

# LEPOARD syndrome: A report of a case with a novel PTPN11 mutation



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**Key words:** autosomal dominant; B-RAF; lentiginos; leopard syndrome; macules; missense mutation; PTPN11.

## INTRODUCTION

LEOPARD syndrome (LS) is an autosomal dominant inherited or sporadic disease associated with high penetrance and phenotypic variability.<sup>1</sup> It is caused by mutations in the protein tyrosine phosphatase nonreceptor 11 (*PTPN11*), *B-RAF*, and *RAF1* genes.<sup>2</sup> The acronym LEOPARD refers to the main manifestations of the syndrome, namely, Lentiginos, Electrocardiogram conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retarded growth, and sensorineural Deafness.

Herein, we report a case of LS, in which we identified a novel mutation in the *PTPN11* gene.

## CASE REPORT

A 43-year-old Jewish man born to healthy, non-consanguineous parents presented at the dermatology ward for the evaluation of multiple pigmented lesions, which, according to the patient, initially appeared at the age of 3 years and gradually increased in number. The patient was otherwise healthy.

The patient was born at term after a pregnancy with no significant complications or neonatal problems. Cutaneous examination revealed numerous flat brown-to-black-colored macules (lentiginos) on the face, neck, torso, back, and limbs (Figs 1 and 2). Physical examination revealed a facial dysmorphism, including ocular hypertelorism, broad nasal root, low set ears, and pectus excavatum. A skin biopsy specimen showed features suggestive of lentigo simplex (Fig 3).

### Abbreviations used:

LS: LEOPARD syndrome  
 PTP: protein tyrosine phosphatase

There was no previous family history of lentiginos. Since LS was clinically suspected, the following further investigations were conducted: Audiometry revealed bilateral sensorineural hearing loss (>2000 Hz). Cardiac evaluation revealed a conduction abnormality (AV Block, Mobitz 1) in Holter, electrocardiogram values were within the normal limits, and Echo was normal with no evidence of pulmonary stenosis. Sanger sequencing of the coding regions of the *PTPN11* gene revealed a novel heterozygous mutation at C.380C>T in exon 4 (Thr127Ile). The patient's parents were not found to carry the same genomic change.

## DISCUSSION

LS is a rare disease. Approximately 200 patients have been reported worldwide, but the real incidence of LS is not known.<sup>1</sup> Most cases are caused by a germline *PTPN11* missense mutation. However, mutations in the *RAF1* and *B-RAF* genes have also been reported.<sup>2</sup>

According to Sarkozy et al, in approximately 85% of the cases, a heterozygous missense mutation is detected in exons 7, 12, or 13 of the *PTPN11* gene.<sup>3</sup> In our case report, we present a novel mutation located at exon 4 in the *PTPN11* gene.

The *PTPN11* gene encodes for the SRC homology 2 (SH2) domain-containing PTPase protein,

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;11:57-9.  
 2352-5126

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<https://doi.org/10.1016/j.jidcr.2021.03.022>



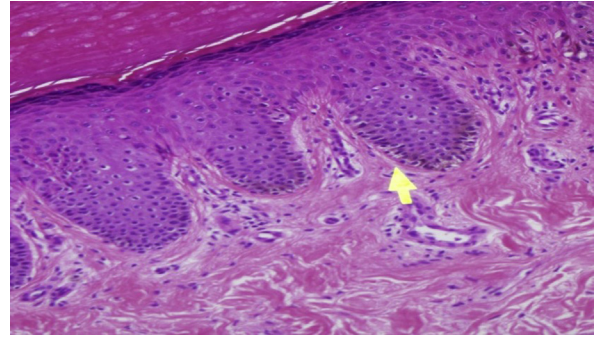
**Fig 1.** Multiple lentiginos on the face and neck along with hypertelorism, broad nasal root, and low set ears.



**Fig 2.** Multiple lentiginos on the back along with winged scapula.

characterized by 2 tandemly arranged SH2 (N-SH2 and C-SH2) domains and one protein tyrosine phosphatase (PTP) domain. SRC homology 2 (SH2) domain-containing PTPase functions as a cytoplasmic signaling transducer downstream of multiple receptors for growth factors, cytokines, and hormones, with a particular role through the RAS-mitogen activated protein kinase pathway.<sup>4,5</sup>

These genes are considered oncogenes. Once mutated, oncogenes have the potential to cause normal cells to become cancerous. Therefore,



**Fig 3.** Histopathology showed mild epidermal acanthosis, increased numbers of melanocytes without atypia in the basal layer, and variable basal hyperpigmentation. (Hematoxylin-eosin stain.)

patients with LS are possibly at an increased risk of malignancy.<sup>6</sup>

The differential diagnosis of patients with multiple lentiginos includes the following in addition to LS: Carney Complex, Laugier-Hunziker syndrome, Ruvalcaba-Myhre-Smith syndrome, Bannayan-Zonnana syndrome, Cowden disease, Peutz-Jeghers syndrome, and benign lentiginos.<sup>7</sup>

Voron et al<sup>8</sup> proposed that diagnostic criteria of LS should require diffuse lentiginos and 2 other syndrome traits. If diffuse lentiginos are absent, the presence of a first-degree affected relative and 3 other distinct features are necessary for diagnosis.

In our case, the current clinical diagnostic criteria were fulfilled by lentiginos and 4 minor criteria (cephalofacial dysmorphism, cardiac findings, deafness, and pectus excavatum). In addition, genetic analysis confirmed the diagnosis (novel mutation in PTPN11).

In this report, we would like to emphasize the importance of detailed clinical evaluation and appropriate assessment in patients with multiple lentiginos.

Genetic testing of patients with suspected or established diagnosis of LS is highly advisable, since it may assist in making the diagnosis or confirm it. However, more importantly, it may provide familial genetic counseling.

There is no published accepted follow-up protocol for patients with LS. However, we suggest the following clinical follow-up protocol based on the various possible types of systemic involvement: hearing test, cardiologic evaluation (echocardiography and electrocardiogram), growth parameter monitoring in children, neurological, and urogenital evaluations. Full-body photography and dermoscopy follow-up are also important due to the possibly large number of nevi.

The frequency by which these assessments should be conducted remains unclear, but we would advise evaluation at least once every 2 years, and surely earlier, if clinical symptoms and/or signs appear.

**Conflicts of interest**

None disclosed.

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