

Very few *clinically significant* NF1 genotype-phenotype correlations are known up till today, which does not mean there aren't more that need to be discovered. The first known concerns a constitutional **1.4 Mb microdeletion** encompassing the *NF1* gene. Patients carrying this deletion present with a more severe phenotype, including increased neurofibroma burden starting at a younger age, facial dysmorphism and developmental delay/ intellectual disability or learning problems. In addition, congenital cardiac defects, connective tissue and skeletal anomalies are more frequently found in these patients. These patients have an increased life-time risk for a malignant peripheral nerve sheath tumor.

A second known correlation involves a specific deletion of a single amino acid in the *NF1* gene, **p.Met992del**. Patients with this mutation develop a milder phenotype consisting mainly of café-au-lait macules and skinfold freckling but lack of cutaneous or externally visible plexiform neurofibromas. This mild phenotype overlaps with and is clinically non-distinguishable from Legius syndrome, caused by mutations in *SPRED1*.

We recently completed a study and reported in the journal "Human Mutation" on a large cohort of 136 patients from 98 unrelated families carrying one of five different missense mutations affecting *NF1* **codon 1809**. This mutation is the second most frequent mutation in the UAB cohort, identified in 1.23% of unrelated probands carrying an *NF1* mutation, second only to the 1.4 Mb *NF1* type 1 microdeletion. Patients presented with multiple café-au-lait macules, with or without freckling and Lisch nodules, but externally visible plexiform neurofibromas, symptomatic optic pathway glioma or clear cutaneous or subdermal neurofibromas were not found. There was, however, a high incidence of developmental delay/intellectual disability/learning disorder, pulmonic stenosis, short stature and Noonan syndrome features. Therefore, the phenotype in patients with a missense mutation affecting *NF1* codon 1809 is not necessarily "mild" *per se*, but it definitively is *distinct* from classic NF1.

Even though the study we just published is heartening for patients carrying an *NF1* missense mutation at codon 1809, caution is still needed: the current study, combining all reported data on Arg1809-positive individuals who are ≥5 years of age, has a power of 92% to detect complications with a prevalence of at least 3%. Complications associated with this mutation, that are even rarer (e.g. 1%), would require larger cohorts (minimum of 250 individuals). Therefore, we call for an international effort to carefully collect accurate phenotypic data on these patients given the uplifting prospect for their management.

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