variants in *ABCC9 and KCNJ8*; thus, testing for deletion (haploinsufficiency) or duplication (overexpression) is not indicated.

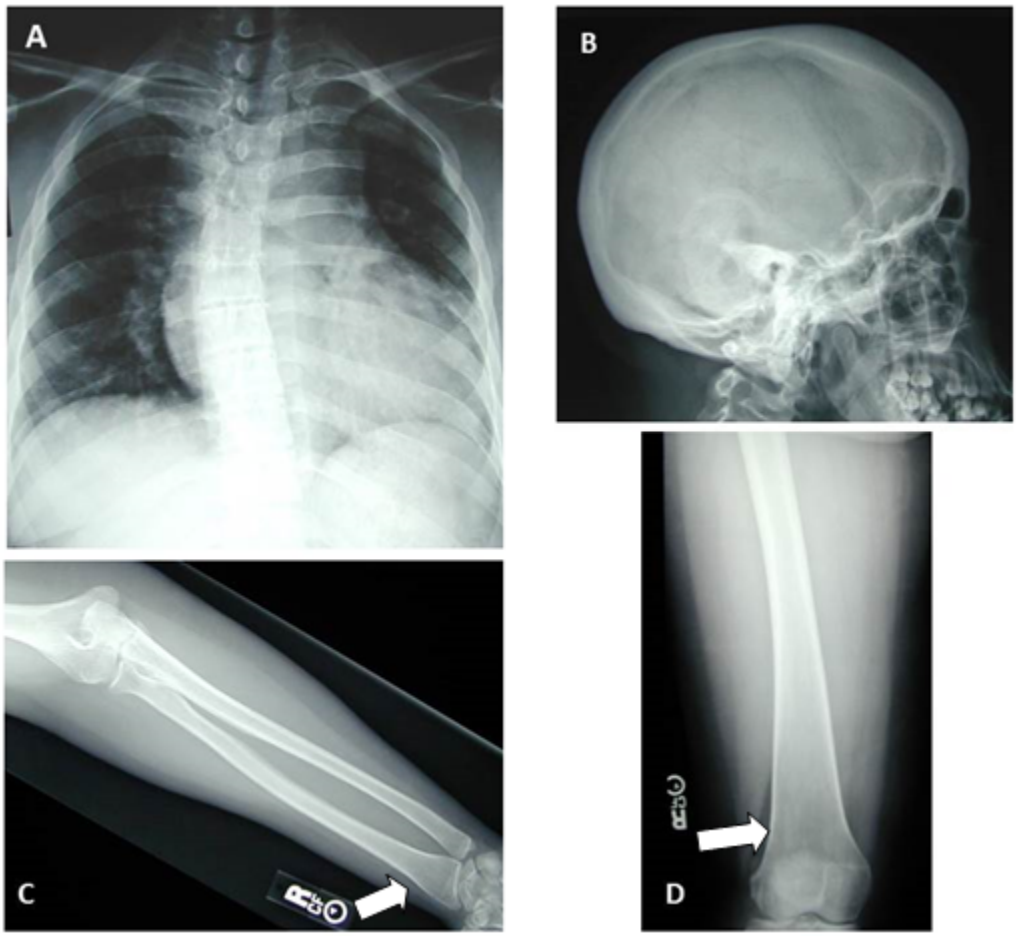

Figure 3. Woman age 40 years with Cantù syndrome

A. Chest x-ray showing marked cardiomegaly

B. Lateral skull x-ray showing thickened calvarium

C. Erlenmeyer flask deformity with metaphyseal flaring of the distal radius (arrow)

D. Metaphyseal flaring of the distal femur (arrow)

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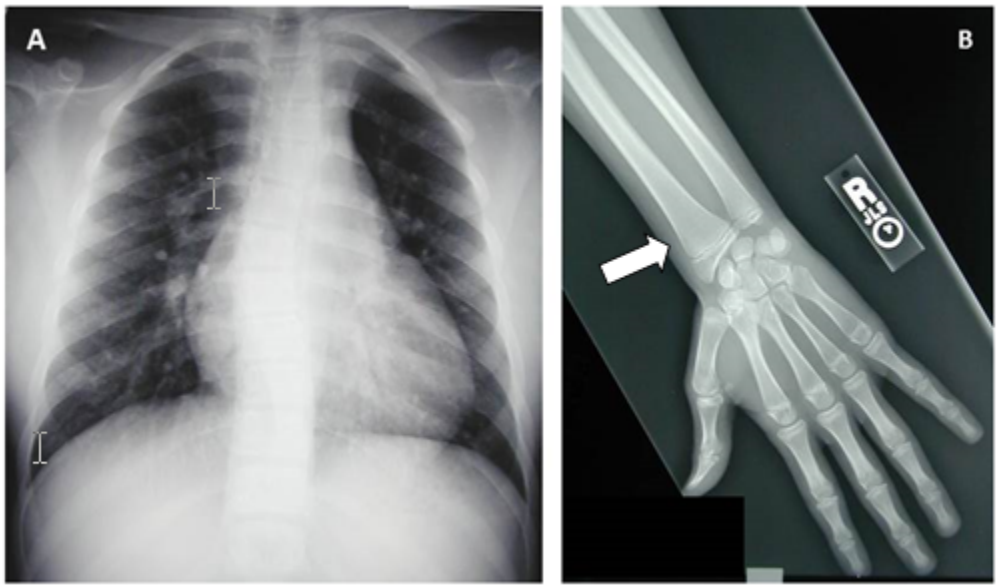

Figure 4. Girl age 16 years with Cantù syndrome

A. Chest x-ray showing cardiomegaly

B. Early metaphyseal flaring of the distal radius (arrow)

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Table 1. Molecular Genetic Testing Used in Cantú Syndrome

Gene [1, 2]	Proportion of Cantú Syndrome Attributed to Pathogenic Variants in Gene [6]	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ABCC9	97%	100% [6]	Not applicable [7]
KCNJ8	1%-2%	3/3 tested [8]	Not applicable [7]
Unknown [9]	NA		

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Grange et al [2019]
7. All pathogenic variants reported to date are gain-of-function variants in *ABCC9 and KCNJ8*; thus, testing for deletion (haploinsufficiency) or duplication (overexpression) is not indicated.
8. Brownstein et al [2013], Cooper et al [2014], Chihara et al [2020]
9. A small number (<1%) of individuals with a clinical diagnosis of Cantú syndrome in whom no *ABCC9 or KCNJ8* variant was found raises the possibility that other as-yet unidentified genes may be involved [DK Grange, personal observation].

Clinical Characteristics

Clinical Description

To 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 Features

Feature		% of Persons w/Feature	Comment
Polyhydramnios		57%	
Prematurity (<37 weeks)		58%	
Neonatal hypertrichosis		99%	
Macrosomia		38%	Birth weight >4,000 g
Generalized edema at birth		43%	
Macrocephaly		48% of adults studied	
Skeletal abnormalities		19%	Usually asymptomatic so detection dependent on imaging; not all persons had full skeletal survey
Gastroesophageal reflux		42%	
Cardiovascular findings	PDA	58%	
	Valvular defects	18%	Bicuspid aortic valve, mitral valve regurgitation, aortic valve stenosis
	Cardiac enlargement	64%	
	Dilated aortic root	32%	
	Pericardial effusion	25%	
Tortuous vascularity		100% (10/10) on neurovascular imaging	True 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 hypertension		24%	Seen in infancy; typically resolves w/age
Peripheral edema		51%	Usually develops in teenagers & young adults
Developmental delays		63%	Present in infants & young children related to hypotonia, but improve over time; most have normal intellect.
Hypotonia		65%	
Headaches		40%	Often migraine-type headache w/assoc symptoms
Seizures		24%	Various types

Table 2. continued from previous page.

Feature		% of Persons w/Feature	Comment
Behavioral issues [1]	ADHD	19%	
	ASD	16%	
	OCD	13%	
	Anxiety	13%	
	Depression	19%	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OCD = obsessive-compulsive disorder; PDA = patent ductus arteriosus
1. Self-reported in many individuals

Prenatal. 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 childhood
- Bicuspid aortic valve with and without stenosis
- Pericardial 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 hernia
- Pyloric stenosis
- Poor intestinal motility [Grange et al 2019]
- Ptosis
- Craniosynostosis 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 individuals

The 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 callosum
- Multiple tortuous venous collaterals and lack of flow in the inferior sagittal sinus
- Systemic vasculature: dilated hepatic and celiac arteries, dilated and tortuous intrahepatic arteries and veins

Genotype-Phenotype Correlations

Current information about genotype-phenotype correlation in Cantú syndrome is limited.

No significant genotype-phenotype correlations for *ABCC9* or *KCNJ8* have been identified.

Penetrance

Penetrance 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].

Nomenclature

Cantú syndrome may also be referred to as hypertrichotic osteochondrodysplasia.

Prevalence

The 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 facial features (HAFF) syndrome, are now realized to be cases of Cantú syndrome with variable and sometimes milder phenotypic features. Cantú syndrome has been reported worldwide and in all ethnic groups.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *ABCC9* and *KCNJ8* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Disorder	Reference
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)	Bienengraeber et al [2004]
	Brugada syndrome	Brugada syndrome
	Early repolarization syndrome	Hu et al [2014]
	ABCC9 intellectual disability myopathy syndrome	Smeland et al [2019]

Table 3. continued from previous page.

Gene	Disorder	Reference
KCNJ8	Brugada syndrome	Brugada syndrome
	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].

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of Cantú Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of This Disorder	
			Overlapping w/Cantú Syndrome	Distinguishing from Cantú Syndrome
Abnormal methylation at 11p15.5 *CDKN1C* [1]	Beckwith-Wiedemann syndrome	Variable [2]	Neonatal macrosomia; coarse facial features w/ macroglossia; umbilical hernia	Neonatal hypoglycemia, & hyperinsulinism; ear pits & creases; omphalocele; hemihypertrophy; abdominal tumors in childhood (Wilms tumor, hepatoblastoma)
ATP6V1B2 *KCNH1* *KCNN3*	Zimmermann-Laband syndrome (OMIM PS135500)	AD	Hypertrichosis; coarse facial features; full lips; macrosomia at birth; PDA; aortic root dilatation; scoliosis; hypotonia	Gingival 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	AR	Muscular build w/↓ subcutaneous fat in assoc w/ cardiomegaly	Insulin resistance; diabetes mellitus; hepatomegaly & hepatic steatosis; hypertrophy of skeletal muscles; hypertrophic cardiomyopathy different from cardiac involvement in Cantú syndrome
ANKRD1 *BAG3* *LMNA* *MYBPC3* *MYH6* *MYH7* *SCN5A* *TNNT2* *TTN* (~30 genes) [3]	Dilated cardiomyopathy	AD	Cardiomegaly	Absence 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.)
MYBPC3 *MYH7* *TNNI3* *TNNT2* (~30 genes) [4]	Hypertrophic cardiomyopathy	AD		
KCNK4	FHEIG syndrome (Bauer-Tartaglia syndrome) (OMIM 618381)	AD	Hypertrichosis; coarse facial features; thick scalp hair; large mouth; hypotonia	Ocular abnormalities (e.g. nystagmus & optic nerve hypoplasia); severe gingival hyperplasia; brachydactyly; ID/DD; epilepsy; lack of cardiac manifestations

Table 4. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of This Disorder	
			Overlapping w/Cantú Syndrome	Distinguishing from Cantú Syndrome
GALNS	MPS IVA (Morquio syndrome type A)	AR	Coarse 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 I	AR		
MAN2B1	Alpha-mannosidosis	AR		

AD = 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-linked

1. 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 Conditions

Congenital 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*.

Management

Evaluations Following Initial Diagnosis

To 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 Syndrome

System/Concern	Evaluation	Comment
Cardiac	Cardiology assessment to incl echocardiogram & electrocardiogram	
Brain imaging	Brain MRI w/MRA & MRV	Should be considered for all persons, but esp if history of headaches, migraine headaches, or hemiparesis
Skeletal	• Radiographic skeletal survey to assess for bone abnormalities • Eval for scoliosis	
Development	Developmental eval for infants & young children	
	Neuropsychological eval for older persons	Especially for those w/concern for ASD, ADHD, OCD, or depression
Genetic counseling	By genetics professionals [1]	To 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 disorder
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Cantú Syndrome

Manifestation/Concern	Treatment	Considerations/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 options	Possible 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 arteriosus

Developmental Delay Management Issues

The 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 Delay

Gross 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 Concerns

Children 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.

Surveillance

Table 7. Recommended Surveillance for Individuals with Cantú Syndrome

System/Concern	Evaluation	Frequency
Cardiac issues	• Echocardiogram & EKG to monitor cardiac size & function & for evidence of pericardial effusion starting in infancy • Clinical eval & cardiac biomarkers such as BNP to monitor late development of high-output cardiac failure	Per cardiologist or annually
Peripheral edema	Monitor w/history & exam	Annually starting in adolescence
Cerebral vasculature abnormality	Brain MRI w/MRA & MRV	If persistent headaches or other neurologic symptoms develop

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Headaches/ Migraines	Eval by neurologist	Per neurologist
Scoliosis	• Spine radiographs • Orthopedic eval if scoliosis is present	If concern based on physical exam

BNP = brain natriuretic peptide; EKG = electrocardiogram; MRA = magnetic resonance angiogram; MRV = magnetic resonance venography

Agents/Circumstances to Avoid

Avoid the following:

- Minoxidil
- Diazoxide
- Angiotensin-converting enzyme inhibitors

Evaluation of Relatives at Risk

It 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 Management

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

Therapies Under Investigation

Search 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 Inheritance

Cantú 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 Issues

See 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 Testing

If 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.

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

cantu.wustl.edu/registry

Molecular Genetics

Information 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 Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
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

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. 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)

239850	CANTU SYNDROME
600935	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 8; KCNJ8
601439	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9; ABCC9

Molecular Pathogenesis

ABCC9 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 *hyper*polarization and decrease in voltage-dependent Ca^{2+} 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 Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005691.4 NP_005682.2	c.3461G>A	p.Arg1154Gln	Recurrent variants [Grange et al 2019]
	c.3460C>T	p.Arg1154Trp	
	c.3346C>T	p.Arg1116Cys	
	c.3347G>A	p.Arg1116His	

Variants 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 Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter 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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