

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_Strong¹

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.

Evidence Description	Points
Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met 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)	0.5
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
Reduced or constitutive cytokine-induced JAK3 tyrosine phosphorylation in patient cells	1
Reduced cytokine-induced phosphorylation of STAT5 in patient-derived T or B cells	1
SCID phenotype corrected by JAK3 gene therapy WITHOUT CNV testing performed	1
SCID phenotype corrected by JAK3 gene therapy WITH CNV testing performed	6
T-B+NK- lymphocyte subset profile* (See notes)	0.5

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).