*Correspondence*

DOI: 10.5582/irdr.2025.01014

# Pathonign variants in recessive disorders: How extremely hypomorphic variants can be pathogenic and benign depending on the allele in trans

**Alexandre Fabre[1,2,*], Paul Guerry[3]**

[1] APHM, Timone Enfant, Service de pédiatrie multidisciplinaire, Marseille, France;
[2] Aix Marseille Univ, INSERM, MMG, Marseille, France;
[3] Green Grow Scientific, Marseille, France.

**SUMMARY**: In recessive monogenic diseases, individuals with a single pathogenic variant are typically asymptomatic and symptomatic disease is only observed in patients with two pathogenic variants. Assuming that disease only occurs where protein concentrations or activity are below 50% of normal (since in recessive diseases, most carriers are asymptomatic) some hypomorphic variants could be deleterious in association with a LoF variant, but nevertheless yield > 50% protein activity/concentration when homozygous. These types of variants would be very weakly eliminated by natural selection, if at all, and thus their frequency in the population could increase by genetic drift. Thus the population frequency criterion often used to qualify variants as benign would be misleading. One such variant may be c.5603A>T (p.Asn1868Ile), in *ABCA4* (which causes Stargardt disease-1). This variant is pathogenic in trans with a null or missense variant but not when homozygous. We refer to these variants using the blend word "pathonign", since they are simultaneously pathogenic and benign in the population.

***Keywords***: monogenic disorder, hypomorphic allele, disease-causing variant, benign variant, phenotypic severity, recessive disorder

## 1. Introduction

In recessive monogenic diseases, individuals with a single pathogenic variant are typically asymptomatic and symptomatic disease is only observed in patients with two pathogenic variants (*1*). For some genes however, particular variant combinations can give rise to specific disease expression profiles. For example, we recently highlighted the Goldilocks situation that can arise for Mendelian diseases where the presence of two loss of function (LoF) variants is lethal prenatally, and symptoms are only observed in individuals with a LoF-hypomorphic variant combination (*2*) as in the case of recessive diseases linked to aminoacyl-tRNA synthetases (*2*) and thrombocytopenia-absent radius syndrome (*3*). In some cases therefore, phenotypic severity depends on the combined activities of pathogenic variants. While it is clear that some LoF variants are lethal when homozygous, conversely, extremely hypomorphic variants could be benign when homozygous and pathogenic only in association with a more severe variant. In this article, we briefly outline the mechanisms and consequences of this Schrödinger cat-like effect and its implications for patient care, with reference to *ABCA4* variants and Stargardt disease-1 (STGD1).

## 2. The importance of the variant in trans: A theoretical illustration

In recessive disorders, assuming that disease only occurs where protein concentrations or activity are below 50% of normal (since in recessive diseases, most carriers are asymptomatic) some hypomorphic variants could be deleterious in association with a LoF variant, but nevertheless yield > 50% protein activity/concentration when homozygous (Figure 1A). In theory for example, a hypomorphic variant producing a protein with 25% activity will be pathogenic in association with a null variant, but not when homozygous (50% activity) or with a > 25% functional allele in trans. The distribution of these variants in the population may depend on (or reflect) the clinical threshold of the corresponding disease, which is not necessarily 50%, as illustrated in Figure 1.

One such variant may be c.5603A>T (p.Asn1868Ile), in *ABCA4*, which is pathogenic in trans with a null or

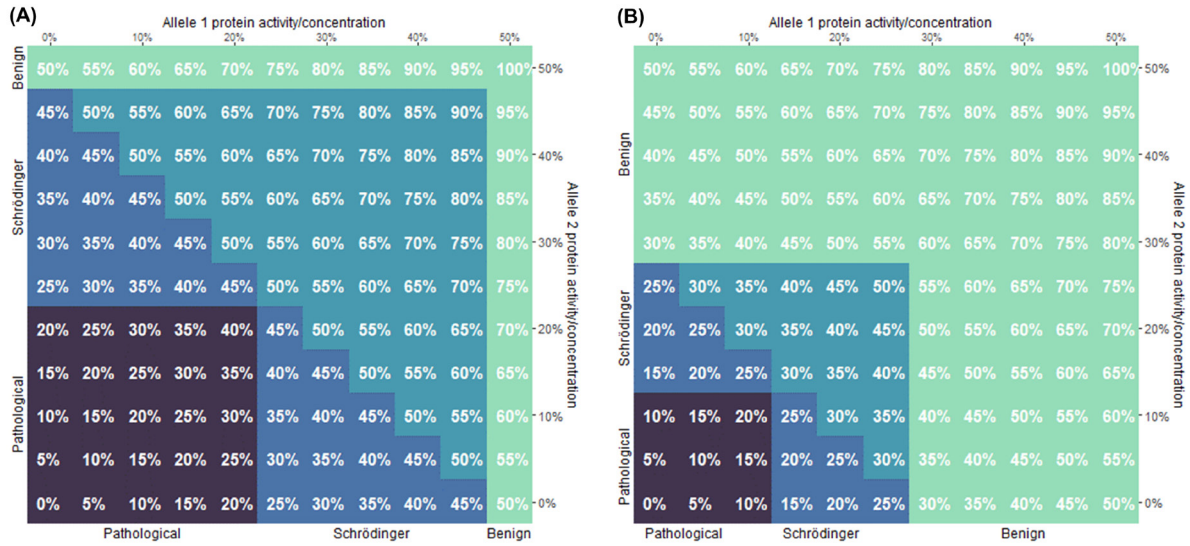


**Figure 1. Tile plots of the combined activity (not frequency) of hypothetical variants in which the disease threshold is (A) 50% and (B) 30% protein activity/concentration.** The tiles are colored in *dark blue* when the variants are pathological when homozygous and when combined with a hypomorphic variant, *light green* when the variants are always benign, and *blue* when the variants' pathogenicity is defined by the variant in trans (what we call pathonign variants): pathogenic (*denim blue*) when the combined activity from the two variants is below the disease threshold, but benign (*light blue*) when the combined activity from the two variants is above the disease threshold.

missense variant but not when homozygous (except if it is associated with a deleterious variation in cis). Pathogenic variations in the *ABCA4* gene cause STGD1, the most common cause of Mendelian recessive retinal dystrophy. c.5603A>T (p.Asn1868Ile) is a common variant (minor allele frequency, 5.8% in gnomAD) and has been implicated in 50% of cases of Stargardt disease-1 previously thought to be monoallelic (which represent 25% of cases of STGD1), with a milder phenotype and later onset (*4*,*5*). It is notable that this association was only identified because Zernant *et al*.'s study was large enough (> 600 patients) to significantly identify its overrepresentation in STGD1 patients (*4*). Patel *et al*. have also recently suggested that this type of variant may also be implicated in some cases of Knobloch syndrome (*6*).

These examples highlight both the existence of extremely hypomorphic variants and their potential phenotypic expression in patients in association with a more pathogenic variant. Presumably, these types of variants would be very weakly eliminated by natural selection, if at all, and thus their frequency in the population could increase by genetic drift. The population frequency criterion often used to qualify variants as benign (*7*) would be misleading in these cases, as would the presence of homozygous occurrences in databases (there are 2,989 homozygous occurrences of p.Asn1868Ile in GnomAD for example). In patients, these variants should occur more often than in the general population, and be associated with an extremely deleterious variant (either null or missense), and probably milder phenotypes. Proof of pathogenicity would require functional studies with a null allele in trans, because the homozygous state would not be pathogenic. The fact that p.Asn1868Ile is classified by AlphaMissense as likely benign (*https://alphamissense.hegelab.org/results*), suggests that pathogenicity prediction is insufficient. Note that this concept differs from those of risk alleles or low/reduced penetrance alleles in dominant disorders (*8-11*), because in recessive disorders, alleles cannot be considered in isolation and "penetrance" always depends on the variant in trans. In our theoretical example, the variant would be 0% penetrant when isolated or homozygous but 100% penetrant when associated with a LoF variant.

## 3. Conclusion

In conclusion, we think clinicians should be aware that in some cases, notably in trans of very deleterious variants, the second allele may have the features we describe theoretically here. We refer to these variants as pathonign variants, since they are simultaneously pathogenic and benign in the population.

*Funding*: None.

*Conflict of Interest*: The authors have no conflicts of interest to disclose.

## References

1. Zschocke J, Byers PH, Wilkie AOM. Mendelian inheritance revisited: Dominance and recessiveness in medical genetics. Nat Rev Genet. 2023; 24:442-463.
2. Fabre A, Guerry P. Goldilocks principle and recessive disease. Eur J Hum Genet. 2024; 32:143-145.
3. Albers CA, Newbury-Ecob R, Ouwehand WH, Ghevaert C. New insights into the genetic basis of TAR

(thrombocytopenia-absent radii) syndrome. Curr Opin Genet Dev. 2013; 23:316-323.
4. Zernant J, Lee W, Collison FT, Fishman GA, Sergeev YV, Schuerch K, Sparrow JR, Tsang SH, Allikmets R. Frequent hypomorphic alleles account for a significant fraction of ABCA4 disease and distinguish it from age-related macular degeneration. J Med Genet. 2017; 54:404-412.
5. Simcoe MJ, Arno G, Hysi PG, Ko T, Michaelides M, Hammond CJ, Patel PJ, Mahroo OA, Webster AR; UK Biobank Eye and Vision Consortium. An Analysis of the Effect of ABCA4 p.Asn1868Ile Genotypes on Retinal Structure in 26,558 Participants in the UK Biobank. Invest Ophthalmol Vis Sci. 2023; 64:31.
6. Patel CK, Broadgate S, Shalaby A, Yu J, Nemeth AH, Downes SM, Halford S. Whole genome sequencing in a Knobloch syndrome family confirms the molecular diagnosis. Ophthalmic Genet. 2022; 43:201-209.
7. Harrison SM, Biesecker LG, Rehm HL. Overview of Specifications to the ACMG/AMP Variant Interpretation Guidelines. Curr Protoc Hum Genet. 2019; 103:e93.
8. Webb EL, Rudd MF, Sellick GS, El Galta R, Bethke L, Wood W, Fletcher O, Penegar S, Withey L, Qureshi M, Johnson N, Tomlinson I, Gray R, Peto J, Houlston RS. Search for low penetrance alleles for colorectal cancer through a scan of 1467 non-synonymous SNPs in 2575 cases and 2707 controls with validation by kin-cohort analysis of 14704 first-degree relatives. Hum Mol Genet. 2006; 15:3263-3271.
9. Pal T, Mundt E, Richardson ME, Chao E, Pesaran T, Slavin TP, Couch FJ, Monteiro ANA. Reduced penetrance BRCA1 and BRCA2 pathogenic variants in clinical germline genetic testing. NPJ Precis Oncol. 2024; 8:247.
10. Ciesielski TH, Sirugo G, Iyengar SK, Williams SM. Characterizing the pathogenicity of genetic variants: the consequences of context. NPJ Genom Med. 2024; 9:3.
11. Low Penetrance/Risk Allele - ClinGen. Clinical Genome Resource. *https://clinicalgenome.org/working-groups/low-penetrance-risk-allele-working-group* (accessed April 8, 2025).

Received April 9, 2025; Revised May 22, 2025; Accepted May 27, 2025.

**Address correspondence to:*
Alexandre Fabre, APHM, Timone Enfant, Service de pédiatrie multidisciplinaire, 264 rue Saint Pierre, 13005 Marseille, France.
E-mail: alexandre.fabre@ap-hm.fr

Released online in J-STAGE as advance publication May 30, 2025.