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NLM Citation: Morrow EM, Pescosolido MF. Christianson Syndrome. 2018 Jan 11. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Christianson Syndrome

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Created: January 11, 2018.

Summary

Clinical characteristics

Christianson syndrome (referred to as CS in this *GeneReview*), an X-linked disorder, is characterized in males by cognitive dysfunction, behavioral disorder, and neurologic findings (e.g., seizures, ataxia, postnatal microcephaly, and eye movement abnormalities). Males with CS typically present with developmental delay, later meeting criteria for severe intellectual disability (ID). Behaviorally, autism spectrum disorder and hyperactivity are common, and may resemble the behaviors observed in Angelman syndrome. Hypotonia and oropharyngeal dysphagia in infancy may result in failure to thrive. Seizures, typically beginning before age three years, can include infantile spasms and tonic, tonic-clonic, myoclonic, and atonic seizures. Subsequently, regression (e.g., loss of ambulation and ability to feed independently) may occur. Manifestations in heterozygous females range from asymptomatic to mild ID and/or behavioral issues.

Diagnosis/testing

The diagnosis of CS is established in a male proband by identification of a hemizygous pathogenic variant in *SLC9A6* on the X chromosome and in a female proband by identification of a heterozygous *SLC9A6* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: Management of neurodevelopmental disorders, feeding difficulties, and seizures are per standard care.

Surveillance: At the time of follow-up clinical examinations, the following are recommended:

- Measurement of weight and height (and calculation of body mass index)
- Assessment for scoliosis/kyphoscoliosis

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- Detailed history and related assessments in adolescents and young adults for evidence of possible loss of any of the following skills: feeding, fine/gross motor skills, ambulation, and use of words/sounds

Genetic counseling

CS is inherited in an X-linked manner. The risk to sibs depends on the genetic status of the mother. Heterozygous (carrier) females have a 50% chance of transmitting the *SLC9A6* pathogenic variant in each pregnancy. Sons who inherit the pathogenic variant will have CS; daughters who inherit the pathogenic variant may be asymptomatic or have mild ID and/or behavioral issues. Males with CS are not known to reproduce. Once the *SLC9A6* pathogenic variant has been identified in an affected family member, carrier testing for at-risk female relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Christianson syndrome (referred to as CS in this *GeneReview*) **should be suspected** in an individual with the following clinical manifestations observed in the majority of affected males [Pescosolido et al 2014].

Clinical manifestations

- Developmental delay / intellectual disability (usually severe to profound)
- Absent to minimal language development
- Hyperkinesis
- Epilepsy (onset usually before age three years)
- Truncal ataxia
- Postnatal-onset microcephaly
- Nondysmorphic facial features

Establishing the Diagnosis

The diagnosis of CS **is established** in a male proband by identification of a hemizygous pathogenic variant in *SLC9A6* and in a female proband by identification of a heterozygous *SLC9A6* pathogenic variant on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (typically exome sequencing).

Gene-Targeted Testing

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotypes of ID often overlap, most individuals with CS are diagnosed by either multigene panel or exome sequencing. Single-gene testing (sequence analysis of *SLC9A6*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

A multigene panel for intellectual disability, autism spectrum disorder, and/or epilepsy that includes *SLC9A6* and other genes of interest (see Differential Diagnosis) may be used. 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*; thus, clinicians need to determine which multigene panel 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. Of note, given the rarity of Christianson syndrome, panels

for ID may not include *SLC9A6*. (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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive Genomic Testing

Comprehensive genomic testing (when clinically available) typically includes exome sequencing and genome sequencing.

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

Table 1. Molecular Genetic Testing Used in Christianson Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SLC9A6	Sequence analysis [3]	29/32 (91%) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	3/32 (9%) [4, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. 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.
4. Some probands were detected by screening large cohorts.
5. Christianson et al [1999], Gilfillan et al [2008], Fichou et al [2009], Garbern et al [2010], Schroer et al [2010], Takahashi et al [2011], Mignot et al [2013], Riess et al [2013], Pescosolido et al [2014], Zanni et al [2014], Coorg & Weisenberg [2015], Masurel-Paulet et al [2016], Sinajon et al [2016], Trump et al [2016]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Tzschach et al [2011], Tzschach et al [2015] (See Molecular Genetics, **Pathogenic variants**.)

Clinical Characteristics

Clinical Description

Christianson syndrome (CS), an X-linked disorder, typically manifests in males in the first few years of life with delayed developmental milestones and seizures. Additional findings in affected males include intellectual disability (ID), absent-to-limited speech, postnatal microcephaly, truncal ataxia, hyperkinesis, and nondysmorphic facial features. Affected males may also manifest signs of autism spectrum disorder (ASD) and behaviors typically associated with Angelman syndrome. Of note, approximately one third of those with CS had received a prior clinical diagnosis of Angelman syndrome [Pescosolido et al 2014]. Other common problems include eye movement abnormalities, hypotonia, gastroesophageal reflux disease, feeding difficulties, and poor weight gain despite normal caloric intake. Regression (e.g., loss of ambulation and ability to feed independently) may occur.

The phenotypic spectrum in females heterozygous for a *SLC9A6* pathogenic variant ranges from moderate ID, behavioral problems, and hyperactivity to asymptomatic.

Affected Males

Common manifestations (from Pescosolido et al [2014] and additional references where indicated):

- **Developmental delay and intellectual disability** typically range from moderate to profound, although mild ID has been reported [Masurel-Paulet et al 2016].
  - Gross motor milestones are delayed. Independent ambulation is achieved approximately one to two years later than average.
  - Speech is generally absent. Very limited receptive language and use of a few single words may emerge in the first years of life; however, these words may subsequently be lost. To date, speech was unaffected in one adult male [Masurel-Paulet et al 2016].
  - IQ is generally well below 35-40.
- **ASD or autistic behaviors.** Notable findings include poor eye contact, lack of use of facial expressions to communicate, using bodies of others as a tool (e.g., to turn a doorknob), unusual sensory interests and preoccupations, and lack of reciprocal play / social interest [Garbern et al 2010, Mignot et al 2013, Pescosolido et al 2014, Coorg & Weisenberg 2015]. In one cohort, 43% of affected males were previously diagnosed with ASD by a clinician [Pescosolido et al 2014]. The authors caution that diagnosis of ASD – even with standardized assessments – in nonverbal individuals with cognitive impairments may be challenging.
- **Hyperkinesis.** Affected males are commonly described as having hyperkinesis (i.e., hyperactive and described by parents as "always on the go") [Gilfillan et al 2008, Fichou et al 2009, Schroer et al 2010, Takahashi et al 2011, Mignot et al 2013].
- **Epilepsy.** Seizure onset is typically before age three years and is consistent with generalized epilepsy, although focal-onset seizures have been reported. Specific seizure types include infantile spasms, tonic, tonic-clonic, myoclonic, drop (unknown whether tonic or atonic), and absence seizures. Seizure frequency can range from daily clusters to seizure-free periods longer than one year.

  EEG findings include abnormalities in both background (e.g., generalized slowing) and epileptiform activity (e.g., frequent generalized spike-wave complexes, irregular generalized spike-wave pattern, and multifocal independent and sometimes synchronous spikes). One individual had generalized discharges in more than 85% of slow-wave sleep recordings, a pattern associated with electrographic status epilepticus of sleep [Coorg & Weisenberg 2015].

  Clinical and EEG findings suggestive of Lennox-Gastaut syndrome, a syndromic epileptic encephalopathy, have been reported [Schroer et al 2010].

  Epileptic encephalopathy (childhood-onset epilepsies characterized by severe, intractable, multiform seizures associated with cognitive impairments) has been reported [Zanni et al 2014]. Some suggest that epileptic encephalopathy appears in up to 20% of affected individuals [Pescosolido et al 2014].
- **Truncal ataxia,** a nearly universal finding, is manifest in ambulatory males as an ataxic, unsteady gait. While ataxia is typically present with emergence of independent ambulation and is lifelong, late-onset worsening of ataxia at age 13 years [Mignot et al 2013] and in the 40s-50s [Garbern et al 2010] has been reported.

  In one family, an affected boy and his maternal uncle did not have ataxia [Masurel-Paulet et al 2016].

  Progressive cerebellar atrophy, particularly affecting the vermis, is one of the most common neuroimaging findings [Garbern et al 2010, Schroer et al 2010, Mignot et al 2013].

- **Postnatal microcephaly.** Head circumference is typically normal at birth. Microcephaly becomes evident over time.

Distinctive features seen in some affected males (from Christianson et al [1999], Gilfillan et al [2008], and Pescosolido et al [2014], and additional references where indicated):

- **Abnormal eye movements,** such as convergent strabismus and esotropia, are common [Garbern et al 2010, Schroer et al 2010, Takahashi et al 2011, Mignot et al 2013, Riess et al 2013, Masurel-Paulet et al 2016]. Abnormal horizontal eye movements or the inability to look laterally, presumably due to dysfunction of cranial nerve VI and/or lateral recti muscles, are common [Schroer et al 2010, Mignot et al 2013].
- **Feeding difficulties.** Open mouth and drooling are common [Gilfillan et al 2008]. Feeding difficulties can include sucking and swallowing problems in infancy as well as lack of coordination in chewing later in infancy. Gastroesophageal reflux disease may be present often requiring Nissen fundoplication surgery (see Management, Treatment of Manifestations).
- **Poor weight gain** occurs despite normal caloric intake. Low body mass index (BMI) becomes more pronounced with age. Older males have been described as appearing "emaciated."

  Of note, birth weight (when reported) was normal in the majority of affected males.
- **Constipation** can be significant.
- **Regression,** typically beginning between ages 15 months and 16 years, can include loss of previously acquired skills such as independent ambulation, use of words/sounds, independent feeding, establishing eye contact / facial expressions, and fine/gross motor skills [Garbern et al 2010, Schroer et al 2010, Takahashi et al 2011, Mignot et al 2013].

  Medical illness and/or severe or worsening seizure episodes usually precede regressions [Schroer et al 2010, Takahashi et al 2011].

  The risk for regression appears to increase after the first decade of life as regression has been reported in males in their 40s-50s [Garbern et al 2010].

Findings identified in a few affected males include the following:

- Sleep disturbances, including frequent nighttime waking, an inability to fall asleep, and, in two males, no discernable sleep pattern [Christianson et al 1999, Gilfillan et al 2008, Garbern et al 2010, Mignot et al 2013, Pescosolido et al 2014]
- Scoliosis and one individual with severe kyphoscoliosis [Gilfillan et al 2008, Schroer et al 2010, Riess et al 2013]
- High pain threshold resulting in serious injury [Pescosolido et al 2014]
- Osteoporosis observed in some cases [Pescosolido et al 2014]

Life expectancy. Data on life expectancy are limited. Death in the second to fifth decade has been reported in a few individuals [Gilfillan et al 2008]. Causes have included pyogenic bronchopneumonia superimposed on miliary tuberculosis [Christianson et al 1999] and epileptic seizures [Schroer et al 2010].

Pathology. Postmortem brain examination in two adult males with CS from the same family showed diffuse glial tau deposition in cerebellar, brain stem, and centrum semiovale white matter tracts [Garbern et al 2010]. In addition, tau-positive inclusions were found throughout the substantia nigra, locus coeruleus, pontine nuclei, basal ganglia, thalamus, and cranial nerve nuclei.

Heterozygous Females (i.e., Carriers)

To date, 43 heterozygous females in 17 families have been reported [Christianson et al 1999, Gilfillan et al 2008, Fichou et al 2009, Garbern et al 2010, Schroer et al 2010, Takahashi et al 2011, Riess et al 2013, Pescosolido et al 2014, Zanni et al 2014, Masurel-Paulet et al 2016, Sinajon et al 2016].

Manifestations range from no reported abnormal neurologic or psychological findings [Gilfillan et al 2008, Fichou et al 2009, Takahashi et al 2011, Riess et al 2013] to mild or (rarely) moderate ID, behavioral issues, and hyperactivity [Pescosolido et al 2014, Masurel-Paulet et al 2016].

The most common findings:

- Mild developmental delay (especially with speech/language) and/or mild intellectual disability [Christianson et al 1999, Schroer et al 2010, Pescosolido et al 2014, Zanni et al 2014, Sinajon et al 2016]
- In some, a notable discrepancy on neuropsychological testing between verbal and performance IQ, with verbal IQ being much lower [Masurel-Paulet et al 2016]
- Speech disorder/dysphasia [Schroer et al 2010, Masurel-Paulet et al 2016, Sinajon et al 2016]
- Dyslexia [Gilfillan et al 2008, Masurel-Paulet et al 2016]
- Behavior problems including aggression [Christianson et al 1999, Schroer et al 2010, Sinajon et al 2016]
- Hyperactivity/hyperkinesia [Schroer et al 2010, Pescosolido et al 2014, Sinajon et al 2016]

Genotype-Phenotype Correlations

To date, no genotype-phenotype correlations have been identified.

Prevalence

The estimated prevalence of CS is between 1:16,000 and 1:100,000 [Pescosolido et al 2014].

CS may be among the most common X-linked neurodevelopmental disorders based on X-chromosome sequencing of approximately 200 families with suspected X-linked intellectual disability [Tarpey et al 2009].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SLC9A6*.

Differential Diagnosis

Angelman syndrome (AS) is characterized by severe developmental delay or ID, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavioral profile with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are common. Developmental delays are first noted around age six months; however, the unique clinical features of AS do not become manifest until after age one year, and it can take several years before the correct clinical diagnosis becomes apparent. The diagnosis of AS is established in a proband who meets the consensus clinical diagnostic criteria and/or who has findings on molecular genetic testing that suggest deficient expression or function of the maternally inherited *UBE3A* allele.

Christianson syndrome (CS) can be clinically distinguished from AS in the following ways:

- The presence of progressive cerebellar atrophy in CS [Pescosolido et al 2014], which generally occurs after the first decade of life but can occur before age ten years

- Lifelong problems with weight gain with a low body mass index in individuals with CS. Those with AS may have poor weight gain in early childhood with later normal weight gain or even obesity in young adulthood.

All genes known to be associated with intellectual disability should be included in the differential diagnosis of Christianson syndrome. More than 180 have been identified; see OMIM Phenotypic Series – Intellectual disability:

- Autosomal dominant
- Autosomal recessive
- Nonsyndromic, X-linked
- X-linked syndromic

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Christianson syndrome (CS), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Establishment of baseline neurologic functioning with:
  - Assessment of adaptive functioning (e.g., Vineland, Bayley Scales of Infant Development)
  - Occupational therapy and physical therapy assessment regarding fine motor and gross motor functioning
  - Speech/language/communication assessment
  - Assessment of behavioral issues, as needed, using such evaluation tools as Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R)]
  - Neurologic examination
  - EEG
  - Brain MRI (based on the clinician's judgment) to determine if any structural brain abnormalities are present, especially cerebellar / brain stem atrophy
- Evaluation of swallowing function, feeding, and nutrition as needed
- Ophthalmologic assessment, including evaluation for eye movement abnormalities and visual acuity, when warranted
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability 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. In the US, early intervention is a federally funded program available in all states.

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 (IEP) is developed.

Ages 5-21 years

- In the United States, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion regarding transition plans and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive functions, such as feeding.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

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 is 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 when necessary.

Other

Seizures. Currently, no guidelines exist for seizure control in Christianson syndrome. A range of anti-seizure medications have been used, including levetiracetam, valproic acid, clonazepam, clobazam, diazepam, lamotrigine, phenobarbital, oxcarbazepine, carbamazepine, zonisamide, and topiramate [Pescosolido et al 2014].

GI manifestations. Fundoplication has been pursued to treat gastroesophageal reflux disease in some individuals. In a minority, a gastrostomy tube has been placed to improve nutrition. A bowel regimen to prevent constipation is recommended as needed.

Post-hospitalization. Because hospitalization for complications such as pneumonia or epileptic seizures may be particularly high-risk for subsequent regression in psychomotor skills [Pescosolido et al 2014], physical therapy following such an illness may be warranted in some instances.

Surveillance

At the time of follow-up clinical examinations, the following are recommended:

- Measurement of weight and height (and calculation of BMI) because of the increased age-related risk for poor weight gain despite normal or even high caloric intake
- Assessment for scoliosis/kyphoscoliosis
- In adolescents / young adults regarding possible regression:
  - Evaluation for loss of any of the following: feeding skills, fine/gross motor skills, ambulation, use of words/sounds
  - Repeat neuropsychologic assessments (as needed)
  - Assessment using an ataxia rating scale

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

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

Christianson syndrome (CS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have CS nor will he be hemizygous for the *SLC9A6* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected male, the mother is an obligate carrier. Note: If a woman has more than one affected child and no other affected relatives and if the *SLC9A6* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.

- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo SLC9A6* pathogenic variant, in which case the mother is not a carrier. In 40% of families published to date, the proband has had a *de novo SLC9A6* pathogenic variant [Christianson et al 1999, Gilfillan et al 2008, Fichou et al 2009, Garbern et al 2010, Schroer et al 2010, Takahashi et al 2011, Tzschach et al 2011, Riess et al 2013, Pescosolido et al 2014, Zanni et al 2014, Masurel-Paulet et al 2016, Trump et al 2016].
- Molecular genetic testing of the mother can determine if the *SLC9A6* pathogenic variant was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *SLC9A6* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may be unaffected or have a range of clinical manifestations (see Clinical Description, Heterozygous Females).
- If a male represents a simplex case (i.e., a single occurrence in a family), and if the *SLC9A6* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still less than 1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Males with CS are not known to reproduce.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the *SLC9A6* pathogenic variant and the aunts' offspring may be at risk of being carriers or being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the pathogenic variant in the family.

Note: Females who are heterozygous for this X-linked disorder may have a range of clinical manifestations (see Clinical Description, Heterozygous Females).

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC9A6* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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.

- **Christianson Syndrome Association**
  15201 Mason Road
  Suite 1000 #173
  Cypress TX 77433
  Phone: 281-723-5989
  Email: info@csa-cares.org
  www.csa-cares.org
- **National Library of Medicine Genetics Home Reference**
  Christianson syndrome
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **EuroMRX Consortium Registry**
  Radboud University Nijmegen Medical Centre, Department of Human Genetics
  PO Box 9101
  Nijmegen 6500 HB
  Netherlands
  Phone: +31 24 3614017
  Fax: +31 24 3668752
  Email: a.debrouwer@antrg.umcn.nl
  www.euromrx.com

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. Christianson Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC9A6	Xq26.3	Sodium/hydrogen exchanger 6	SLC9A6 @ LOVD	SLC9A6	SLC9A6

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 Christianson Syndrome (View All in OMIM)

300231	SOLUTE CARRIER FAMILY 9, MEMBER 6; SLC9A6
300243	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, CHRISTIANSON TYPE; MRXSCH

Molecular Pathogenesis

SLC9A6 encodes a Na+/H+ exchanger (NHE). There are nine different NHEs in the mammalian genome. Members of the SLC9 family localize to different membranes in cells where they are thought to influence the pH of luminal areas [Ohgaki et al 2011].

Gene structure. *SLC9A6* is approximately 59 kb; the longest transcript, NM_001042537.1 (or ENST00000370695), has 16 coding exons [Pescosolido et al 2014]. Alternate splicing results in multiple transcript variants. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Variants in *SLC9A6* include nonsense, missense, and splice variants and small deletions and insertions. Additionally, three gross deletions have been reported, including a 336-bp deletion involving exon 1 and a 314-kb deletion including *SLC9A6* exons 15-16 and adjacent genes [Tzschach et al 2011, Pescosolido et al 2014, Tzschach et al 2015].

Normal gene product. *SLC9A6* encodes the 12-membrane spanning sodium-hydrogen exchanger 6 (NHE6) protein, which is composed of 701 amino acids (NP_001036002.1). The membrane domains encode an exchanger that mediates the electroneutral exchange of sodium for protons. In most cases, the exchanger is thought to mediate the entrance of Na+ into the organelle and to permit the efflux of H+ from intracellular membranes [Ohgaki et al 2011]. NHE6 is known as an endosomal NHE and has been localized to early, recycling, and late endosomes [Nakamura et al 2005, Ouyang et al 2013]. NHE6 has been associated with clathrin-dependent transferrin endocytosis [Xinhan et al 2011].

Studies have implicated defects in brain-derived neurotrophic factor (BDNF) endosomal signaling in a mouse model of Christianson syndrome [Ouyang et al 2013]. In general, it appears that one role of NHE6 is to regulate intra-endosomal pH. This process can have multiple roles in protein trafficking and turnover.

Abnormal gene product. The gross deletion variants clearly result in NHE6 loss of function, which is consistent with the predicted consequences of the majority of other pathogenic variants. Missense and in-frame variants have been rarely described and may alter protein transport.

References

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Chapter Notes

Author Notes

Dr Eric Morrow's research interests in understanding the genetic and molecular mechanisms of neurodevelopmental disorders, including intellectual disability and autism. His research program has a focus in Christianson syndrome and related neurologic conditions. People interested in learning more about ongoing research studies involving Christianson syndrome may contact him at emorrow@lifespan.org.

Acknowledgments

We would like to thank the families of individuals diagnosed with Christianson syndrome for their support and participation in research. This work has been supported by the Hassenfeld Child Health Innovation Institute at Brown University, the Angelman Syndrome Foundation general research grant and National Institutes of Health/National Institute of Mental Health grants R01MH105442, R01MH102418, and R21MH115392 (to EMM); and National Institutes of Health/National Institute of Neurological Disorders and Stroke grant F31NS093880 (to MFP).

Revision History

- 11 January 2018 (bp) Review posted live
- 19 January 2015 (emm) Original submission

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