

Familial Lipomas Without Classic Neurofibromatosis-1 Caused by a Missense Germline NF1 Mutation

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Neurofibromatosis type 1 (NF1; OMIM 162200) is an autosomal dominant disorder caused by a wide variety of germline mutations in the *NF1* gene. Nearly all individuals with NF1 exhibit café-au-lait macules before the age of 2,¹ but can also develop numerous other medical problems, including autism, cognitive deficits, tumors, and congenital heart defects. Although the clinical variability inherent in NF1 has been attributed to stochastic events, it is possible that the specific germline *NF1* mutation might be one factor underlying this heterogeneity. To illustrate this point, we report a family with 2 affected members harboring a missense mutation in the *NF1* gene who lack the classic features of NF1.

The proband came to medical attention for failure to thrive, hypotonia, global delay, projectile vomiting, and feeding problems, necessitating the placement of a gastrostomy tube at 9 months of age. Although the pregnancy and vaginal delivery at 39 weeks of gestation were uncomplicated, soon after birth, a patent foramen ovale and pulmonic valve stenosis were noted. Because her father had several cutaneous masses, later pathologically determined to be lipomas, the patient underwent chromosomal microarray (normal) and NF1 genetic testing, revealing a c.3445A>G (p.Met1149Val) germline mutation in the *NF1* gene, which was paternally inherited based on parental NF1 genetic testing. Her father had no Lisch nodules, café-au-lait macules, or skinfold freckling. The patient also had no café-au-lait macules or skinfold freckling at 20 months of age, but had 2 mobile subcutaneous nodular masses on her left chest, suggestive of neurofibromas. No plexiform neurofibromas were appreciated on either the patient or her father, and no other members of their extended family had features of NF1. The patient underwent brain and total spine neuroimaging, based on a left-hand preference, axial hypotonia and a reluctance to bear weight on her legs, which were completely normal.

The finding of a germline *NF1* mutation in this family raises several important points. First, this missense mutation results in a methionine to valine change in an amino acid residue conserved in vertebrates and flies and predicted to be pathogenic using both PolyPhen (isoform-1, possibly_damaging, 0.557; isoform-2, probably_damaging, 0.909) and SIFT (both isoforms, deleterious, 0) variant pathogenicity analysis programs. Of interest, the mutated amino acid is 5' to the RAS GTPase activating protein-related domain and is located within a segment involved in tubulin binding and neurofibromin homodimerization (residues 1,085–1,172).² This variant has a frequency of 1 in 251,376 alleles in control individuals (0.000003978; gnomAD database). It has also been reported in a 56-year-old woman with malignant melanoma whose tumor harbored both the Met1149Val mutation and another *NF1* mutation, creating a premature protein truncation (Leu1109X) within the same domain and resulting in 5% of normal *NF1* gene expression (cBioPortal).³ For these reasons, it is highly likely that the Met1149Val mutation is pathogenic in this family.

Second, although this family did not have NF1, patients with NF1 and Met1149Val *NF1* gene mutations tend to exhibit a mild clinical phenotype, with a paucity of optic gliomas or plexiform neurofibromas.⁴ In contrast to the family reported herein, of the 48 patients with clinical assessments,⁴ 94% had greater than 5 café-au-lait macules: Only 2 of these individuals had lipomas, and only 1 had

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pulmonic stenosis. The finding of this mutation in a family without NF1 extends the spectrum of clinical manifestations that likely arise from Met1149Val mutation.

Third, the lack of classic features of NF1 in these 2 individuals add to the growing list of specific genotype-phenotype correlations in patients with NF1, including patients harboring Arg1809 missense and Met991 codon deletion mutations who do not develop optic gliomas or neurofibromas.⁴ Similarly, patients with missense mutations located in residues spanning 844 to 848 have been reported to exhibit more severe disease complications.⁵ As the differential effects of specific germline *NF1* gene mutations become elucidated, it is possible that they will help to define specific contact points for neurofibromin binding partners that underlie these unique effects.

Finally, previous work from our laboratory has shown that different germline *NF1* gene mutations create dissimilar biological effects. Using human-induced pluripotent stem cells and mice genetically engineered with NF1 patient *NF1* gene mutations, we found striking differences in neuronal differentiation⁶ and optic glioma formation.⁷ Surprisingly, this variability was not the result of different levels of RAS hyperactivation, but rather reflected other functions of neurofibromin, some of which remain to be defined. These observations suggest that other readouts for neurofibromin activity, besides RAS pathway signaling, are needed to characterize the contributions of different germline *NF1* gene mutations to human disease pathobiology.

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