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 Criterion2)[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
Reduced ADA enzyme activity in patient cells (<1-2% of normal ADA catalytic activity) AND/OR increased dAdo nucleotides (dATP or dAXP) in pretreatment or non-transfused erythrocytes above the reference range PMIDs 20301656 and 39182630.	5
ADA-SCID phenotype corrected by exogenous ADA supplementation WITHOUT CNV testing performed	4.5
ADA-SCID phenotype corrected by exogenous ADA supplementation WITH CNV testing performed	6
ADA-SCID phenotype corrected by ADA gene therapy **WITHOUT** CNV testing performed	4.5
ADA-SCID phenotype corrected by ADA 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).