Neurofibromatosis type 1-like syndrome or Legius syndrome: an update.

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Multiple café-au-lait spots are the hallmark of Von Recklinghausen disease or neurofibromatosis type 1. In 2007 our group reported that some individuals with multiple café-au-lait spots have a heterozygous mutation in the *SPRED1* gene and have neurofibromatosis type 1-like syndrome or Legius syndrome. It is estimated that about 1-4% of individuals with multiple café-au-alit spots have a heterozygous *SPRED1* mutation. Mutational data on *SPRED1* and clinical data from 146 patients are tabulated in an online database (http://www.lovd.nl/SPRED1). The *SPRED1* gene was identified in 2001 and codes for a protein that downregulates the RAS-MAPKinase pathway similar to neurofibromin, the protein encoded by the *NF1* gene. Individuals with Legius syndrome have multiple café-au-lait spots with or without freckling, but they do not show the typical NF1 associated tumors such as neurofibromas or optic pathway gliomas. Neurofibromatosis type 1 associated bone abnormalities and Lisch nodules are also not reported in patients with Legius syndrome. It was however shown that children with Legius syndrome have a higher incidence of learning disabilities and attention deficit disorder compared to the general population. Mice with a homozygous knock-out of the *Spred1* gene show similar learning deficits and decreased synaptic plasticity in hippocampal neurons as seen in *Nf1* heterozygous mice, underlining the importance of the RAS-MAPKinase pathway for learning and memory. Recently a specific binding between neurofibromin and SPRED1 was demonstrated. SPRED1 seems to be important to recruit neurofibromin to the plasma membrane.