Blueprint Genetics Variant Classification Scheme for Dominant Monogenic Disorders

CLASSIFICATION	CATEGORY	CRITERIA
PATHOGENIC	1 Point Needed	1. Well-established mutation and wide consensus in the field on pathogenicity of the mutation. (Typically significant family segregation has been established and several publications support pathogenicity). **– 1 Point**
	OR	
	5 Points Needed	**COMPULSORY A OR B:** A) Positive segregation with the disease (≥2 families) and at least 5 unrelated patients with same variant and phenotype. **2 Points** **OR** B) ≥ 5 cases with same variant and phenotype reported. **1 Point** **ADDITIONAL POINTS:** 1. Variant is novel or very rare in control populations (cannot be applied for ethnic backgrounds absent from control populations). **1 Point** 2. Loss of gene function has been established as a mechanism of pathogenicity; scientific evidence for genotype – phenotype association exists. **1 Point** 3. A missense variant predicted deleterious by majority of *in silico* tools applied and/or well-established paralogue mutation exists. **1 Point** 4. *De novo* alteration in the setting of a novel disease in the family (paternity unconfirmed). **1 Point** 5. Variants considered deleterious (a substitution or indel in consensus splice site (+/-1, 2), nonsense and frameshift variants). **1 Point** 6. Deficient protein function in appropriate functional assay(s), e.g. an animal model with equivalent mutation or splice site defect confirmed on mRNA level. **1 Point** 7. Well-characterized other mutation at the same codon or same splice consensus site (+/-1, 2). **1 Point** 8. Other strong data supporting pathogenic classification. **1 Point**
LIKELY PATHOGENIC	2 Points Needed	1. Alterations resulting in premature truncation (e.g. frameshift, nonsense or consensus splice site (+/-1, 2) in a gene where loss-of gene function has been established as a mechanism of pathogenicity for patient´s disease. **- 1 Point** 2. Variant is novel or very rare in control populations (cannot be applied for ethnic backgrounds absent from control populations). **- 1 Point**
	OR	
	4 Points Needed	1. Clear genotype phenotype correlation exist (e.g. MfS and *FBN1*) **- 1 Point** 2. Variant is novel or very rare in control populations (cannot be applied for ethnic backgrounds absent from control populations). **- 1 Point** 3. Missense variant predicted deleterious by majority of *in silico* tools applied. **- 1 Point** 4. Variant has been identified in ≥2 individuals with same disease manifestation. **- 1 Point** 5. Evidence of a well-established paralogue mutation exists. **- 1 Point** 6. *De novo* alteration in the setting of a novel disease in the family (paternity unconfirmed). **- 1 Point** 7. Variants considered deleterious (a substitution or indel in consensus splice sites (+/-1, 2), nonsense and frameshift variants) identified in a gene with weak evidence for causativity in the disease type. **- 1 Point** 8. Deficient protein function in appropriate functional assay(s), e.g. an animal model with equivalent mutation or splice site defect confirmed on mRNA level **- 1 Point** 9. Well-characterized mutation at the same codon or same splice consensus site (+/-1, 2). **- 1 Point** 10. Other strong data supporting pathogenic classification. **- 1 Point**
Variant of unknown significance (VUS)	Variant has characteristics of being independent disease-causing mutation, however, insufficient or conflicting evidence exists.	
LIKELY BENIGN	1 Point Needed	1. Control population minor allele frequency (1000G, ESP, SISu, ExAC) is considerable (MAF>0.001) - (disease prevalence must be taken into account). **- 1 Point**
	OR	
	2 Points Needed	1. MAF <0.001 in control populations but variant is detected in healthy controls with no disease association in a case-control study/studies. **- 1 Point** 2. Homozygous variant in a gene with no association to the disease. **- 1 Point** 3. Co-occurrence with a pathogenic mutation in the same gene (phase unknown) or in another gene that clearly explains the proband's phenotype. **- 1 Point** 4. Majority of the *in silico* tools predict the substitution to be benign. **- 1 Point** 5. Intact protein function observed in appropriate functional assay(s), e.g. splice region variant without abnormal splicing. **- 1 Point** 6. Other data supporting benign classification. **- 1 Point**
BENIGN	2 Points Needed	1. Does not segregate with the disease in family/ies with 2 or more affected individuals. **- 1 Point** 2. Any additional criteria described below. **- 1 Point**
	OR	
	4 Points Needed	1. Control population minor allele frequency (1000G, ESP, SISu, ExAC) is considerable (MAF>0.001) - (prevalence of the disease must be taken into account). **- 1 Point** 2. Homozygous variant in a gene with no association to the disease. **- 1 Point** 3. Intact protein function observed in appropriate functional assay(s), e.g. splice region variant without abnormal splicing. **- 1 Point** 4. Co-occurrence with a pathogenic mutation in the same gene (phase unknown) or in another gene that clearly explains the proband's phenotype. **- 1 Point** 5. No disease association in small case-control study. **- 1 Point** 6. Majority of the *in silico* tools predict the substitution to be benign. **- 1 Point** 7. Other data supporting benign classification. **- 1 Point**

Disclaimers:

- Every case is examined by our team in the light of the literature, publicly available clinical databases and the BpG in-house mutation database. Exceptions to the scheme can be made in complex cases or in the setting of poorly described patient phenotype.
- This classification scheme is not designed for the interpretation of variants considered as genetic modifiers or alleles predisposing to a disease with low-risk. Several variants classified with this scheme as likely benign or benign could function as disease modifiers. Classification as disease modifier can be applied when adequate scientific evidence has been established for a variant.
- It is not optimal for interpretation of alterations confounded by incomplete penetrance, variable expressivity, recessive inheritance, oligogenic inheritance, or skewed X-inactivation.
- Final classifications are subject to review and approval by Blueprint Genetics clinical staff and may differ from those predicted by the scheme.

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