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Variant: NM_024675.4(PALB2):c.1592del (p.Leu531fs)

Version: 2.0

CA250432

126609 (ClinVar)

Gene: PALB2 (HGNC:79728)
Condition: PALB2-related cancer predisposition (MONDO:0700272)
Inheritance Mode: Autosomal dominant inheritance
UUID: 725ba8c8-354c-473f-9133-b2c40facf7ec
Approved on: 2022/9/15
Published on: 2025/9/16

HGVS expressions

NM_024675.4(PALB2):c.1592del (p.Leu531fs)
NM_024675.4:c.1592del
NC_000016.10:g.23634957del
CM000678.2:g.23634957del
NC_000016.9:g.23646278del
CM000678.1:g.23646278del
NC_000016.8:g.23553779del
NG_007406.1:g.11404del
ENST00000561514.3:c.1598del
ENST00000565038.2:c.211+2896del
ENST00000566069.6:c.1592del
ENST00000697377.2:c.1598del
ENST00000697379.2:c.1598del
ENST00000561514.2:c.707del
ENST00000697374.1:c.707del
ENST00000697375.1:n.2939del
ENST00000697376.1:c.707del
ENST00000697377.1:c.707del
ENST00000697378.1:n.2112del
ENST00000697379.1:c.707del
ENST00000697382.1:c.707del
ENST00000697383.1:c.49-5679del
ENST00000697384.1:n.1746del
ENST00000261584.9:c.1592del
ENST00000261584.8:c.1592del
ENST00000565038.1:c.86+2896del
ENST00000568219.5:c.707del
NM_024675.3:c.1592del

Pathogenic

Met criteria codes 4

PVS1 PP1_Strong PS4 PM5_Supporting

Not Met criteria codes 3

BS1 PS3 PM2

Expert Panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specification: *ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PALB2 Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hereditary Breast, Ovarian and Pancreatic Cancer VCEP

The c.1592del (p.L531Cfs*30) variant in PALB2 is a frameshift variant observed to cause a premature stop codon in biologically-relevant-exon 4 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [HR 6.1 (95% CI 2.2-17.2, p = 0.01)] (PMID: 18628482). This alteration results in a termination codon upstream of the most C-terminus pathogenic alteration (PALB2 p.Tyr1183*) as classified by the HBOP VCEP, and is expected to be more deleterious. The variant has been reported to segregate with breast cancer in 6 affected family members from three families (Ambry Genetics and Invitae). The minor allele frequency in gnomAD v2.1.1 is 0.001871 in the Finnish population; however, this variant known to be a Finnish founder mutation thus explaining the higher than expected population frequency (PM2_Supporting, BS1, and BA1 are not met; PMID: 17287723). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant hereditary breast and pancreatic cancer and autosomal recessive FANCN based on the ACMG/AMP criteria applied as specified by the HBOP VCEP. (PVS1, PS4, PP1_Strong, PM5_Supporting)

Met criteria codes

PVS1	✔	The c.1592delT (p.L531Cfs*30) variant in PALB2 is a frameshift variant observed to cause a premature stop codon in biologically-relevant-exon 4/13 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PMID: 31757951).
PP1_Strong	✔	COOL segregation analysis from 3 families (Ambry and Invitae internal data) Co-segregation overall LOD score: 1.6056 Co-segregation overall Bayes factor: 40.32737929761131281396 Co-segregation in each pedigree (empty if there is only one pedigree): Ped1=0.550991 Ped2=0.587469 Ped3=0.467144
PS4	✔	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [HR 6.1 (95% CI 2.2-17.2, p = 0.01)] (PMID: 18628482).
PM5_Supporting	✔	This alteration results in a termination codon upstream of the most C-terminus pathogenic alteration (PALB2 p.Tyr1183*) as classified by the HBOP VCEP, and is expected to be more deleterious.

Not Met criteria codes

BS1	✖	Finnish minor allele frequency in gnomAD v2.1.1 is 0.187% (47/25120 alleles) in the Finnish population, which is higher than the HBOP VCEP threshold (>0.01%) for BS1; however, this is a known founder variant thus explaining the high population frequency.
PS3	✖	This variant is non-functional in protein assays (PMID: 31757951); however, due to a lack of positive missense controls with known clinical impact, these assays do not meet the requirements for use by the HBOP VCEP.

PM2	✖	Finnish minor allele frequency in gnomAD v2.1.1 is 0.187% (47/25120 alleles) in the Finnish population, which is higher than the HBOP VCEP threshold (>0.01%) for BS1; however, this is a known founder variant thus explaining the high population frequency.

Curation History

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