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POT1 Tumor Predisposition

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Summary

Clinical characteristics

POT1 tumor predisposition (*POT1*-TPD) is characterized by an increased lifetime risk for multiple cutaneous melanomas, chronic lymphocytic leukemia (CLL), angiosarcoma (particularly cardiac angiosarcomas), and gliomas. Additional cancers (e.g., colorectal cancer, thyroid cancer, breast angiosarcomas) have been reported in individuals with *POT1*-TPD but with very limited evidence. The age of onset for first primary cutaneous melanoma ranges from 15 to 80 years. The majority of *POT1* associated cancers are diagnosed in adulthood.

Diagnosis/testing

The diagnosis of *POT1*-TPD is established in a proband with suggestive findings and a heterozygous germline pathogenic variant in *POT1* identified by molecular genetic testing.

Management

Treatment of manifestations: The treatments for *POT1*-TPD tumors are those used in standard practice.

Surveillance: Full skin examination by a dermatologist beginning at age 18 years at least every six months with excision of any lesions suspicious for melanoma; consider exams every three months in individuals with multiple atypical nevi, history of melanoma, and/or family history of melanoma. CBC with differential annually beginning at age 18 years to screen for CLL. Annual comprehensive physical examination including examination of lymph nodes. Whole-body MRI annually in families fulfilling Li-Fraumeni syndrome or Li-Fraumeni-like criteria beginning at age 18 years; Consider whole-body MRI every one to two years depending on personal and family history of non-cutaneous, non-brain malignancies. Consider brain MRI every one to two years beginning at age 18 years depending on family history of glioma.

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Agents/circumstances to avoid: Tanning bed use and unprotected sun exposure. Avoid radiation in diagnostic procedures.

Evaluation of relatives at risk: Molecular genetic testing for the familial *POT1* pathogenic variant should be offered to first-degree relatives to identify those who would benefit from early surveillance and intervention. Although molecular genetic testing for *POT1*-TPD is generally not recommended for at-risk individuals younger than age 18 years, a history of early cancers in the family may warrant predictive testing prior to age 18.

Genetic counseling

POT1-TPD is inherited in an autosomal dominant manner. To date, most individuals diagnosed with *POT1*-TPD have an affected parent; the proportion of *POT1*-TPD caused by a *de novo* pathogenic variant is unknown. Each child of an individual with *POT1*-TPD has a 50% chance of inheriting the *POT1* pathogenic variant. It is important to note that clinical manifestations of *POT1*-TPD cannot be predicted in heterozygous family members because the full phenotypic spectrum and penetrance of *POT1*-TPD are unknown. The types of *POT1*-related tumors can vary among different members of the same family and current evidence is limited to disease-focused studies. Once the germline *POT1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for *POT1*-TPD and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

POT1 tumor predisposition (*POT1*-TPD) **should be suspected** in an individual with the following:

- Multiple cutaneous melanomas
- One of the *POT1*-TPD core cancers and a first- or second-degree relative with a confirmed *POT1*-TPD core cancer. *POT1*-TPD core cancers include cutaneous melanoma, chronic lymphocytic leukemia, angiosarcoma, and glioma.
- A *POT1* pathogenic variant identified on somatic tumor tissue testing

Establishing the Diagnosis

The diagnosis of *POT1*-TPD **is established** in a proband with suggestive findings and a heterozygous germline pathogenic variant in *POT1* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *POT1* variant of uncertain significance does not establish or rule out the diagnosis of this disorder. To date, however, most *POT1* variants are classified as variants of uncertain significance due to insufficient data according to ACMG classification criteria. Due to limited evidence currently available, decision making should rely on clinical history, family history, segregation of the variant, and *in silico* analysis within the family.

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. 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 has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis and deletion/duplication analysis of *POT1* is performed.

A hereditary cancer multigene panel that includes *POT1* 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*. Of note, given the rarity of *POT1* tumor predisposition, some panels for melanoma, brain tumors, and/or hereditary cancer panels may not include this gene. (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

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *POT1* Tumor Predisposition

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
POT1	Sequence analysis [3]	All reported sequence variants to date [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [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. Shi et al [2014], Calvete et al [2017]
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

POT1 tumor predisposition (*POT1*-TPD) is associated with an increased risk for multiple cutaneous melanomas, chronic lymphocytic leukemia (CLL), angiosarcoma (particularly cardiac angiosarcomas), and gliomas. To date, fewer than than 100 families with a germline *POT1* variant have been identified. Disease-associated *POT1* variants were initially identified in families with cutaneous melanoma [Robles-Espinoza et al 2014, Shi et al 2014], chronic lymphocytic leukemia [Speedy et al 2016], cardiac and breast angiosarcomas [Calvete et al 2015],

and brain tumors [Bainbridge et al 2014]. Initial studies were biased by the cohorts included, which focused on a single disease entity. Additional cancers have been reported in individuals with a germline *POT1* variant. However, due to limited data it is unclear if these cancers are associated with *POT1* germline variants.

Cutaneous melanoma is the most commonly reported malignancy in individuals with *POT1*-TPD. The range of onset for first primary cutaneous melanoma is age 15 to 80 years [Robles-Espinoza et al 2014, Shi et al 2014]. Multiple synchronous or metachronous primary cutaneous melanomas are common, with reports ranging from two primary melanomas to eight primary melanomas [Robles-Espinoza et al 2014]. The time between diagnoses of first and second melanoma varied significantly (average ~9 years).

Chronic lymphocytic leukemia (CLL). Disease-associated *POT1* variants have been identified in familial CLL. A 3.6-fold increased risk for CLL was reported for individuals with *POT1* germline variant p.Gln376Arg [Speedy et al 2016]. This cohort also exhibited a younger average age of diagnosis than in sporadic CLL (59 years vs 70 years). *POT1* variants have been identified on somatic testing of CLL (tumor tissue) (see Molecular Genetics, Cancer and Benign Tumors); Germline *POT1* molecular testing can distinguish somatic and germline variants.

Angiosarcoma. The germline *POT1* variant p.Arg117Cys was identified in three Li-Fraumeni-like (LFL) families with members affected with cardiac angiosarcoma [Calvete et al 2015] and in an individual with a cardiac sarcoma with a negative family history [Calvete et al 2017]. Other germline *POT1* variants have been reported in families with LFL in which members had angiosarcoma, and in simplex cases of angiosarcoma or cardiac sarcoma [Kunze et al 2014, Calvete et al 2017]. Germline *POT1* variants were found in 27.3% (6/22) of *TP53*-negative LFL families with members affected with angiosarcoma [Calvete et al 2015, Calvete et al 2017]. Germline *POT1* variants were also found in 11.4% (4/35) of individuals with an angiosarcoma or cardiac sarcoma without a family history of sarcomas or a family history suggestive of LFL syndrome [Kunze et al 2014, Calvete et al 2017]. No germline *POT1* variants were reported in 34 LFL families without angiosarcoma [Calvete et al 2015, Calvete et al 2017].

Glioma. Two families with more than one individual with glioma were found to have a germline *POT1* variant [Bainbridge et al 2014]. One or more individuals in these families presented with oligodendroglioma, suggesting a glioma type-specific susceptibility in these families.

Other cancers reported in individuals with a germline *POT1* variant include most notably differentiated thyroid cancer (4 families, 7 individuals) and colorectal cancer (3 individuals) [Chubb et al 2016]. Several other benign and malignant neoplasias have been reported in individuals with a germline *POT1* variant; data are too limited to determine if the *POT1* variant is causative.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been confirmed.

The p.Arg117Cys *POT1* variant has been reported in three families with LFL in which members had cardiac angiosarcoma, in one family with LFL in which a member had breast angiosarcoma, and in one individual with cardiac sarcoma in the absence of family history [Calvete et al 2015, Calvete et al 2017].

Penetrance

The penetrance of *POT1*-TPD is currently unknown, fewer than 100 families have been described. Initial studies suggest a very high penetrance but are subject to a selection bias for research cohorts/families. In more than half of reported families only the proband was tested. Many individuals with germline *POT1* variants were ascertained based on a strong family history of cancer from tumor-specific consortiums (e.g., The Gliogene Consortium, UK National Study of Colorectal Cancer Genetics, UK Familial Melanoma Study).

Prevalence

The prevalence of *POT1*-TPD is currently unknown. However, data emerging from studies in individuals with familial melanoma suggest that 2.4% have a germline *POT1* variant [Robles-Espinoza et al 2014, Shi et al 2014]. Limited data suggest that a germline *POT1* variant was identified in up to 6% of families with familial CLL [Speedy et al 2016].

Genetically Related (Allelic) Disorders

Homozygosity for the p.Ser322Leu variant, which is not currently considered a pathogenic variant for *POT1* tumor predisposition syndrome, has been described in two sibs with the diagnosis of Coats plus syndrome (a telomere biology disorder) [Takai et al 2016].

Somatic *POT1* pathogenic variants have been reported in 3.5% of individuals with chronic lymphocytic leukemia on tumor tissue testing and are believed to function as drivers of disease progression [Ramsay et al 2013].

Differential Diagnosis

Table 2. Autosomal Dominant Tumor Predisposition Syndromes of Interest in the Differential Diagnosis of *POT1* Tumor Predisposition

Cancer Type	Gene(s)	Associated Disorder / Reference
Cutaneous melanoma	*BAP1*	*BAP1* tumor predisposition syndrome
	BRCA2	*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer
	CDK4	Susceptibility to cutaneous malignant melanoma 3 (OMIM 609048)
	CDKN2A	Hereditary melanoma/pancreatic cancer syndrome (OMIM 606719)
	MITF	Susceptibility to cutaneous malignant melanoma 8 (OMIM 614456)
	PTEN	*PTEN* hamartoma tumor syndrome (incl Cowden syndrome)
	TERT	Susceptibility to cutaneous malignant melanoma 9 (OMIM 615134)
Chronic lymphocytic leukemia	Unknown	Chronic lymphocytic leukemia (OMIM 151400)
Angiosarcoma	*TP53*	Li-Fraumeni syndrome
Glioma	*NF1*	Neurofibromatosis 1
	NF2	Neurofibromatosis 2
	TP53	Li-Fraumeni syndrome
	EPCAM *MLH1* *MSH2* *MSH6* *PMS2*	• Lynch syndrome • Constitutional mismatch repair deficiency [1]

1. Biallelic pathogenic variants in *MLH1, MSH2*, *MSH6*, or *PMS2* are associated with constitutional mismatch repair deficiency (an autosomal recessive variant of Lynch syndrome).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *POT1*-TPD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended. The majority of *POT1*-associated cancers are diagnosed in adulthood. Therefore, screening should begin at age 18 years.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *POT1* Tumor Predisposition

System/Concern	Evaluation	Comment
Cutaneous melanoma	Full skin exam by dermatologist	Beginning at age 18 yrs
Chronic lymphocytic leukemia	• CBC w/differential • Comprehensive physical exam incl lymph nodes	Beginning at age 18 yrs (See Surveillance.)
	Review of whole-body MRI for enlarged lymph nodes	In persons who undergo MRI for angiosarcoma screening or another reason.
Angiosarcoma (incl cardiac & breast angiosarcoma)	Consider whole-body MRI.	Beginning at age 18 yrs: • In persons in families fulfilling LFS or LFL 1 criteria • In persons w/personal & family history of non-cutaneous, non-brain malignancies
Brain tumors (glioma)	Brain MRI w/& w/o contrast	Beginning at age 18 yrs

LFS = Li-Fraumeni syndrome; LFL = Li-Fraumeni-like syndrome
1. See OMIM 151623 for description of Li-Fraumeni-like syndrome criteria

Treatment of Manifestations

The treatments for *POT1*-TPD tumors are those used in standard practice.

Surveillance

There are no published guidelines for surveillance for individuals with *POT1*-TPD. Decisions regarding individual surveillance protocols should be based on the emerging phenotypic spectrum of *POT1*-TPD, as well as on the affected individual's personal and family history. In addition, individuals should be educated regarding general signs and symptoms of malignant diseases and advised to seek medical attention with any concerning findings. Due to the similarity to Li-Fraumeni syndrome (LFS) and Li-Fraumeni-like syndrome, it seems appropriate to employ screening similar to that used in LFS.

Table 4. Recommended Surveillance for Individuals with *POT1* Tumor Predisposition

System/Concern	Evaluation	Frequency
Cutaneous melanoma	Dermatologic exam	• Beginning at age 18 yrs at least every 6 mos w/excision of any lesions suspicious for melanoma • Consider every 3 mos in persons w/multiple atypical nevi, history of melanoma, &/or family history of melanoma.

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Chronic lymphocytic leukemia	CBC w/differential	Annually beginning at age 18 yrs
	Comprehensive physical exam incl lymph nodes	Annually
	Evaluate results of whole-body MRI for enlarged lymph nodes.	When imaging is performed (e.g., in families fulfilling LFL criteria [1])
Angiosarcoma (incl cardiac & breast angiosarcoma)	Whole-body MRI	• Annually in families fulfilling LFS or LFL criteria beginning at age 18 yrs • Consider every 1-2 yrs depending on personal & family history of non-cutaneous, non-brain malignancies.
Brain tumors (glioma)	Brain MRI [2]	Consider every 1-2 years depending on family history beginning at age 18 yrs.

LFS = Li-Fraumeni syndrome; LFL = Li-Fraumeni-like syndrome
1. See OMIM 151623 for description of Li-Fraumeni-like syndrome criteria
2. The initial brain MRI should be done with contrast, and subsequent brain MRIs may be done without contrast if the previous MRI was normal and there is no new abnormality [Kratz et al 2017].

Agents/Circumstances to Avoid

To date, there is no evidence that UV light contributes to the pathogenesis of *POT1*-TPD-associated melanoma. However, individuals with *POT1*-TPD should be counseled against tanning bed use, as well as unprotected sun exposure.

It is currently unknown, whether ionizing radiation poses an increased risk to individuals with *POT1*-TPD, but because of the need for lifelong surveillance, it seems reasonable to avoid radiation in diagnostic procedures and instead recommend MRI or ultrasonography.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of first-degree relatives of an affected individual by molecular genetic testing for the *POT1* pathogenic variant in the family in order to identify those who would benefit from screening for *POT1*-associated cancers. Early recognition of cancers associated with *POT1* tumor predisposition (*POT1*-TPD) may allow for timely intervention and improved final outcome.

In general, molecular genetic testing for *POT1*-TPD 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 a *POT1* pathogenic variant, screening should begin at age 18 years (see Table 3) or two to five years earlier than the earliest diagnosis in the family. Therefore, a history of early cancers in the family may also warrant testing prior to age 18 years.

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

POT1 tumor predisposition (*POT1*-TPD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, most individuals diagnosed with *POT1*-TPD have an affected parent. An affected parent may have *POT1*-related tumors that differ from those of the proband.
- Some individuals diagnosed with *POT1*-TPD have the disorder as the result of a *de novo* germline pathogenic variant. The proportion of individuals with *POT1*-TPD caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* germline *POT1* pathogenic variant (i.e., a proband who appears to be the only affected family member).
- If the germline *POT1* pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism. No instances of parental germline mosaicism for a *POT1* pathogenic variant have been reported to date.
- The family history of some individuals diagnosed with *POT1*-TPD may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has confirmed that neither of the parents has the germline *POT1* pathogenic variant identified in the proband.

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

- If a parent of the proband has a germline *POT1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. It is important to note that clinical manifestations of *POT1*-TPD cannot be predicted in heterozygous family members because the full phenotypic spectrum and penetrance of *POT1*-TPD are unknown. The types of *POT1*-related tumors can vary among members of the same family and current evidence is limited to disease-focused studies.
- If the *POT1* pathogenic variant identified in the proband 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].
- The sibs of a proband with clinically unaffected parents are still at increased risk for *POT1*-TPD because of the possibility of reduced penetrance in a parent.

Offspring of a proband

- Each child of an individual with *POT1*-TPD has a 50% chance of inheriting the *POT1* pathogenic variant. It is important to note that clinical manifestations of *POT1*-TPD cannot be predicted in heterozygous family members because the full phenotypic spectrum and penetrance of *POT1*-TPD are unknown. The types of *POT1*-related tumors can vary among members of the same family and current evidence is limited to disease-focused studies.
- The likelihood that an individual who inherits a familial *POT1* pathogenic variant will develop a *POT1*-related tumor is unknown.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the germline *POT1* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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

- Predictive testing for at-risk relatives is possible once the *POT1* pathogenic variant has 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 younger than age 18 years)

- In general, genetic testing for *POT1*-TPD 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 unaffected individuals with *POT1*-TPD, screening is recommended beginning at age 18 years (see Table 3), or two to five years prior to the earliest diagnosis in the family. Therefore, a history of early cancers in the family may also 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.

In a family with an established diagnosis of *POT1*-TPD, it is appropriate to consider testing of symptomatic individuals regardless of age.

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 - for health professionals (part of PDQ®, National Cancer Institute).

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *POT1* pathogenic variant has been identified in an affected family member, prenatal testing 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
  www.cancer.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  www.cancercare.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. POT1 Tumor Predisposition: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
POT1	7q31.33	Protection of telomeres protein 1	POT1	POT1

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 POT1 Tumor Predisposition (View All in OMIM)

606478	PROTECTION OF TELOMERES 1; POT1
615848	TUMOR PREDISPOSITION SYNDROME 3; TPDS3
616568	none found

Molecular Pathogenesis

POT1 encodes protection of telomeres protein 1 (POT1), which together with other components of the telomere associated protein complex (shelterin), regulates telomerase access to the telomere and suppresses the DNA damage response. POT1 interacts with the single-stranded part of telomeric DNA, an interaction strengthened by POT1 binding to TPP1 [Gong et al 2020]. The protein contains four main domains [Gong et al 2020]:

- OB1 and OB2 (oligosaccharide/oligonucleotide) folds; facilitate initial interaction with telomeric single-stranded DNA
- OB3 fold; important for POT1-TPP1 interaction

- Holliday junction resolvase-like domain; important for POT1-TPP1 interaction

Disruption of single-stranded DNA binding and/or TPP1 binding domains have been shown to lead to lengthened telomeres, which are believed to lead to increased tumorigenesis via three putative mechanisms:

- Longer telomeres could delay replicative senescence, increase the replicative lifespan of cells, and thus lead to the accumulation of pathogenic variants.
- Longer telomeres predispose to fragility and genomic instability.
- Chromosomal aberrations, such as sister telomere fusions, have been reported in cells with abnormal POT1.

Pathogenic variants in *POT1* may lead to telomere lengthening, thereby eliminating the need for telomerase activation (observed in ~85% of all cancers) or alternative telomere lengthening. None of these mechanisms of tumorigenesis has been proven.

Mechanism of disease causation. Loss of function. Haploinsufficiency is the proposed underlying mechanism for overall telomere lengthening and resulting fragile and dysfunctional telomeres [Chen et al 2017, Rice et al 2017, Gong et al 2020].

***POT1*-specific laboratory technical considerations.** Telomere length testing could provide a future adjunct clinical laboratory assay, with potential use in further characterizing *POT1* variants [Aoude et al 2014, Robles-Espinoza et al 2014]. However, this analysis is currently not widely available.

Table 5. Notable *POT1* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_015450.2 NP_056265.2	c.349C>T	p.Arg117Cys	Reported in 3 families w/LFL & familial cardiac angiosarcoma [Calvete et al 2015]
	c.809G>A	p.Ser270Asn	Founder variant in Romagna region of Italy [Shi et al 2014]
	c.1127A>G	p.Gln376Arg	A 3.6-fold ↑ risk for CLL reported for individuals w/this variant [Speedy et al 2016]

CLL = chronic lymphocytic leukemia; LFL = Li-Fraumeni-like
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.

Cancer and Benign Tumors

Somatic *POT1* variants have been frequently identified in aggressive forms of chronic lymphocytic leukemia (CLL) [Ramsay et al 2013]. Because *POT1* variants arise early in CLL pathogenesis, they are believed to function as drivers in disease progression. Loss of heterozygosity rarely occurs [Ramsay et al 2013, Calvete et al 2015].

Chapter Notes

Revision History

- 10 March 2022 (sw) Revision: added Coats plus syndrome to Genetically Related Disorders
- 29 October 2020 (sw) Review posted live
- 12 May 2020 (te) Original submission

References

Literature Cited

Aoude LG, Pritchard AL, Robles-Espinoza CD, Wadt K, Harland M, Choi J, Gartside M, Quesada V, Johansson P, Palmer JM, Ramsay AJ, Zhang X, Jones K, Symmons J, Holland EA, Schmid H, Bonazzi V, Woods S, Dutton-Regester K, Stark MS, Snowden H, van Doorn R, Montgomery GW, Martin NG, Keane TM, López-Otín C, Gerdes AM, Olsson H, Ingvar C, Borg A, Gruis NA, Trent JM, Jönsson G, Bishop DT, Mann GJ, Newton-Bishop JA, Brown KM, Adams DJ, Hayward NK. Nonsense mutations in the shelterin complex genes ACD and TERF2IP in familial melanoma. J Natl Cancer Inst. 2014;107:dju408. PubMed PMID: 25505254.

Bainbridge MN, Armstrong GN, Gramatges MM, Bertuch AA, Jhangiani SN, Doddapaneni H, Lewis L, Tombrello J, Tsavachidis S, Liu Y, Jalali A, Plon SE, Lau CC, Parsons DW, Claus EB, Barnholtz-Sloan J, Il'yasova D, Schildkraut J, Ali-Osman F, Sadetzki S, Johansen C, Houlston RS, Jenkins RB, Lachance D, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Walsh KM, Davis FG, Lai R, Shete S, Aldape K, Amos CI, Thompson PA, Muzny DM, Gibbs RA, Melin BS, Bondy ML, et al. Germline mutations in shelterin complex genes are associated with familial glioma. J Natl Cancer Inst. 2014;107:384. PubMed PMID: 25482530.

Calvete O, Garcia-Pavia P, Domínguez F, Bougeard G, Kunze K, Braeuninger A, Teule A, Lasa A, Ramón Y, Cajal T, Llort G, Fernández V, Lázaro C, Urioste M, Benitez J. The wide spectrum of POT1 gene variants correlates with multiple cancer types. Eur J Hum Genet. 2017;25:1278–81. PubMed PMID: 28853721.

Calvete O, Martinez P, Garcia-Pavia P, Benitez-Buelga C, Paumard-Hernández B, Fernandez V, Dominguez F, Salas C, Romero-Laorden N, Garcia-Donas J, Carrillo J, Perona R, Triviño JC, Andrés R, Cano JM, Rivera B, Alonso-Pulpon L, Setien F, Esteller M, Rodriguez-Perales S, Bougeard G, Frebourg T, Urioste M, Blasco MA, Benítez J. A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families. Nat Commun. 2015;6:8383. PubMed PMID: 26403419.

Chen C, Gu P, Wu J, Chen X, Niu S, Sun H, Wu L, Li N, Peng J, Shi S, Fan C, Huang M, Wong CC, Gong Q, Kumar-Sinha C, Zhang R, Pusztai L, Rai R, Chang S, Lei M. Structural insights into POT1-TPP1 interaction and POT1 C-terminal mutations in human cancer. Nat Commun. 2017;8:14929. PubMed PMID: 28393832.

Chubb D, Broderick P, Dobbins S, Frampton M, Kinnersley B, Penegar S, Price A, Ma YP, Sherborne AL, Palles C, Timofeeva MN, Bishop DT, Dunlop MG, Tomlinson I, Houlston RS. Rare disruptive mutations and their contribution to the heritable risk of colorectal cancer. Nat Commun. 2016;7:11883. PubMed PMID: 27329137.

Gong Y, Stock AJ, Liu Y. The enigma of excessively long telomeres in cancer: lessons learned from rare human POT1 variants. Curr Opin Genet Dev. 2020;60:48–55. PubMed PMID: 32155570.

Kratz CP, Achatz MI, Brugieres L, Frebourg T, Garber J, Greer MLC, Hansford JR, Janeway KA, Kohlmann WK, McGee R, Mullighan CG, Onel K, Pajtler KW, Pfister SM, Savage SA, Schiffman JD, Schneider KA, Strong LC, Evans DGR, Wasserman JD, Villani A, Malkin D. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res. 2017;23:e38–45. PubMed PMID: 28572266.

Kunze K, Spieker T, Gamerdinger U, Nau K, Berger J, Dreyer T, Sindermann JR, Hoffmeier A, Gattenlöhner S, Bräuninger A. A recurrent activating PLCG1 mutation in cardiac angiosarcomas increases apoptosis resistance and invasiveness of endothelial cells. Cancer Res. 2014;74:6173–83. PubMed PMID: 25252913.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Ramsay AJ, Quesada V, Foronda M, Conde L, Martínez-Trillos A, Villamor N, Rodríguez D, Kwarciak A, Garabaya C, Gallardo M, López-Guerra M, López-Guillermo A, Puente XS, Blasco MA, Campo E, López-

Otín C. POT1 mutations cause telomere dysfunction in chronic lymphocytic leukemia. Nat Genet. 2013;45:526–30. PubMed PMID: 23502782.

Rice C, Shastrula P, Kossenkov A, Hills R, Baird DM, Showe LC, Doukov T, Janicki S, Skordalakes E. Structural and functional analysis of the human POT1-TPP1 telomeric complex. Nat Commun. 2017;8:14928. PubMed PMID: 28393830.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Robles-Espinoza CD, Harland M, Ramsay AJ, Aoude LG, Quesada V, Ding Z, Pooley KA, Pritchard AL, Tiffen JC, Petljak M, Palmer JM, Symmons J, Johansson P, Stark MS, Gartside MG, Snowden H, Montgomery GW, Martin NG, Liu JZ, Choi J, Makowski M, Brown KM, Dunning AM, Keane TM, López-Otín C, Gruis NA, Hayward NK, Bishop DT, Newton-Bishop JA, Adams DJ. POT1 loss-of-function variants predispose to familial melanoma. Nat Genet. 2014;46:478–81. PubMed PMID: 24686849.

Shi J, Yang XR, Ballew B, Rotunno M, Calista D, Fargnoli MC, Ghiorzo P, Bressac-de Paillerets B, Nagore E, Avril MF, Caporaso NE, McMaster ML, Cullen M, Wang Z, Zhang X, Bruno W, Pastorino L, Queirolo P, Banuls-Roca J, Garcia-Casado Z, Vaysse A, Mohamdi H, Riazalhosseini Y, Foglio M, Jouenne F, Hua X, Hyland PL, Yin J, Vallabhaneni H, Chai W, Minghetti P, Pellegrini C, Ravichandran S, Eggermont A, Lathrop M, Peris K, Scarra GB, Landi G, Savage SA, Sampson JN, He J, Yeager M, Goldin LR, Demenais F, Chanock SJ, Tucker MA, Goldstein AM, Liu Y, Landi MT, et al. Rare missense variants in POT1 predispose to familial cutaneous malignant melanoma. Nat Genet. 2014;46:482–6. PubMed PMID: 24686846.

Speedy HE, Kinnersley B, Chubb D, Broderick P, Law PJ, Litchfield K, Jayne S, Dyer MJS, Dearden C, Follows GA, Catovsky D, Houlston RS. Germ line mutations in shelterin complex genes are associated with familial chronic lymphocytic leukemia. Blood. 2016;128:2319–26. PubMed PMID: 27528712.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Takai H, Jenkinson E, Kabir S, Babul-Hirji R, Najm-Tehrani N, Chitayat DA, Crow YJ, de Lange T. A. POT1 mutation implicates defective telomere end fill-in and telomere truncations in Coats plus. Genes Dev. 2016;30:812–26. PubMed PMID: 27013236.

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