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Char Syndrome

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Summary

Clinical characteristics

Char syndrome is characterized by the triad of typical facial features, patent ductus arteriosus, and aplasia or hypoplasia of the middle phalanges of the fifth fingers. Typical facial features are depressed nasal bridge and broad flat nasal tip, widely spaced eyes, downslanted palpebral fissures, mild ptosis, short philtrum with prominent philtral ridges with an upward pointing vermilion border resulting in a triangular mouth, and thickened (patulous) everted lips. Less common findings include other types of congenital heart defects, other hand and foot anomalies, hypodontia, hearing loss, myopia and/or strabismus, polythelia, parasomnia, craniosynostosis (involving either the metopic or sagittal suture), and short stature.

Diagnosis/testing

The diagnosis of Char syndrome is established in a proband with suggestive clinical findings and/or a heterozygous pathogenic variant in *TFAP2B* identified by molecular genetic testing.

Management

Treatment of manifestations: Management of patent ductus arteriosus after the immediate newborn period is determined by the degree of shunting from the aorta to the pulmonary artery; options are surgical ligation or ductal occlusion at catheterization. Hypodontia/tooth anomalies, vision problems, hearing loss, other hand/foot anomalies, parasomnias, and craniosynostosis are treated in a routine manner.

Surveillance: Assessment for signs and symptoms of sleep problems at each visit; monitoring of head shape and size at each visit during the first year of life; vision and hearing screening annually or as clinically indicated; dental evaluations every six months starting at age three years.

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Genetic counseling

Char syndrome is inherited in an autosomal dominant manner. The proportion of cases caused by a *de novo* pathogenic variant is unknown. If a parent of the proband is affected, the risk to the sibs is 50%. When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. Each child of an individual with Char syndrome has a 50% chance of inheriting the pathogenic variant and having the disorder. If the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for Char syndrome have not been published.

Suggestive Findings

Char syndrome **should be suspected** in individuals with the following clinical and family history findings.

Clinical features

- Typical facial features with depressed nasal bridge and broad flat nasal tip, widely spaced eyes, downslanted palpebral fissures, mild ptosis, short philtrum with prominent philtral ridges with an upward pointing vermilion border resulting in a triangular mouth, and thickened (patulous) everted lips
- Patent ductus arteriosus
- Aplasia or hypoplasia of the middle phalanges of the fifth fingers

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Char syndrome **is established** in a proband with suggestive clinical findings and/or a heterozygous pathogenic variant in *TFAP2B* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, 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. Because the phenotype of Char syndrome is broad, 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 Char syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Char syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TFAP2B* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

- **A multigene panel** that includes *TFAP2B* 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 2

When the diagnosis of Char syndrome is not considered 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 the most commonly used genomic testing method; **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.

Table 1. Molecular Genetic Testing Used in Char Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TFAP2B	Sequence analysis [3]	15/15 probands [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]
Unknown	NA	

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. Satoda & Gelb [2003]
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. Because most of the pathogenic variants identified to date result in mutated protein with dominant-negative effects, it is likely that variants will be missense defects in the coding region for critical domains, particularly the basic domain. Rare pathogenic changes altering splice sites & engendering haploinsufficiency have also been reported [Mani et al 2005, Massaad et al 2019].

Clinical Characteristics

Clinical Description

Char syndrome is characterized by the triad of typical facial features (see Figure 1), patent ductus arteriosus (PDA), and stereotypic hand anomalies (see Diagnosis).

Table 2. Features of Char Syndrome

Feature	% of Persons with Feature	Comment
Facial dysmorphia	86%	Higher prevalence in those w/missense variants (98%) vs loss-of-function variants (59%) (See Genotype-Phenotype Correlations.)
PDA	68%	
Other congenital heart defects	6%	
Hand anomalies	57%	Higher prevalence in those w/missense variants altering the basic domain (residues 223-301; 79%) than in the transactivation domain (residues 65-86; 0%) (See Genotype-Phenotype Correlations.)

PDA. The ductus arteriosus, the fetal arterial connection between the aorta and pulmonary artery that shunts blood away from the lungs, constricts shortly after birth. If the ductus arteriosus remains patent, left to right shunting (from the systemic circulation into the pulmonary circulation) occurs, resulting in pulmonary hypertension if not corrected. No information is available concerning the likelihood of spontaneous closure of a PDA after the first weeks of life in individuals with Char syndrome, but it is likely to be rather low.

Less common features associated with Char syndrome:

- Other heart defects (e.g., muscular ventricular septal defects, complex congenital defects)
- Other hand abnormalities including interstitial polydactyly [Slavotinek et al 1997], distal symphalangism of the fifth fingers (fusion of distal interphalangeal joints), and hypoplasia of the third fingers [Babaoğlu et al 2012]
- Foot anomalies including interphalangeal joint fusion or clinodactyly [Sweeney et al 2000], interstitial polydactyly [Slavotinek et al 1997], and syndactyly [Slavotinek et al 1997]
- Hypodontia. Lack of second and/or third molars in all four quadrants [Mani et al 2005; Author, unpublished observation]
- Visual impairment. Myopia [Bertola et al 2000], strabismus [Bertola et al 2000, Sweeney et al 2000]
- Hearing abnormalities including profound bilateral hearing loss in two affected individuals [Edward et al 2019; Author, unpublished observation in a member of the enlarged version of the original family studied by Char]
- Polythelia (supernumerary nipples) [Zannolli et al 2000]
- Parasomnia [Mani et al 2005]
- Craniosynostosis involving either the metopic or sagittal suture reported in four affected individuals [Timberlake et al 2019]
- Short stature (≤3 SD below the mean) reported in two affected individuals [Massaad et al 2019, Timberlake et al 2019]

Genotype-Phenotype Correlations

Among the 16 different pathogenic variants in *TFAP2B* described in publications, seven are loss-of-function alleles and nine are missense changes. For the latter, eight of the nine alter residues in the DNA binding domain (basic domain; residues 223-301) and one is in the transactivation domain (residues 65-86).

- Individuals harboring basic domain alleles tend to have the classic form of Char syndrome (97% with facial features, 58% with PDA, and 79% with hand anomalies) [Satoda et al 1999, Satoda et al 2000, Zhao et al 2001].
- For individuals in the one family inheriting the transactivation domain-altering variant, the facial features were prevalent (14/14) but mild, PDA was generally present (10/14), but hand anomalies were not observed in any [Zhao et al 2001].

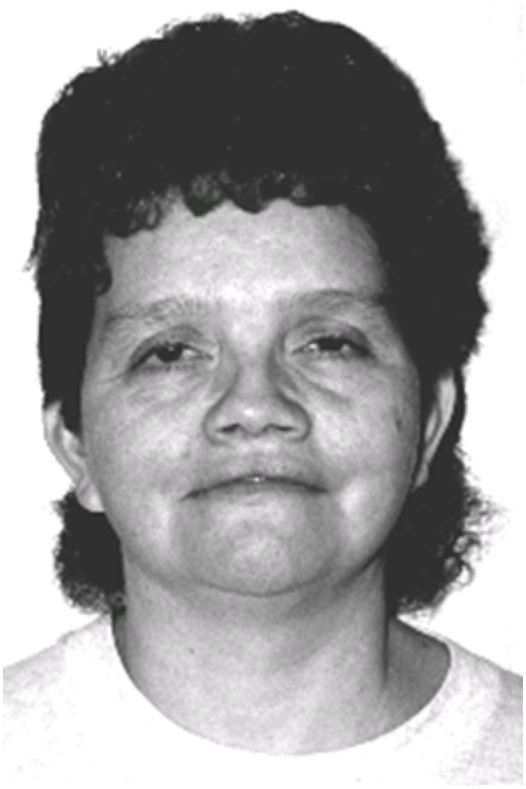

Figure 1. Typical facial features in a woman with Char syndrome

Reprinted with permission from Satoda et al [1999]

- The phenotypes associated with loss-of-function pathogenic variants often included PDA (32/40; 80%) but facial features of Char syndrome were less prevalent (23/39; 59%); features in these individuals not observed in those with missense variants included craniosynostosis (n = 3) and short stature (n = 2) [Massaad et al 2019, Timberlake et al 2019].

Penetrance

The penetrance of Char syndrome has not been formally determined. Two asymptomatic individuals with *TFAP2B* pathogenic variants have been described [Mani et al 2005, Timberlake et al 2019].

Prevalence

The prevalence of Char syndrome has not been determined but is thought to be quite low.

Genetically Related (Allelic) Disorders

TFAP2B pathogenic variants have been found in individuals with patent ductus arteriosus (PDA) but without other features of Char syndrome (nonsyndromic PDA; OMIM 617035) [Khetyar et al 2008, Chen et al 2011].

Differential Diagnosis

Facial features. The typical facial features associated with Char syndrome are usually striking and not often confused with facial features observed in other disorders. The facial profile is similar to that of maxillonasal dysplasia (Binder syndrome; OMIM 155050).

Hand anomalies. The hand anomalies associated with Char syndrome can be as minimal as fifth finger clinodactyly, which can be a normal finding and overlaps with numerous other syndromes.

Patent ductus arteriosus (PDA) constitutes about 10% of all congenital heart disease.

Isolated PDA (in the absence of other congenital heart defects) occurs in about one in 2,000 full-term infants. PDA is considerably more common in premature infants. It is one of the cardiac lesions observed in congenital rubella syndrome and may occur in autosomal dominant and recessive disorders that are nonsyndromic [Mani et al 2002].

Note: Screening of a group of individuals with isolated PDA rarely revealed the presence of *TFAP2B* pathogenic variants [Khetyar et al 2008, Chen et al 2011].

Heart-hand syndromes. See Table 3.

Table 3. Genes Associated with Heart-Hand Syndromes in the Differential Diagnosis of Char Syndrome

Gene(s)	Disorder	MOI	Congenital Heart Defects	Hand Abnormalities	Other Clinical Characteristics
CREBBP *EP300*	Rubinstein-Taybi syndrome	AD	Present in ~1/3 of affected persons; CHDs incl ASD, VSD, PDA, CoA.	Broad & often angulated thumbs & halluces	Distinctive facial features, short stature, & moderate-to-severe ID
DVL1 *DVL3* *WNT5A*	Autosomal dominant Robinow syndrome	AD	Present in <25% of affected persons; CHDs incl pulmonary valve stenosis/ atresia, ASD, VSD, & CoA.	Brachydactyly	Skeletal dysplasia; short stature; dysmorphic facial features resembling a fetal face
EVC *EVC2*	Ellis-van Creveld syndrome	AR	Present in 50-60% of affected persons; CHDs incl common atrium, mitral & tricuspid valve defects, PDA, VSD, & hypoplastic left heart syndrome.	Postaxial polydactyly	Short stature w/shortening of the long bones; hidrotic ectodermal dysplasia of the nails, hair, & teeth
GPC3 *GPC4*	Simpson-Golabi-Behmel syndrome type 1	XL	• CHDs variable; septal defects common • Pulmonic stenosis, CoA, transposition of the great vessels, & PDA or patent foramen ovale reported	Hand anomalies incl large hands & postaxial polydactyly.	Pre- & postnatal macrosomia; distinctive facies; variable visceral, skeletal, & neurodevelopmental abnormalities
RBM8A	Thrombocytopenia-absent radius syndrome	AR	Present in 15%-22% of affected persons (usually septal defects rather than complex cardiac malformations)	Thumbs of near-normal size but somewhat wider & flatter than usual; they are also held in flexion against the palm, & tend to have limited function.	Bilateral absence of the radii & thrombocytopenia (<50 platelets/nL) that is generally transient

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Congenital Heart Defects	Hand Abnormalities	Other Clinical Characteristics
ROR2	*ROR2* Robinow syndrome	AR	• Present in 15% of affected persons • CHDs include pulmonary valve stenosis/ atresia, ASD, VSD, CoA, tetralogy of Fallot, & tricuspid atresia • CHDs are the major cause of early death.	• Phalanges & carpal bones may be fused. • Partial cutaneous syndactyly or ectrodactyly (i.e., split hand) may be seen.	Face in early childhood resembling a fetal face at 8 wks' gestation; skeletal abnormalities; short stature
TBX3	Ulnar-mammary syndrome (OMIM 181450)	AD	VSD	Postaxial polydactyly; camptodactyly, missing digits	Hypoplastic or missing ulnae; hypoplasia of the apocrine & mammary glands; facial dysmorphia
TBX5	Holt-Oram syndrome	AD	Present in 75% of affected persons; CHDs most commonly involving the septum	Upper-limb malformations may be unilateral, bilateral/ symmetric, or bilateral/ asymmetric & range from triphalangeal or absent thumb(s) to phocomelia.	Cardiac conduction disease

AD = autosomal dominant; AR = autosomal recessive; ASD = atrial septal defect; CHD = congenital heart disease; CoA = coarctation of the aorta; ID = intellectual disability; MOI = mode of inheritance; PDA = patent ductus arteriosus; VSD = ventricular septal defect; XL = X-linked

Heart-hand disorders of unknown genetic etiology to consider:

- PDA and bicuspid aortic valve with hand anomalies (fifth metacarpal hypoplasia and brachydactyly), but normal facies (OMIM 604381). This disorder is genetically distinct from Char syndrome, documented using linkage exclusion for the TFAP2B locus.
- Tabatznik syndrome [Silengo et al 1990]
- Heart-hand syndrome type III (OMIM 140450)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Char syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Char Syndrome

System/Concern	Evaluation	Comment
Dental	Dental eval after age 3 yrs	To assess for hypodontia & other tooth anomalies
Eyes	Ophthalmology eval	To assess for strabismus & refractive error
Hearing	Audiology eval	To assess for hearing loss
Cardiovascular	Cardiac eval, usually incl echocardiogram	To screen for PDA &/or other cardiac anomalies [1]
Musculoskeletal	Physical exam for polydactyly, symphalangism, & syndactyly	Hand &/or foot radiographs may be considered.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Sleep	Assessment for sleep disorders incl abnormal movements during sleep	
Craniofacial	Assessment of head shape & size	Imaging may be needed if craniosynostosis suspected.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support & resources	Use of community or online resources such as Parent to Parent

PDA = patent ductus arteriosus
1. Evaluation in the newborn nursery may not be completely informative, as the ductus arteriosus may remain open for several days in any neonate.

Treatment of Manifestations

The most striking external aspects of Char syndrome, namely the dysmorphia and hand anomalies, require no special care early in life. The dysmorphic features do become important as affected individuals go through childhood and adolescence because of their stigmatizing effects. No data on the success of plastic surgical intervention for the facial features in Char syndrome are available.

Table 5. Treatment of Manifestations in Individuals with Char Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Hypodontia / Tooth anomalies	Standard treatment per orthodontist	
Strabismus / Refractive error	Standard treatment per ophthalmologist	
Hearing loss	Hearing aids may be helpful as per otolaryngologist	Community hearing services through early intervention or school district
PDA / Congenital heart defects	Management of PDA after immediate newborn period determined by degree of shunting from aorta to pulmonary artery	Surgical ligation or ductal occlusion at catheterization are treatment options.
Polydactyly, symphalangism, &/or syndactyly	Standard treatment per orthopedist	
Parasomnias	Standard treatment through a sleep disorders clinic	
Craniosynostosis	Standard treatment through plastic surgery	

PDA = patent ductus arteriosus

Surveillance

Children with Char syndrome need pediatric attention during infancy and childhood.

Table 6. Recommended Surveillance for Individuals with Char Syndrome

System/Concern	Evaluation	Frequency
Dental	Dental eval	Every 6 mos starting at age 3 yrs
Eyes	Vision screening	Annually or as clinically indicated in childhood
Hearing	Audiology eval	Annually or as clinically indicated in childhood

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Sleep	Assessment for signs & symptoms of sleep disorder	At each visit
Craniofacial	Monitor head shape & size in infancy.	At each visit during 1st yr of life

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 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

Char syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with Char syndrome have an affected parent.
- A proband with Char syndrome may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with Char syndrome caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent negative family history include molecular genetic testing (if a *TFAP2B* pathogenic variant has been identified in the proband), physical examination (focusing on the facial appearance, heart, and extremities), radiographs (if abnormalities of the hands or feet are detected), and echocardiogram if the cardiac exam is abnormal.
- If the proband has a known *TFAP2B* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.* Though theoretically possible, no instance of a proband inheriting a pathogenic variant from a parent with germline mosaicism has been reported.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with Char syndrome may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation and/or molecular

genetic testing (if the causative variant in the proband is known) to establish that neither parent is heterozygous for the causative pathogenic variant.

Sibs of a proband. The risk to sibs of a proband depends on the clinical/genetic status of the parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *TFAP2B* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but have not undergone molecular genetic testing (and/or a pathogenic variant has not been identified in the proband), the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for Char syndrome because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *TFAP2B* pathogenic variant has a 50% chance of inheriting the pathogenic variant and having Char syndrome.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have a *TFAP2B* pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

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

Molecular genetic testing. Once the *TFAP2B* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Char syndrome are possible.

Ultrasound examination. For pregnancies at increased risk, prenatal ultrasound examination may identify abnormal hands or feet as well as complex congenital heart defects. Since patent ductus arteriosus is a normal feature in fetuses, it has no diagnostic value in utero.

The prenatal finding of complex congenital heart disease could alter the management of the infant at birth as well as suggest a need to change the delivery site to a center able to provide urgent interventions for complex heart defects.

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.

- **The Children's Heart Foundation**
  Phone: 847-634-6474
  Email: info@childrensheartfoundation.org
  www.childrensheartfoundation.org

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. Char Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TFAP2B	6p12.3	Transcription factor AP-2-beta	TFAP2B database	TFAP2B	TFAP2B

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 Char Syndrome (View All in OMIM)

169100	CHAR SYNDROME; CHAR
601601	TRANSCRIPTION FACTOR AP2-BETA; TFAP2B

Molecular Pathogenesis

TFAP2B encodes a transcription factor belonging to the AP-2 class. AP-2 transcription factors act as dimers, either as homodimers (e.g., AP-2β/AP-2b) or as heterodimers (AP-2α/AP-2β). AP-2 dimers bind DNA sequence targets with their basic domains (also known as the DNA binding domain) and have transactivation domains, which affect the transcriptional effects.

Mechanism of disease causation. Evidence for dominant negative AND loss of function. The pathogenic missense variants associated with Char syndrome predominantly alter the basic domain. The effects of those missense alterations appear to be dominant negative, either through altered DNA binding of AP-2 dimers or altered transactivation [Satoda et al 2000, Zhao et al 2001]. In contrast, loss-of-function alleles are likely to act through haploinsufficiency.

Chapter Notes

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