

Neurofibromatosis Type 1

Genotype-Phenotype Correlations

Symptoms compared to a "classic" NF1 presentation

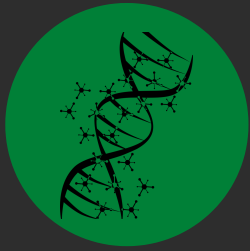
Missense variants affecting p.Arg1809 ²	NF1 Microdeletions ³	Missense variants affecting codons 844-848 ⁴	3-bp In-Frame Deletion, c.2970_2972del (p.Met992del) ¹
Mild phenotype	Severe phenotype	Severe phenotype	Mild phenotype
Lack externally visible plexiform, cutaneous, or subcutaneous neurofibromas	Type-1 microdeletions have an increased amount of subcutaneous (76%), spinal (64%) and plexiform (76%) neurofibromas	Major superficial plexiform (~39%) and/or symptomatic spinal (~10-15%) neurofibromas more prevalent	Lack externally visible plexiform, cutaneous, or subcutaneous neurofibromas
Higher frequency of Noonan-like features including pulmonic stenosis (~12%) and short stature (~35%)	Higher frequency of facial dysmorphism (90%) and tall stature (46%)	Higher frequency of skeletal abnormalities (~33-42%) and optic pathway gliomas (~9-31%)	Higher frequency of Noonan-like features including pulmonic stenosis (5%)
Present with >5 CAL spots (~91%) with or without skinfold freckling	Typically have >5 CAL spots (93%) with or without skinfold freckling	Typically have >5 CAL spots (~83%) with or without skinfold freckling	Present with >5 CAL spots (~91%) with or without skinfold freckling
Significantly less symptomatic optic gliomas and pectus abnormalities	Higher frequency of cognitive delay (48%), scoliosis (43%), and bone cysts (50%)	Higher chance to develop malignancies (~9%)	Significant risk for cognitive impairment or learning disability (33%) and nonoptic brain tumors (~5%)

¹ Koczkowska et al. (2018). Expanding the clinical phenotype of individuals with a 3-bp in-frame deletion of the NF1 gene (c.2970_2972del): an update of genotype-phenotype correlation. *Genetics in Medicine*, 21(4), 867-876.

² Rojnueangnit et al. (2015). High Incidence of Noonan Syndrome Features Including Short Stature and Pulmonic Stenosis in Patients carrying NF1 Missense Mutations Affecting p.Arg1809: Genotype-Phenotype Correlation. *Human Mutation*, 0(0), 1-12.

³ Kehrer-Sawatzki, H., Mautner, V-F., and Cooper, D. N. (2017). Emerging genotype-phenotype relationships in patients with large NF1 deletions. *Human Genetics*, 136, 349-376.

⁴ Koczkowska et al. (2018). Genotype-Phenotype Correlation in NF1: Evidence for a More Severe Phenotype Associated with Missense Mutations Affecting NF1 Codons 844-848. *The American Journal of Human Genetics*, 102, 69-87.



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NF1 Missense variants affecting p.Met1149, p.Arg1276, and p.Lys1423

p.Met1149

Mild phenotype

Lack externally visible plexiform, cutaneous, or subcutaneous neurofibromas

High frequency of Noonan-like features (29%)

Present with >5 CAL spots (~90%) with or without skinfold freckling

No symptomatic optic gliomas or malignant neoplasms observed

p.Arg1276

Mild phenotype but more severe than p.Met1149

High prevalence of symptomatic spinal neurofibromas (~19%) and lower prevalence of cutaneous neurofibromas

Higher frequency of Noonan-like features (~21%)

Present with >5 CAL spots (~93%) with or without skinfold freckling

Higher incidence of skeletal abnormalities (32%)

p.Lys1423

Mild phenotype but more severe than p.Met1149

May be predisposed to major external plexiform neurofibromas (~29%)

Higher frequency of Noonan-like features (~29%)

Present with >5 CAL spots (~95%) with or without skinfold freckling

Higher incidence of skeletal abnormalities (41%)