

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-<2.5 points: PP4
 - 2.5 -<6 points: PP4_Moderate
 - ≥6 points: PP4_Strong¹

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
Absent CD132 expression (demonstrated by RT-PCR, Western blot, flow cytometry)	4.5
Reduced CD132 expression (demonstrated by RT-PCR, Western blot or flow cytometry) as established by the laboratory	3
Reduced IL-2-induced phosphorylation of JAK3 or STAT5 in patient-derived cells as established by the laboratory AND pathogenic or likely pathogenic variants in JAK3, STAT5A, STAT5B, IL2RA, and IL2RB have been excluded PMID: 10794431, 31799703, 32072341	3
Reduced IL-2-induced phosphorylation of JAK3 or STAT5 in patient-derived cells as established by the laboratory AND pathogenic or likely pathogenic variants in JAK3, STAT5A, STAT5B, IL2RA, and IL2RB have NOT been excluded PMID: 10794431, 31799703, 32072341	1.5
Reduced IL-21-induced phosphorylation of STAT3 in total lymphocytes or B cells as established by the laboratory AND pathogenic or likely pathogenic variants in JAK3, STAT3, and IL21R have been excluded PMID: 25042067, 32072341	3
Reduced IL-21-induced phosphorylation of STAT3 in total lymphocytes or B cells as established by the laboratory AND pathogenic or likely pathogenic variants in JAK3, STAT3, and IL21R have NOT been excluded PMID: 25042067, 32072341	1.5
SCID phenotype corrected by IL2RG gene therapy WITHOUT CNV testing performed	4.5
SCID phenotype corrected by IL2RG gene therapy WITH CNV testing performed	6
T-B+ lymphocyte subset profile* (See notes)	0.5
NK cells below the normal reference range or absent	1

¹CNV (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. ²The 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).