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.

Neurofibromatosis Type 1

Genotype-Phenotype Correlations

Symptoms compared to a "classic" NF1 presentation

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

p.Met1149	p.Arg1276	p.Lys1423
Mild phenotype	Mild phenotype but more severe than p.Met1149	Mild phenotype but more severe than p.Met1149
Lack externally visible plexiform, cutaneous, or subcutaneous neurofibromas	High prevalence of symptomatic spinal neurofibromas (~19%) and lower prevalence of cutaneous neurofibromas	May be predisposed to major external plexiform neurofibromas (~29%)
High frequency of Noonan-like features (29%)	Higher frequency of Noonan-like features (~21%)	Higher frequency of Noonan-like features (~29%)
Present with >5 CAL spots (~90%) with or without skinfold freckling	Present with >5 CAL spots (~93%) with or without skinfold freckling	Present with >5 CAL spots (~95%) with or without skinfold freckling
No symptomatic optic gliomas or malignant neoplasms observed	Higher incidence of skeletal abnormalities (32%)	Higher incidence of skeletal abnormalities (41%)

5 Koczkowska, M. et al. (2019). Clinical spectrum of individuals with pathogenic NF1 missense variants affecting p.Met1149, p.Arg1276, and p.Lys1423: genotype-phenotype study in NF1. *Human Mutation*, 1-17.