PP4

Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.

- PP4 applicability and strength is determined by the total points accumulated by a single affected individual according to the table below and the following total point ranges:
  - <1 point: PP4 not met
  - 1-<2 points: PP4
  - 2-<6 points: PP4_Moderate
  - ≥ 6 points: PP4_Strong[1]

Evidence Description	Points
Diagnostic criteria met for SCID (Criteria 1 and 3 or Criterion 4 by itself) or Leaky SCID/Omenn syndrome (excluding Criterion 2)[2]	0.5
SCID gene panel or exome/genome sequencing conducted (only applicable if genetic testing did not provide an alternative genetic explanation for SCID/Leaky SCID/Omenn syndrome phenotype)	1
Family history of SCID (only applicable if SCID gene panel or exome/genome sequencing was conducted on proband and did not provide an alternative genetic explanation for phenotype)	0.5
Navajo or Apache descent	0.25
Increased cellular radiosensitivity as determined by >1 log of decreased proliferation or survival OR impaired gH2AX correction compared to wild-type controls AND pathogenic or likely pathogenic variants in PRKDC, NHEJ1, and LIG4 have been excluded PMID 11336668, 26476407, 27611239, and 25917813	4.5
Increased cellular radiosensitivity as determined by >1 log of decreased proliferation or survival OR impaired gH2AX correction compared to wild-type controls AND pathogenic or likely pathogenic variants in PRKDC, NHEJ1, and LIG4 have NOT been excluded PMID 11336668, 26476407, 27611239, and 25917813	0.5
Decreased V(D)J recombination as established by the laboratory AND pathogenic or likely pathogenic variants in RAG1, RAG2, PRKDC, NHEJ1, LIG4, and NUDCD3 have been excluded (4.5 pt) PMID 11336668, 15071507, 25917813, and 29906526	4.5
Decreased V(D)J recombination as established by the laboratory AND pathogenic or likely pathogenic variants in RAG1, RAG2, PRKDC, NHEJ1, LIG4, and NUDCD3 have NOTbeen excluded (4.5 pt) PMID 11336668, 15071507, 25917813, and 29906526	1
Vector-based complementation corrected increased cellular radiosensitivity (as determined by >1 log of decreased proliferation or survival OR impaired gH2AX correction compared to wild-type controls) and/or decreased V(D)J recombination (as established by the laboratory) and/or led to in vitro restoration of hematopoietic stem cell maturation into T cells.	5
SCID phenotype corrected by DCLRE1C gene therapy **WITHOUT** CNV testing performed	4.5
SCID phenotype corrected by DCLRE1C gene therapy **WITH** CNV testing performed	6
T-B-NK+ lymphocyte subset profile* (See notes)	0.5

[1]CNV (Copy number variation) testing is required to consider PP4_Strong in order to certify that the variant in question is the causative for the phenotype, and not one CNV event corrected by gene therapy and not identified previously. [2]The diagnostic criteria should follow the PIDTC 2022 specification, summarized here. *Notes: 1) If NK cells are not noted or are present, criteria may still be applied if SCID gene panel or exome/genome sequencing has ruled out alternative causes; 2) If maternal T cells are present, the T lymphocyte profile is still considered to be T- (autologous T cells are absent).