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NTHL1 Tumor Syndrome

Synonym: *NTHL1*-Associated Polyposis

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Summary

Clinical characteristics

NTHL1 tumor syndrome is characterized by an increased lifetime risk for colorectal cancer (CRC), breast cancer, and colorectal polyposis. Colorectal polyps can be adenomatous, hyperplastic, and/or sessile serrated. Duodenal polyposis has also been reported. Additional cancers reported in individuals with *NTHL1* tumor syndrome include endometrial cancer, cervical cancer, urothelial carcinoma of the bladder, meningiomas, unspecified brain tumors, basal cell carcinomas, head and neck squamous cell carcinomas, and hematologic malignancies. The cumulative lifetime risk of developing extracolonic cancer by age 60 years has been estimated at 35% to 78%.

Diagnosis/testing

The diagnosis is established in a proband by identification of germline biallelic pathogenic variants in *NTHL1* on molecular genetic testing.

Management

Treatment of manifestations: Colorectal polyps should be removed (polypectomy) until polypectomy alone cannot manage the large size and density of the polyps. At that point, either subtotal colectomy or proctocolectomy is performed based on polyp features and location. Large duodenal polyps or those polyps showing dysplasia or villous changes should be excised during endoscopy.

Surveillance: Due to the limited number of affected individuals reported, surveillance recommendations are likely to evolve. They currently include: colonoscopy with polypectomy every two years beginning at age 18-20 years; breast MRI examination annually between ages 30 and 60 years; mammography annually between ages 40 and 50 years, then every two years between ages 50 and 75 years; transvaginal ultrasound examination and

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endometrial biopsy to screen for endometrial cancer every two years between ages 40 and 60 years; upper endoscopy and side-viewing duodenoscopy every five years beginning at age 25 years.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an individual who has germline biallelic *NTHL1* pathogenic variants in order to identify as early as possible those who would benefit from appropriate surveillance, early diagnosis, and treatment of *NTHL1*-associated tumors.

Genetic counseling

NTHL1 tumor syndrome 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 a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Formal diagnostic criteria for *NTHL1* tumor syndrome have not been established.

Suggestive Findings

NTHL1 tumor syndrome **should be suspected** in an individual with the following clinical findings, family history, and/or molecular genetic findings on tumor tissue.

Clinical findings

- Presence of multiple primary cancers before age 50 years, especially including breast, colon, or urothelial cell cancer, brain tumors, head and neck squamous cell carcinoma, hematologic malignancies, endometrial malignancies and premalignancies, and/or basal cell carcinoma
- Colorectal cancer (CRC) diagnosed before age 40 years
- One or more colorectal adenomas in an individual age ≤40 years
- A personal cumulative lifetime history of ten or more colorectal adenomas in an individual age ≤60 years
- A personal cumulative lifetime history of any combination of 20 or more colorectal adenomas, hyperplastic polyps, and/or sessile serrated polyps in an individual of any age

Family history is consistent with autosomal recessive inheritance of multiple cancers (especially when including breast, colorectal, or urothelial cell cancer, brain tumors, head and neck squamous cell carcinoma, hematologic malignancies, endometrial malignancies and premalignancies, and/or basal cell carcinoma).

Molecular genetic findings on tumor tissue. A specific mutational signature due to a high percentage of somatic C>T transversions (e.g., COSMIC Signature 30) is identified on tumor tissue testing [Grolleman et al 2019].

Establishing the Diagnosis

The diagnosis of *NTHL1* tumor syndrome **is established** in a proband with biallelic germline *NTHL1* pathogenic variants identified on molecular genetic testing [Weren et al 2015] (see Table 1).

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *NTHL1* tumor 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 *NTHL1* tumor syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When phenotypic findings suggest the diagnosis of *NTHL1* tumor syndrome, molecular genetic testing approaches can include use of a **multigene panel** or **single-gene testing**:

- **A CRC and polyposis multigene panel** that includes *NTHL1*, *APC*, *MUTYH*, and other genes of interest (see Differential Diagnosis) is most likely to identify *NTHL1* tumor syndrome 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*. Of note, given the rarity of *NTHL1* tumor syndrome, some cancer-predisposition multigene panels may not include *NTHL1*. (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.

- **Single-gene testing.** Sequence analysis of *NTHL1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Sequence analysis of all six exons of *NTHL1* is recommended. No large exon or whole-gene deletions or duplications in *NTHL1* have yet been reported, but their contribution to *NTHL1* tumor syndrome cannot be excluded. Therefore, copy number analysis is recommended, particularly when only one germline *NTHL1* pathogenic variant has been identified in an individual with findings suggestive of *NTHL1* tumor syndrome.

Option 2

When the diagnosis of *NTHL1* tumor 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 most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, an **exome array** (when clinically available) may be considered to detect the known pathogenic variants as well as (multi)exon deletions or duplications. Thus far, *NTHL1* copy number aberrations have not been described in individuals with *NTHL1* tumor syndrome.

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 *NTHL1* Tumor Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
NTHL1	Sequence analysis [3]	23/23 [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Rivera et al [2015], Weren et al [2015], Chubb et al [2016], Belhadj et al [2017], Fostira et al [2018], Altaraihi et al [2019], Belhadj et al [2019], Grolleman et al [2019], Groves et al [2019]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

NTHL1 tumor syndrome has been described in 20 families including 33 affected individuals [Rivera et al 2015, Weren et al 2015, Belhadj et al 2017, Broderick et al 2017, Fostira et al 2018, Altaraihi et al 2019, Belhadj et al 2019, Grolleman et al 2019, Groves et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Colon polyps. The 24 individuals reported by Grolleman et al [2019] who had been evaluated by colonoscopy were all found to have adenomatous polyps (range 1-100). Seven of these individuals had hyperplastic/sessile serrated polyps.

Colorectal cancer (CRC). Nineteen of 33 individuals reported to date developed CRC. The median age of onset was 61 years (range 33-73 years). Nine individuals were diagnosed with CRC before age 50 years [Fostira et al 2018, Belhadj et al 2019, Grolleman et al 2019]. CRC in individuals with *NTHL1* tumor syndrome was mostly right-sided, but has been observed throughout the colon, from the rectum to the appendix [Rivera et al 2015, Weren et al 2015, Belhadj et al 2017, Grolleman et al 2019]. Metachronous or synchronous tumors were identified in six individuals [Grolleman et al 2019]. The limited number of families and the presence of a selection bias in the individuals reported to date hamper accurate cancer risk analysis. In the absence of timely surveillance, the lifetime risk for CRC in individuals with *NTHL1* tumor syndrome is likely to be high.

Breast cancer was observed in nine of 15 women with *NTHL1* tumor syndrome with a median age of onset of 49 years (range 38-63 years) [Grolleman et al 2019]. Three women had bilateral breast cancer. The reported subtypes included ductal, lobular, and mixed ductal/papillary. Hormone receptor status (triple negative) was reported in one individual.

Duodenal polyps and cancer. Multiple duodenal polyps were reported in two individuals with *NTHL1* tumor syndrome [Weren et al 2015, Fostira et al 2018]. One individual also developed esophageal polyps. Another individual developed duodenal cancer at age 52 years [Weren et al 2015].

Other cancers. Endometrial cancer has been diagnosed in five of the 17 women with *NTHL1* tumor syndrome reported thus far, with a median age of diagnosis of 57 years (range 47-74 years). Additional cancers reported in individuals with *NTHL1* tumor syndrome include cervical cancer, urothelial carcinoma of the bladder,

meningiomas, unspecified brain tumors, basal cell carcinomas, head and neck squamous cell carcinomas, and hematologic malignancies [Rivera et al 2015, Weren et al 2015, Belhadj et al 2017, Grolleman et al 2019]. Grolleman et al [2019] reported the presence of multiple primary tumors in 16 of 29 individuals (55%). Based on these findings, the cumulative lifetime risk of developing extracolonic cancer by age 60 years was estimated at 35% to 78% (95% CI) [Grolleman et al 2019].

Benign extraintestinal manifestations reported in some individuals include: skin hemangiomas, seborrheic keratosis, and intradermal nevi; ovarian and hepatic cysts; and breast papillomas. To date, the number of individuals reported with these features is low and an association with *NTHL1* tumor syndrome is as yet unclear.

***NTHL1* heterozygotes.** The risk of developing CRC or other malignancy in individuals with a heterozygous germline *NTHL1* pathogenic variant is unclear. In the eleven families reported by Grolleman et al [2019], three confirmed heterozygotes developed cancer. A previously reported individual with breast cancer was found to have a germline heterozygous *NTHL1* variant (p.Gln287Ter) and loss of heterozygosity in tumor tissue [Nik-Zainal et al 2016, Drost et al 2017].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

This condition has been referred to as *NTHL1* polyposis and familial adenomatous polyposis 3 (OMIM 616415), terms which emphasize the similarity with *MUTYH* polyposis [Belhadj et al 2017, Groves et al 2019, Valle et al 2019]. Considering the broad tumor spectrum reported in individuals with biallelic *NTHL1* pathogenic variants, and the fact that the diagnosis has been identified in individuals without CRC and/or (suspected) polyposis, the term *NTHL1* tumor syndrome is preferred.

Prevalence

The prevalence of *NTHL1* tumor syndrome is unknown. Based on the prevalence of *NTHL1* pathogenic variants in the population, it has been estimated that in Europeans, *NTHL1* tumor syndrome would occur with a frequency approximately one fifth (1:114,770) that of *MUTYH* polyposis (1:19,079) [Weren et al 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *NTHL1*.

Differential Diagnosis

Table 2. Genes to Consider in the Differential Diagnosis of *NTHL1* Tumor Syndrome

MOI	Gene(s) [1]	DiffDx Disorder	Clinical Features of DiffDx Disorder	
			Overlapping w/*NTHL1* tumor syndrome	Distinguishing from *NTHL1* tumor syndrome
AR	*MSH3*	Familial adenomatous polyposis 4 (OMIM 617100)	• ↑ CRC risk • 10-100 adenomas • Duodenal adenomas	No other cancer risk reported
	MUTYH	*MUTYH* polyposis	• ↑ CRC risk • Usually 10-100 adenomas • Serrated polyps also observed • Duodenal adenomas	
AD	*APC*	Attenuated familial adenomatous polyposis	• ↑ CRC risk • Usually 10-100 adenomas • Duodenal adenomas	Extracolonic manifestations (e.g., desmoid tumors, fundic gland polyps, congenital hypertrophy of retinal pigmented epithelium, dental abnormalities, fibromas, lipomas, & osteomas)
	BMPR1A *SMAD4*	Juvenile polyposis syndrome	↑ CRC risk	• GI hamartomatous (juvenile) polyps • ↑ risk of cancers of upper GI tract & pancreas • Hereditary hemorrhagic telangiectasia (*SMAD4*-related)
	EPCAM *MLH1* *MSH2* *MSH6* *PMS2*	Lynch syndrome	• ↑ CRC risk • Endometrial cancer	• Usually <10 adenomas • ↑ risk for ovarian cancer • Sebaceous skin tumors • Mismatch repair deficient tumors
	Duplication upstream of *GREM1*	Hereditary mixed polyposis syndrome (OMIM 601228)	• Adenomatous polyps • ↑ CRC risk	Mixed polyposis (hyperplastic, atypical juvenile & adenomatous polyps)
	POLD1	CRC, susceptibility to, 10 (OMIM 612591)	• 10-100 adenomas • ↑ CRC & endometrial cancer risk	Astrocytoma risk
	POLE	CRC, susceptibility to, 12 (OMIM 615083)	• 10-100 adenomas • ↑ CRC, ureter, & endometrial cancer	↑ risk for ovarian, gastric cancer, & astrocytoma
	PTEN	*PTEN* hamartoma tumor syndrome	↑ CRC, breast, & endometrial cancer risk	• Multiple hamartomatous & mixed polyps in GI tract • Macrocephaly, lipomas of the skin & multinodular goiter • ↑ risks for melanoma, thyroid, & renal cancers
	STK11	Peutz-Jeghers syndrome	↑ CRC & breast cancer risk	• GI hamartomatous polyps, most often in small bowel • Typical mucocutaneous pigmentation • ↑ risk for lung, gastric, pancreas, & sex organ cancers

Table 2. continued from previous page.

MOI	Gene(s) [1]	DiffDx Disorder	Clinical Features of DiffDx Disorder	
			Overlapping w/*NTHL1* tumor syndrome	Distinguishing from *NTHL1* tumor syndrome
	TP53	Li-Fraumeni syndrome	↑ CRC & breast cancer risk	↑ risk for sarcoma, lung cancer, adrenocortical carcinoma, choroid plexus carcinoma, & additional cancers

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; GI = gastrointestinal; MOI = mode of inheritance; CRC = colorectal cancer

1. Listed by mode of inheritance, then alphabetically by gene

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NTHL1* tumor syndrome, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Due to the lifelong increased cancer risk and the diversity of tumors associated with *NTHL1* tumor syndrome, evaluations for cancer in individuals with *NTHL1* tumor syndrome need to be ongoing and comprehensive (see Surveillance). Individuals with *NTHL1* tumor syndrome should seek a cancer genetics consultation to review the diagnosis and medical management recommendations.

Treatment of Manifestations

In general, the treatment regarding gastrointestinal tumors is similar to that of familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (AFAP) (see *APC*-Associated Polyposis Conditions).

Colon polyps and colon cancer. Colonoscopy is effective surveillance for colon cancer; polyps should be removed (polypectomy) until polypectomy alone cannot manage the large size and density of the polyps. At that point, either subtotal colectomy or proctocolectomy is performed based on polyp features and location [Lipton & Tomlinson 2006, Sampson & Jones 2009].

Breast cancer, endometrial cancer, and other cancers. The treatment for these cancers in individuals with *NTHL1* tumor syndrome is the same as for that of the general population.

Duodenal polyps. Management of polyps is similar to that in individuals with FAP. In particular, large polyps or those polyps showing dysplasia or villous changes should be excised during endoscopy.

Surveillance

Table 3. Recommended Surveillance for Individuals with *NTHL1* Tumor Syndrome

Concern	Evaluation	Frequency
Colon cancer	Colonoscopy	Every 2 yrs starting at age 18-20 yrs
Breast cancer	Breast MRI	Annually between ages 30 & 60 yrs; MRI sensitivity is greater than that of mammography.
	Mammography	• Annually between ages 40 & 50 yrs • Every 2 yrs between ages 50 & 75 yrs
Endometrial cancer	Transvaginal ultrasound exam & endometrial biopsy	Every 2 yrs between ages 40 & 60 yrs

Table 3. continued from previous page.

Concern	Evaluation	Frequency
Duodenal polyps/cancer	Upper endoscopy	Starting at age 25 yrs; frequency per Spigelman criteria (at least every 5 yrs) [Spigelman et al 1989]

Individuals heterozygous for a germline *NTHL1* pathogenic variant. To date, there is no evidence that *NTHL1* heterozygotes are at increased risk for cancer and there are no specific screening recommendations for heterozygous relatives of individuals with *NTHL1* tumor syndrome. *NTHL1* heterozygotes are advised to participate in population screening measures for colorectal cancer and breast cancer, or could be offered screening based on their family history (e.g., incidence of CRC and/or breast cancer in family members who do not have biallelic *NTHL1* pathogenic variants).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an individual who has biallelic germline *NTHL1* pathogenic variants in order to identify as early as possible those who would benefit from appropriate surveillance (beginning at age 18 years), early diagnosis, and treatment of *NTHL1*-associated tumors.

In general, molecular genetic testing for *NTHL1* tumor syndrome is not recommended for at-risk individuals younger than age 18 years. However, predictive testing should be considered if there is a history of early-onset cancer in the family. For unaffected individuals with biallelic *NTHL1* pathogenic variants, screening should begin by age 18 years, or two to five years earlier than the earliest diagnosis in the family [NCCN 2016]. Therefore, a history of early cancers in the family may warrant testing prior to age 18.

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

NTHL1 tumor syndrome is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *NTHL1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for an *NTHL1* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo*

variants are known occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- The risk for cancer in individuals with a heterozygous germline *NTHL1* pathogenic variant is unclear; however, available data do not suggest that heterozygous individuals are at increased risk for colorectal cancer or breast cancer (see Management, Surveillance).

Sibs of a proband

- If each parent is known to be heterozygous for an *NTHL1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of not being a carrier.
- The risk of cancer in individuals with a heterozygous germline *NTHL1* pathogenic variant is unclear; however, available data do not suggest that heterozygous individuals have an increased risk for colorectal cancer or breast cancer (see Management, Surveillance).

Offspring of a proband. Provided the reproductive partner of the proband is not a carrier of an *NTHL1* pathogenic variant, the offspring of an individual with *NTHL1* tumor syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *NTHL1*. Given the very low carrier frequency of *NTHL1* pathogenic variants (see Prevalence), it is unlikely that the reproductive partner of the proband is a carrier of an *NTHL1* pathogenic variant unless consanguinity is a factor.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *NTHL1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *NTHL1* pathogenic variants in the family.

Note: If consanguinity is a factor, the reproductive partner of an individual with one or two *NTHL1* pathogenic variants can be offered *NTHL1* sequence analysis to clarify the risk for *NTHL1* tumor syndrome in their offspring.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of appropriate surveillance, early diagnosis, and treatment of *NTHL1*-associated tumors.

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.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – Health Professional Version (part of PDQ®, National Cancer Institute).

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *NTHL1* pathogenic variants have been identified in an affected family member.

- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- In general, genetic testing for *NTHL1* tumor syndrome is not recommended for at-risk individuals younger than age 18 years. However, predictive testing should be considered if there is a history of early-onset cancer in the family. In asymptomatic individuals with biallelic *NTHL1* pathogenic variants, screening is recommended beginning at age 18 years, or two to five years prior to the earliest diagnosis in the family [NCCN 2016]. Therefore, a history of early cancers in the family may warrant testing prior to age 18.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

Prenatal Testing and Preimplantation Genetic Testing

If the reproductive partner of a proband (or carrier) is also known to have one or two *NTHL1* pathogenic variants, prenatal testing for a pregnancy at increased risk 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.

- **American Cancer Society**

  Phone: 800-227-2345

  cancer.org

- **Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC)**

  cgaigc.com

- **Colorectal Cancer Alliance**

  Phone: 877-422-2030

  colorectalcancer.org

- **Fight Colorectal Cancer**

  Phone: 703-548-1225

  fightcolorectalcancer.org

- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**

  insight-group.org

- **National Cancer Institute (NCI)**
  Email: NCIinfo@nih.gov
  Colorectal Cancer—Patient Version
- **United Ostomy Associations of America, Inc.**
  Phone: 800-826-0826
  ostomy.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. NTHL1 Tumor Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
NTHL1	16p13.3	Endonuclease III-like protein 1	NTHL1	NTHL1

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 NTHL1 Tumor Syndrome (View All in OMIM)

602656	ENDONUCLEASE III-LIKE 1; NTHL1
616415	FAMILIAL ADENOMATOUS POLYPOSIS 3; FAP3

Molecular Pathogenesis

The protein encoded by *NTHL1* is a DNA glycosylase of the base-excision-repair pathway that removes endogenously damaged nucleotides in DNA [Robertson et al 2009]. Various DNA glycosylases target different types of damage caused by oxidation, deamination, or alkylation. NTHL1 specifically targets oxidized pyrimidine residues in DNA and has apurinic/apyrimidinic lyase activity [Wallace et al 2012]. Subsequently, the repair process completes with the incorporation of the correct nucleotide or elongation of multiple nucleotides by a DNA polymerase and sealing of the remaining nick by a DNA ligase [Svilar et al 2011, Wallace et al 2012, Krokan et al 2014].

NTHL1 tumor syndrome is an autosomal recessive condition caused by biallelic *NTHL1* pathogenic variants. Thus far, all nine identified variants are either stop-gain, frameshift-, or splice site variants, likely resulting in disruption of both alleles. Therefore, in affected individuals every cell is NTHL1 deficient, resulting in slow but progressive accumulation of somatic pathogenic variants, thereby increasing the risk of cancer in tissues that are most vulnerable to this type of damage.

Mechanism of disease causation. Currently, the nine different *NTHL1* pathogenic variants identified in *NTHL1* tumor syndrome lead to premature stop codons (see Table 4).

Individuals with biallelic *NTHL1* loss-of-function pathogenic variants develop tumors that have somatic pathogenic variants strongly biased towards C>T transitions, predominantly at non-CpG sites [Weren et al 2015]. Analysis of the somatic mutational patterns in NTHL1-deficient colon organoid clones and in multiple tumors of persons with biallelic germline *NTHL1* pathogenic variants revealed that loss of NTHL1 function elicits a specific mutational signature [Grolleman et al 2019]. The resulting mutational process is most prominent in tissues with higher proliferation rates and/or higher rates of oxidative damage, and increases the chance that

cancer-driver genes are hit by a pathogenic variant. Establishing the mutational pattern in tumor tissue can be of help in proving the pathogenicity of (novel) *NTHL1* variants.

Table 4. Notable *NTHL1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002528.6 NP_002519	c.268C>T	p.Gln90Ter	Founder/recurrent variant [1] [Weren et al 2018, Grolleman et al 2019]
	c.235_236insG	p.Ala79GlyfsTer2	
	c.390>A	p.Tyr130Ter	
	c.545G>A	p.Trp182Ter	
NM_002528.6	c.550-1G>A		Loss splice donor site
NM_002528.6 NP_002519	c.709+1G>A	p.Gly201_Ile236del	
	c.733dup	p.Ile245AsnfsTer28	
	c.806G>A	p.Trp269Ter	
	c.859C>T	p.Gln287Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. This variant is common in the Dutch population, but has also been observed in affected individuals from different ethnic groups, suggesting that there may be multiple independent founders. Fifteen reported families have been homozygous for this variant [Chubb et al 2016, Belhadj et al 2017, Fostira et al 2018, Altaraihi et al 2019, Grolleman et al 2019, Groves et al 2019]

Chapter Notes

Revision History

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