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Trichohepatoenteric Syndrome

Synonyms: Phenotypic Diarrhea of Infancy, Syndromic Diarrhea/Tricho-Hepato-Enteric Syndrome (SD/THE), THES

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Summary

Clinical characteristics

Trichohepatoenteric syndrome (THES), generally considered to be a neonatal enteropathy, is characterized by intractable diarrhea (seen in almost all affected children), woolly hair (seen in all), intrauterine growth restriction, facial dysmorphism, and short stature. Additional findings include poorly characterized immunodeficiency, recurrent infections, skin abnormalities, and liver disease. Mild intellectual disability (ID) is seen in about 50% of affected individuals. Less common findings include congenital heart defects and platelet anomalies. To date 52 affected individuals have been reported.

Diagnosis/testing

The diagnosis of THES is established in a proband with biallelic pathogenic variants in either *SKIC3* (formerly *TTC37*) or *SKIC2* (formerly *SKIV2L*).

Management

Treatment of manifestations: To promote maximal weight gain and linear growth, most children initially require parenteral nutrition (PN). As tolerated, oral feeding (typically a semi-elemental diet) can be combined with PN. On the rare occasion that PN is unnecessary, anecdotal reports describe use of mainly an amino acid-based formula. To reduce the burden of infections, immunoglobulins can be supplemented in those with low immunoglobulin levels or immunoglobulin functional abnormalities. Individual management of ID is based on

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age-appropriate assessments of cognitive development, speech and language development, and psychosocial skills.

Surveillance: For children not receiving PN: close monitoring of nutritional status by a pediatric nutritionist to assure prompt intervention as needed. Yearly assessment of: diarrhea for changes that could suggest inflammatory bowel disease; liver function and size; immunoglobulin serum concentration and functionality; TSH level for evidence of hypothyroidism. Periodic assessment of: cognitive development, speech and language, and psychosocial skills for evidence of ID.

Genetic counseling

THES is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SKIC2* or *SKIC3* pathogenic variants have been identified in an affected family member, carrier testing of at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

To date, no diagnostic algorithm for trichohepatoenteric syndrome (THES) has been published.

Suggestive Findings

THES **should be suspected** in individuals with the following clinical findings [Fabre & Badens 2014, Fabre et al 2014]:

- **Growth failure.*** Intrauterine growth restriction (IUGR) / small for gestational age (SGA), short stature
- **Intractable/chronic diarrhea*** beginning in infancy that persists despite bowel rest or, on rare occasion, shows very early-onset inflammatory bowel disease (VEOIBD) of infancy. Endoscopic evaluation is often normal, but can resemble IBD. Intestinal biopsy findings range from mild villous atrophy to severe villous atrophy [Goulet et al 2008, Fabre et al 2014].
- **Woolly, brittle, easily breakable hair.** Hair analysis using light microscopy showed trichorrhexis nodosa in 42/52 individuals [Fabre & Badens 2014, Fabre et al 2014].
- **Immunodeficiency** that is poorly characterized, but typically low immunoglobulin levels and/or poor antibody production after immunization. Monoclonal hyper-IgA has been described [Fabre & Badens 2014, Fabre et al 2014, Rider et al 2015].
- **Liver disease,** mostly hepatomegaly and/or elevated liver enzymes; fibrosis or cirrhosis can occur. Hemochromatosis has been described, particularly when liver findings are significant [Verloes et al 1997, Hartley et al 2010].
- **Café au lait spots or dyschromic spots** have been described in nearly half of individuals reported [Fabre et al 2014]. Of note, a subset of affected individuals from the Arabian peninsula have pelvic, girdle, and lower-limb skin hyperpigmentation [Monies et al 2015].

* The association of neonatal intractable diarrhea and IUGR suggests the diagnosis of THES.

Establishing the Diagnosis

The diagnosis of THES **is established** in a proband with biallelic pathogenic (or likely pathogenic) variants in *SKIC2* (formerly *SKIV2L*) or *SKIC3* (formerly *TTC37*) (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can

be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SKIC2* or *SKIC3* variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (serial single-gene testing or a multigene panel) and **comprehensive genomic testing** 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 THES is broad, children with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with diarrhea, liver disease, and immunodeficiency will be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Serial single-gene testing.** Sequence analysis of *SKIC3* is performed first and – if no pathogenic variants are identified – followed by sequence analysis of *SKIC2*. If only one pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered; however, to date no exon or whole-gene deletions or duplications have been reported in either gene.
- **A multigene very early-onset IBD (VEOIBD) panel** that includes *SKIC2* and *SKIC3* and other genes of interest (see Differential Diagnosis) typically provides the best opportunity to identify the genetic cause of the condition while limiting identification of 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*; conversely, given the rarity of THES, some panels for diarrhea, hepatic disease, and immunodeficiency may not include these genes. (3) 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 phenotype is indistinguishable from many other inherited disorders with diarrhea, hepatic disease, and immunodeficiency, **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, although not yet easily analyzed in a clinical setting.

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 Trichohepatoenteric Syndrome

Gene [1]	Proportion of THES Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
SKIC2 (*SKIV2L*)	16/52 [5] (31%)	All variants reported to date	Unknown, none reported to date

Table 1. continued from previous page.

Gene [1]	Proportion of THES Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
SKIC3 (*TTC37*)	36/52 [6] (69%)	All variants reported to date	Unknown, none reported to date

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. 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.
5. n=6: Fabre et al [2012]; n=4: Monies et al [2015] (patients #1, 2, 3, 5); n=2: Lee et al [2016b] (patients LL, LF); n=1: Morgan et al [2013], Kammermeier et al [2014], Zheng et al [2016], Kammermeier et al [2017]
6. n=12: Hartley et al [2010]; n=9: Fabre et al [2011]; n=2: Kotecha et al [2012], Chong et al [2015], Lee et al [2016a], Kinnear et al [2017]; n=1: Bozzetti et al [2013], Kammermeier et al [2014], Monies et al [2015] (patient #4), Oz-Levi et al [2015], Rider et al [2015], Lee et al [2016b] (patient CHT), Kammermeier et al [2017]

Clinical Characteristics

Clinical Description

Trichohepatoenteric syndrome (THES) is considered a syndrome of neonatal enteropathy [Canani et al 2015]. THES is characterized by the association of intractable diarrhea (seen in almost all affected children), woolly hair (seen in all, but may not be obvious at a young age or due to cultural grooming practices), intrauterine growth restriction (IUGR), facial dysmorphism, and short stature, as well as poorly characterized immunodeficiency (sometimes with macrophage activation syndrome), recurrent infections, skin abnormalities, and liver disease. Intellectual disability (ID) is seen in about 50% of children. Less common findings include congenital heart defects and platelet anomalies. To date 52 affected individuals have been reported (see Table 1).

Intractable diarrhea usually begins in the first days of life but sometimes can be delayed until later in the first year of life. The diarrhea persists despite bowel rest (i.e., use of parenteral nutrition). Stools are watery; in rare cases blood can be found. The diarrhea leads to malabsorption and failure to thrive, which typically requires parenteral nutrition (see Management). To date, the diarrhea has appeared to be lifelong [Fabre & Badens 2014].

Very rarely, the clinical presentation can resemble so-called very early-onset inflammatory bowel disease (VEOIBD).

In the only instance in which immunodeficiency was reported to be the major clinical finding, the child never manifested the characteristic diarrhea [Rider et al 2015].

Woolly, brittle hair. Detailed clinical descriptions of the hair provided for 41 individuals included the following: woolly (n=22), poorly pigmented / light (n=18), easily removable / brittle (n=19), and unmanageable / unable to be combed (n=15) (e.g., Bozzetti et al [2013], Busoni et al [2017]).

Growth failure

- Intrauterine growth restriction (IUGR) / small for gestational age (SGA). Most children are below the 10th centile at birth either for height or for weight [Fabre & Badens 2014, Fabre et al 2014].

- Short stature. Despite adequate nutrition, the last recorded height in more than 50% of affected individuals was below the 3rd centile [Fabre & Badens 2014].

  Although to date no adult with THES has been described in detail, the heights in the three older individuals for whom that information was available were the following:

  - 148 cm (-2.36 SD) in a woman age 27 years [Martinez-Vinson 2004]
  - 171 cm (-0.74 SD) in a man age 18 years [Martinez-Vinson 2004]
  - -5 SD in a woman age 17 years [Barabino et al 2004]

Immunodeficiency. Children are prone to recurrent infection [Girault et al 1994, Martinez-Vinson 2004, Zheng et al 2016, Bick et al 2017]. Both viral infections (respiratory syncytial virus [Lee et al 2016a], Epstein Barr virus [Martinez-Vinson 2004, Fabre & Badens 2014]) and bacterial infections [Martinez-Vinson 2004, Rider et al 2015] have been reported.

Nine of 15 individuals with THES had a transient hemophagocytic syndrome / macrophage activation syndrome [Fabre & Badens 2014]; however, no specific data were provided about diagnosis or management.

Infection was implicated in the death of seven of 21 affected individuals.

Liver disease, found in about half of affected individuals, is mostly cirrhosis and fibrosis [Fabre et al 2014]. In seven of 17 individuals for whom the cause of death was described, liver disease (mostly liver failure or cirrhosis) was implicated [Girault et al 1994, Verloes et al 1997, Kinnear et al 2017]. One individual developed a hepatoblastoma [Bozzetti et al 2013].

Pathology showed iron overload and sometimes hemochromatosis [Hartley et al 2010, Fabre et al 2014]. In some instances, hemochromatosis improved with time [Fabre et al 2007].

Mild intellectual disability, described in about half of affected individuals [Goulet et al 2008, Fabre & Badens, Fabre et al 2014], is poorly characterized.

Brain MRI – when performed – appears normal [Fabre & Badens 2014].

Skin abnormalities. The most common are café au lait spots that preferentially appear on the lower limbs [Monies et al 2015]. Later in life, xerosis and/or rubbery skin can be observed.

Congenital cardiac defects, which are seldom seen, vary. The following were observed among 12 individuals with cardiac or aortic defects: ventricular septal defect (n=2) [Hartley et al 2010, Bick et al 2017]; atrial septal defect (n=2) [Chong et al 2015, Lee et al 2016a]; tetralogy of Fallot (n=1) [Hartley et al 2010]. Others had a bicuspid aortic valve with or without other anomalies, an aortic defect, or a mildly dilated aortic sinus.

Platelets can be enlarged with no known functional defect [Hartley et al 2010].

Facial dysmorphism that is mild and nonspecific is observed in nearly all affected individuals. The main findings (coarse features, a wide forehead, broad nasal root, and hypertelorism) can become more apparent with time [Fabre & Badens 2014, Fabre et al 2014].

Findings observed in a few affected individuals that could be part of the phenotypic spectrum of THES or unrelated findings include the following:

- Hypothyroidism. n=3/15 affected individuals [Fabre & Badens 2014]
- Dental abnormalities:
  - Peg teeth. n=2 [Monies et al 2015]
  - Narrow pointed teeth and dental dysplasia. n=2 [Fabre & Badens 2014]
- Inguinal hernia. n=2 [Hartley et al 2010, Fabre & Badens 2014]

One individual each:

- Small kidneys [Hartley et al 2010]
- Perthe syndrome [Hartley et al 2010]
- Glaucoma [Fabre & Badens 2014]
- Polycystic kidney [Fabre et al 2014]
- Thymus atrophy (in an individual without a molecular diagnosis) [Stankler et al 1982]

Phenotype Correlations by Gene

Current data suggest that individuals with biallelic pathogenic variants in either *SKIC2* (formerly *SKIV2L*) or *SKIC3* (formerly *TTC37*) are indistinguishable clinically.

Genotype-Phenotype Correlations

Because most pathogenic variants are private, genotype/phenotype correlations are difficult.

Of note, the phenotypes were indistinguishable in the five individuals with the recurrent *SKIC3* variant (Trp936Ter) and those with other *SKIC3* pathogenic variants [Fabre et al 2014].

Prevalence

THES is rare. To date about 50 affected individuals have been reported.

The best estimate of prevalence is 1:1,000,000 births, based on the French cohort of Fabre & Badens [2014].

Affected individuals have been reported worldwide.

As with all autosomal recessive disorders, the prevalence may be increased in highly consanguineous populations.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SKIC2* (formerly *SKIV2L*) or *SKIC3* (formerly *TTC37*).

Differential Diagnosis

Table 3. Monogenic Disorders with Intractable Diarrhea to Consider in the Differential Diagnosis of Trichohepatoenteric Syndrome

Disorder	Gene	MOI	Distinguishing Clinical Features of Differential Diagnosis Disorder
Congenital tufting enteropathy (OMIM 613217)	*EPCAM*	AR	Specific intestinal pathology (tuft)
IPEX syndrome	*FOXP3*	XL	Low regulatory T cells
Gastrointestinal defects and immunodeficiency syndrome (OMIM 243150)	*TTC7A*	AR	Duodenal atresia
Syndromic congenital tufting enteropathy (OMIM 270420)	*SPINT2*	AR	Specific intestinal pathology (tuft) Choanal atresia

AR = autosomal recessive; IPEX = *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked; MOI = mode of inheritance; XL = X-linked

See Diarrhea, congenital: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with trichohepatoenteric syndrome (THES), the following evaluations are recommended:

- Nutritional evaluation by a specialist pediatric nutritionist
- Immunologic assessment with serum IgG, IgM, IgA; immunophenotyping; if immunization has been performed before, evaluation of the level of specific antibodies to detect a rapid loss of protective antibodies, which would require immunoglobulin supplementation
- Liver assessment: ultrasound evaluation; assessment of liver enzymes (ALT/AST, GGT); in case of abnormalities, consult a pediatric hepatologist for recommendations on additional investigations
- Cardiac evaluation for congenital malformations
- Age-appropriate assessment of cognitive development, speech and language development, and psychosocial skills
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No specific treatment is available. The goals of the treatment are to promote maximal weight gain and linear growth, to reduce the burden of infections, and to provide individual management of intellectual disability.

Weight gain. Most children, when first diagnosed, require parenteral nutrition (PN) to achieve appropriate weight gain and catch-up growth. Although PN is usually required, it can be combined (as tolerated) with oral feeding – typically a semi-elemental diet [Goulet et al 2008]. About 30%-50% of affected individuals can become independent of parenteral nutrition after prolonged PN. Of note, promotion of oral feeding as tolerated (rather than enteral tube feeding) should help prevent future eating disorders.

To date nine individuals have been reported in whom PN was unnecessary [Kotecha et al 2012, Chong et al 2015, Rider et al 2015, Lee et al 2016a, Mahjoub et al 2016, Zheng et al 2016]. In three of the nine, the diet was an amino acid formula [Lee et al 2016a, Lee et al 2016b, Zheng et al 2016]; it is not clear if weight gain was adequate, or if catch-up growth was achieved.

When early-onset manifestations are those of inflammatory bowel disease (IBD), infections should be ruled out and routine management of IBD with steroids, azathioprine, and anti-TNF (tumor necrosis factor) antibody can be considered; however, this routine IBD management may result in only transient improvement, or no improvement [Busoni et al 2017, Kammermeier et al 2017].

Growth. Anecdotal experience shows no efficacy of growth hormone treatment [Fabre & Badens 2014].

Infection. Immunoglobulin supplementation for those with low immunoglobulin levels appears to lower the rate of infection [Fabre et al 2014, Rider et al 2015].

Of note, hematopoietic stem cell transplantation (HSCT) – reported twice to date – has been unsuccessful: one individual succumbed to infection [Girault et al 1994] and the other showed only mild improvement [Kammermeier et al 2014].

Intellectual disability is managed specifically according to the results of age-appropriate assessments of cognitive development, speech and language development, and psychosocial skills.

Tooth shape abnormalities. Evaluation of abnormal dentition in children is especially important because teeth are required for development of speech, nutrition, self-esteem, and well-being. The National Foundation for Ectodermal Dysplasias (NFED) website provides further resources and information.

Hair changes. Fragile hair and hair loss can have a deeper-than-expected emotional impact on an affected individual and family. Counseling may be helpful. Also, hair prosthetics (wigs) are available through Locks of Love and other organizations; some insurance provides two wigs per year in growing children with alopecia. A prescription for a cranial prosthesis may or may not aid insurance reimbursement.

Surveillance

Although there are no consensus guidelines, the following surveillance is recommended:

- For children not receiving parenteral nutrition, close monitoring of nutritional status by a pediatric nutritionist to assure prompt intervention should nutritional deficiency become a concern
- Yearly assessment of the following main features:
  - Diarrhea. If the nature of the diarrhea changes (e.g., appearance of bloody diarrhea), investigation of possible inflammatory bowel disease (IBD) is warranted [Busoni et al 2017].
  - Liver function. Ultrasound examination and measurement of liver enzymes (AST, ALT, GGT), International Normalized Ratio (INR), and bilirubin
  - Serum concentration of IgG, IgM, IgA, and immunoglobulin functionality (i.e., immunophenotyping) even if results at the time of initial evaluation were normal. Consultation with an immunologist is warranted if immunoglobulin levels are low or if normal immunoglobulin levels are associated with a loss of specific protective antibody.
  - TSH level for evidence of hypothyroidism
- Assessment of cognitive development, speech and language, and psychosocial skills for evidence of intellectual disability at ages 2, 4, 8, 12, and 15 years unless concerns appear earlier
- As evolution of the dermatologic features (mostly hypo- or hyperpigmented patches and hair abnormalities) is unknown, regular evaluation by a dermatologist seems reasonable.

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

Trichohepatoenteric syndrome (THES) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SKIC2* [formerly *SKIV2L*] or *SKIC3* [formerly *TTC37*] pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with THES syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *SKIC2* or *SKIC3*.
- To date, no individuals with THES syndrome have had children; however, many affected individuals have not yet reached reproductive age.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SKIC2* or *SKIC3* pathogenic variant.

Carrier Detection

Carrier testing for relatives at risk requires prior identification of the *SKIC2* or *SKIC3* pathogenic variants in the family.

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 affected, are carriers, or are at risk of being carriers.

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SKIC2* or *SKIC3* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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**
  Trichohepatoenteric syndrome

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. Trichohepatoenteric Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SKIC2	6p21.33	Superkiller complex protein 2	SKIV2L @ LOVD	SKIC2	SKIC2
SKIC3	5q15	Superkiller complex protein 3	TTC37 database	SKIC3	SKIC3

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 Trichohepatoenteric Syndrome (View All in OMIM)

222470	TRICHOHEPATOENTERIC SYNDROME 1; THES1
600478	SKI2 SUBUNIT OF SUPERKILLER COMPLEX; SKIC2
614589	SKI3 SUBUNIT OF SUPERKILLER COMPLEX; SKIC3
614602	TRICHOHEPATOENTERIC SYNDROME 2; THES2

Molecular Pathogenesis

Trichohepatoenteric syndrome (THES) is caused by loss of function of either protein in the human Ski complex: SKIC3 (a TPR-containing protein) or SKIC2 (an RNA helicase). The Ski complex, a heterotetrameric cytoplasmic cofactor of the RNA exosome in eukaryotic and archeal (prokaryotic) cells, is required for exosome-mediated RNA surveillance including the regulation of normal mRNA and decay of nonfunctional mRNA [Brown et al 2000].

Subsequently Eckard et al [2014] have suggested that SKIC2 and SKIC3 have different and independent functions as the cells of persons with *SKIC2* (formerly *SKIV2L*) pathogenic variants have an interferon 1 signature whereas cells from persons with *SKIC3* (formerly *TTC37*) pathogenic variants do not.

SKIC2

Gene structure. The *SKIC2* transcript NM_006929.4 has 28 exons.

Pathogenic variants. The majority of pathogenic variants are nonsense or small deletions or insertions.

Normal gene product. The helicase SKI2W protein NP_008860.4 comprises 1,246 amino acids, has helicase with ATPase activity, and is thought to be involved in exosome-mediated RNA decay.

Abnormal gene product. See discussion of human SKI complex above.

SKIC3

Gene structure. The transcript NM_014639.3 comprises all 43 exons, the first three of which are noncoding.

Pathogenic variants are missense, nonsense, or splice abnormalities.

Normal gene product. The tetratrichopeptide repeat protein 37 (NP_055454.1) comprises 1,564 amino acids.

The protein contains 20 TRP repeated domains. TPR repeats (which mediate protein-protein interactions and the assembly of multiprotein complexes) are a component of the SKI complex involved in exosome-mediated RNA decay.

Abnormal gene product. Pathogenic variants of *SKIC3* have reduced or absent protein expression or proteins that are mislocalized in cells.

Chapter Notes

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