

Legius Syndrome: A Clinical Observation of a Father-Son Pair

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Case Presentation

A 3-year-old male was referred to our clinic to evaluate multiple café-au-lait macules (CALMs) present since birth. His growth and developmental milestones were age-appropriate, with no other abnormality observed. (Figure 1A). The family history was significant as the patient's father exhibited multiple CALMs, axillary freckling (Figures 1B and 1D), and several subcutaneous lipomas confirmed by ultrasound (Figure 1E). Genetic testing revealed a heterozygous frameshift mutation in exon 7 of the *SPRED1* gene (NM_152594:c.1149_1152delAGAG, p.G385Ifs*20). This mutation was also detected in the affected father, but absent in the mother (Figures 1F–H), confirming Legius syndrome.

Teaching Point

Legius syndrome is an autosomal dominant disorder caused by germline loss-of-function mutations in the *SPRED1* gene.

The clinical features include multiple CALMs, with or without associated intertriginous freckling [1]. Associated findings may encompass lipomas, macrocephaly, or neurodevelopmental manifestations, including learning disabilities, attention-deficit/hyperactivity disorder (ADHD), and mild developmental delays [2]. In contrast to neurofibromatosis type 1 (NF1), Legius syndrome is characterized by the absence of tumorigenic manifestations such as neurofibromas and optic pathway gliomas, and it is associated with a milder clinical phenotype. Current clinical guidelines highlight the importance of monitoring and managing neurodevelopmental issues, given that there is no targeted therapy available for cutaneous lesions. Accurate diagnosis is essential for distinguishing Legius syndrome from NF1, thereby preventing unnecessary surveillance measures such as tumor screening and mitigating familial anxiety associated with NF1-related complications. Genetic counseling and prenatal testing should be made available to affected families.

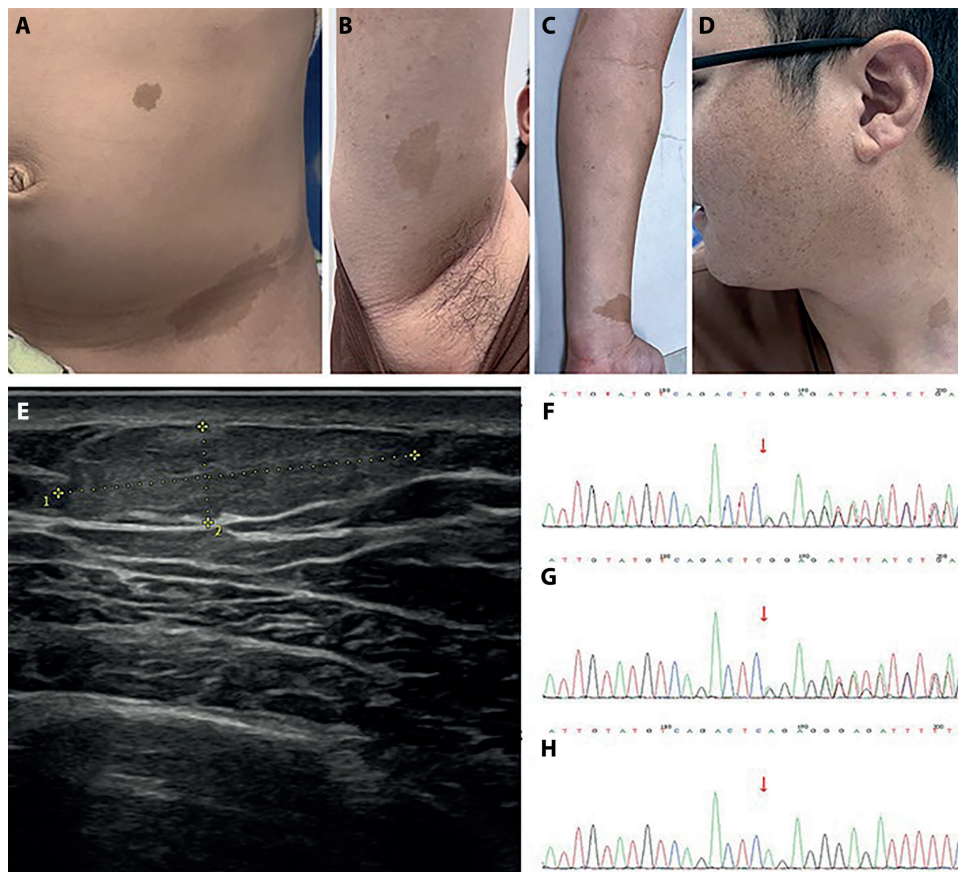


Figure 1. Clinical features included café-au-lait macules in the patient (A) and café-au-lait macules with facial freckles in the father (B–D). Ultrasound examination of the father’s right flank revealed a slightly hyperechoic region (28 mm × 7 mm) with well-defined margins and clear demarcation from surrounding tissues, consistent with lipomas (E). The patient harbored a heterozygous frameshift mutation, c.1149_1152delAGAG (p.G385Ifs*20), in exon 7 of the *SPRED1* gene (F). This mutation was identified in his father (G) but absent in his mother (H).

References

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