

PP4	<p>Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.</p> <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> <1 point: PP4 not met 1-<2 points: PP4 2-<6 points: PP4_Moderate ≥ 6 points: PP4_Strong¹ <p>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.</p> <table border="1"> <thead> <tr> <th>Evidence Description</th><th>Points</th></tr> </thead> <tbody> <tr> <td>Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met²</td><td>0.5</td></tr> <tr> <td>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)</td><td>0.5</td></tr> <tr> <td>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)</td><td>0.5</td></tr> <tr> <td>Reduced CD127 expression (demonstrated by RT-PCR, Western blot, flow cytometry)</td><td>1</td></tr> <tr> <td>Reduced IL-7-induced phosphorylation of STAT5 in patient-derived T-cells</td><td>1</td></tr> <tr> <td>Rescue of defective IL-7-receptor-mediated signaling by IL-2 or IL-15 induction</td><td>1</td></tr> <tr> <td>SCID phenotype corrected by IL7R gene therapy WITHOUT CNV testing performed</td><td>1</td></tr> <tr> <td>SCID phenotype corrected by IL7R gene therapy WITH CNV testing performed</td><td>6</td></tr> <tr> <td>T-B+NK+ lymphocyte subset profile* (See notes)</td><td>0.25</td></tr> </tbody> </table> <p>²The diagnostic criteria should follow the PIDTC 2022 specification, summarized here.</p> <p>*Notes:</p> <p>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;</p> <p>2) If maternal T cells are present, the T lymphocyte profile is still considered to be T- (autologous T cells are absent).</p>	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 CD127 expression (demonstrated by RT-PCR, Western blot, flow cytometry)	1	Reduced IL-7-induced phosphorylation of STAT5 in patient-derived T-cells	1	Rescue of defective IL-7-receptor-mediated signaling by IL-2 or IL-15 induction	1	SCID phenotype corrected by IL7R gene therapy WITHOUT CNV testing performed	1	SCID phenotype corrected by IL7R gene therapy WITH CNV testing performed	6	T-B+NK+ lymphocyte subset profile* (See notes)	0.25
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 CD127 expression (demonstrated by RT-PCR, Western blot, flow cytometry)	1																				
Reduced IL-7-induced phosphorylation of STAT5 in patient-derived T-cells	1																				
Rescue of defective IL-7-receptor-mediated signaling by IL-2 or IL-15 induction	1																				
SCID phenotype corrected by IL7R gene therapy WITHOUT CNV testing performed	1																				
SCID phenotype corrected by IL7R gene therapy WITH CNV testing performed	6																				
T-B+NK+ lymphocyte subset profile* (See notes)	0.25																				