Structural, functional, and clinical characterization of a novel PTPN11 mutation cluster underlying Noonan Syndrome.

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Germline mutations in *PTPN11*, the gene encoding the Src-homology 2 (SH2) domain-containing protein tyrosine phosphatase (SHP2), cause Noonan syndrome (NS), a relatively common, clinically variable, multisystem disorder. Here, we report on the identification of five different *PTPN11* missense changes affecting residues Leu^{261}, Leu^{262}, and Arg^{265} in 16 unrelated individuals with clinical diagnosis of NS or with features suggestive for this disorder, specifying a novel disease-causing mutation cluster. Expression of the mutant proteins in HEK293T cells documented their activating role on MAPK signaling. Structural data predicted a gain-of-function role of substitutions at residues Leu^{262} and Arg^{265} exerted by disruption of the N SH2/PTP autoinhibitory interaction. Molecular dynamics simulations suggested a more complex behavior for changes affecting Leu^{261}, with possible impact on SHP2's catalytic activity/selectivity and proper interaction of the PTP domain with the regulatory SH2 domains. Consistent with that, biochemical data indicated that substitutions at codons 262 and 265 increased the catalytic activity of the phosphatase, while those affecting codon 261 were only moderately activating but impacted substrate specificity. Remarkably, these mutations underlie a relatively mild form of NS characterized by low prevalence of cardiac defects, short stature, and cognitive and behavioral issues, as well as less evident typical facial features.