Clin Pediatr Endocrinol 2008; **17**(4), 121-122

Mutation-in-Brief

A Novel A461S Mutation of *PTPN11* in a Female with LEOPARD Syndrome

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Introduction

LEOPARD syndrome (LS) is a congenital developmental disorder and is an acronym for multiple *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of genitalia, retardation of growth, and sensorineural deafness (1). These clinical features overlap those of Noonan syndrome (NS), and heterozygous germline *PTPN11* mutations have been identified in approximately 45% of NS patients and in >80% of LS patients (1). Herein, we report a novel mutation of *PTPN11* in a female with LS.

Patient Report

A 34-year-old Japanese female was referred to us for molecular diagnosis of LS. She had numerous nevi, ocular hypertelorism, cardiac diseases (mitral valve insufficiency and right bundle branch block with left axis deviation) and sensorineural deafness. Her height was 160 cm (+0.4 SD), and her weight was 62 kg (+1.0 SD). This study was approved by the ethical committee of our institution. After obtaining informed consent, direct sequencing was performed for *PTPN11* using leukocyte genomic DNA from this patient in accordance with previously reported methods (2). Consequently, a novel heterozygous c.1381G>T (p.A461S) mutation was identified on exon 12 (Fig. 1).

Discussion

We identified a novel mutation (c.1381G>T, p.A461S) of *PTPN11* in a female with LS. Recent

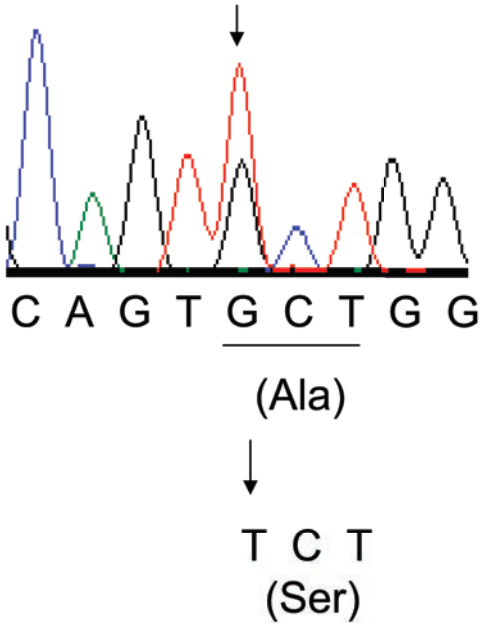

Fig. 1. An electrochromatogram showing a heterozygous c.1381G>T (p.A461S) mutation (an arrow).

Received: August 21, 2008
Accepted: September 18, 2008
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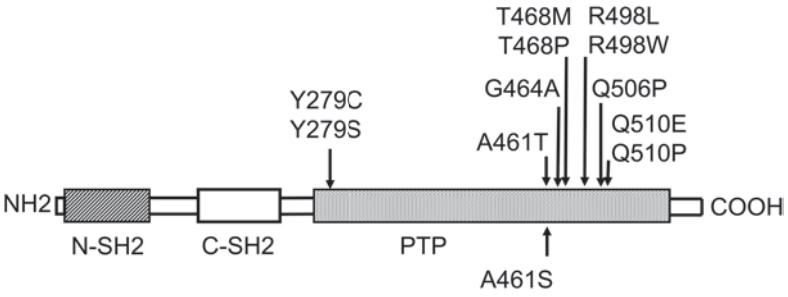

Fig. 2. Schematic representation of PTPN11 protein showing the distribution of mutations reported in LS (above). The position of the mutation detected in this study is also indicated (below). N-SH2 and C-SH2 are the N-terminal and C-terminal tandemly arranged SH2 domains and are followed by a protein PTP domain at the C-terminus.

studies have shown that LS-associated *PTPN11* mutants impair catalytic functions and exert dominant negative effects, whereas NS-associated *PTPN11* mutants exert gain-of-function effects with excessive phosphatase activities (1, 3). Indeed, the mutations in LS and NS are mutually exclusive, and all eleven types of mutation in LS (two recurrent Y279C and T468M mutations and additional Y279S, A461T, T468P, G464A, R498L, R498W, Q506P, Q510E and Q510P mutations) have been identified at the catalytic cleft of the PTPN11 protein (1, 3–5) (Fig. 2). Since the novel c.1381G>T (p.A461S) mutation in this patient also resides at the catalytic cleft, this is consistent with the positional properties of *PTPN11* mutations leading to LS.

Acknowledgements

This work was supported in part by grants for Child Health and Development (17C-2) and for Research on Children and Families (18-005) from the Ministry of Health, Labor and Welfare of Japan.

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