Papers of the Week

Making Sense of Missense Mutations in Noonan Syndrome

♦ See referenced article, *J. Biol. Chem.* 2012, **287**, 27066–27077

Counteracting Effects Operating on Src Homology 2 Domain-containing Protein-tyrosine Phosphatase 2 (SHP2) Function Drive Selection of the Recurrent Y62D and Y63C Substitutions in Noonan Syndrome

Noonan syndrome is a developmental disorder in which patients suffer from growth retardation, facial abnormalities, congenital heart defects, and other problems. Approximately 50% of patients with the syndrome have germline mutations in the *PTPN11* gene. The gene encodes SHP2, a cytoplasmic protein-tyrosine phosphatase (PTP) involved in the RAS signal transduction pathway. The protein has two N-terminal Src homology 2 (SH2) domains, a catalytic domain (PTP), and a C-terminal tail. Y62D and Y63C substitutions in the protein are largely invariant and are among the most common mutations in Noonan syndrome. In this Paper of the Week, Marco Tartaglia at the Istituto Superiore di Sanità in Italy and colleagues characterized all possible amino acid substitutions that result from single-base changes in codons 62 and 63. The investigators found that substitutions in these codons have complex effects on SHP2 structure and function. The mutations cause an extensive structural rearrangement of the first SH2 domain that disrupts its autoinhibitory interaction with the PTP domain and affects proper binding of SHP2 to its signaling partners. The data showed that there is a selection-by-function mechanism acting as a driving force on the largely invariant *PTPN11* mutations in codons 62 and 63. The authors say that the selection-by-function mechanism "implies the existence of counteracting effects operating on the allosteric control of the function of SHP2."

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