ClinGen Lysosomal Diseases Variant Curation Expert Panel
Applying segregation evidence (PP1)
Date: June 7, 2024

This guidance is based on Biesecker et al, 2024, Am J Hum Genet. 111(1):24-38, PMID: 38103548.

		Number of individuals with co-segregations				
		1	2	3	4	5
Affected	Points	2.0	4.0	6.0	8.0	10.0
Unaffected		0.4	0.8	1.2	1.6	2.0

1 point = Supporting
2 points = Moderate
≥4 points = Strong
(Based on the Bayesian points system from Tavtigian et al, Genet Med. 2018 Sep;20(9):1054-1060, PMID: 29300386)

The combination of strengths for PP1 and PP4 MUST NOT exceed strong (2 x moderate, i.e. 4 points using Bayesian system) if cases are also being counted as probands under PM3.

Counting segregations:

- Do not count probands as a segregation.
- Affected segregations = # affected individuals in the family with the variants minus 1.
- Affected segregations are defined as affected family members (typically siblings) who harbor the variant in question and a second variant on the remaining allele.
- Unaffected segregations are defined as unaffected family members, typically siblings, who are at risk to inherit the two variants (or one variant in homozygosity) identified in the proband. These individuals should be either homozygous normal or heterozygous for only one variant.
- Unaffected, carrier parents DO NOT count as unaffected segregations.