

## Mutations in *PTPN11*, Encoding the Protein Tyrosine Phosphatase SHP-2 Cause Noonan Syndrome

In approximately 50% of subjects with Noonan syndrome (NS is mapped to chromosome 12q24.1) the investigators identified mutations in the 15 exon gene (*PTPN11*) encoding the non-receptor protein [tyrosine phosphatase (PTP) - SHP-2]. This protein has two SH2 (Src homology docking) domains and a long enzymatic domain with the sites interacting to achieve an active or inactive state of function. Diverse missense mutations were found in the third exon encoding the amino-terminal SH2 (Src homology) domain and in three exons (7,8,13) encoding the PTP domain that apparently rendered the protein constitutively active. SHP-2 is a component of several intracellular signal transduction systems involved in embryonic development that modulate cell division, differentiation, and migration, including that mediated by the epidermal growth factor receptor. The latter pathway is important in the formation of the cardiac semilunar valves. The mutations associated with NS are in conserved amino acid sites in which the alteration leads to conformational changes that "lock" the protein in its enzymatically active state. The down-stream pathways that are affected by this "positive" change in enzyme activity have yet to be identified.

Tartaglia M, et al. *Nat Genet* 2001;29:465-468.

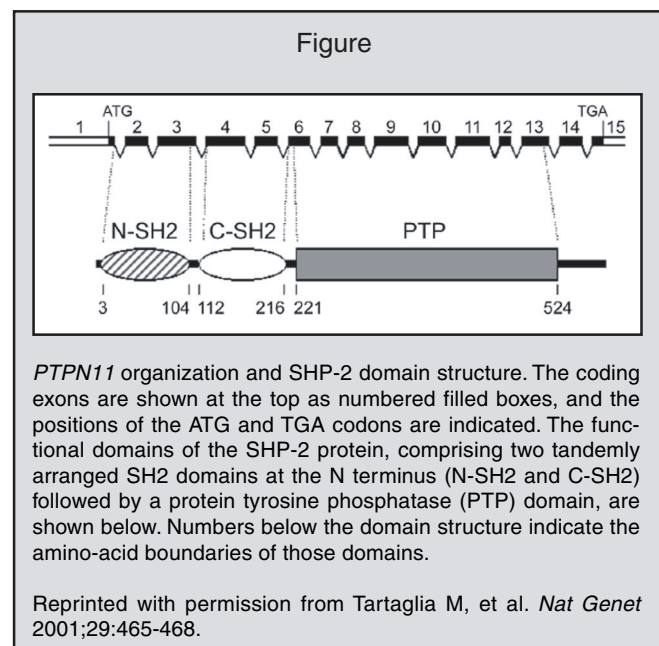
**Editor's Comment:** Noonan syndrome (OMIM 163950) is characterized by "Turner-like" facial features, short stature, webbed neck, cubitus valgus, pulmonic stenosis (rather than coarctation of the aorta which is frequent in Turner syndrome), developmental delay, and bleeding diathesis. Since the Noonan phenotype is genetically heterogeneous, other genetic errors may exist, including mutations in the non-coding regions of *PTPN11* that were not determined in the present report. The short stature and many of the skeletal abnormalities found in patients with Leri-Weill dyschondrosteosis and Turner

syndrome (TS) have been attributed to haploinsufficiency of *SHOX* (chromosome Xpter-p22.32) either due to its deletion or to loss-of-function missense or nonsense mutations.<sup>1,2</sup> Given the visual similarity of the NS and TS phenotype, it will be of interest to determine if the proteins regulated by *PTPN11* and *SHOX* interact. Might the product of *SHOX* be an inhibitor of SHP-2 generation or activity?

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### References

1. Ross JL, et al. *J Clin Endocrinol Metab* 2001;86:5674-5680.
2. Rosenfeld RG. *J Clin Endocrinol Metab* 2001;86:5674-5680.



## Mothers with Congenital Adrenal Hyperplasia (CAH) and their Children: Outcome of Pregnancy, Birth and Childhood

The authors examined the gestational history of 122 women with 21-hydroxylase deficient CAH which was confirmed by genotyping in the majority. These women were born after 1948, followed in the investigators' clinic (University Children's Hospital, Munich) and were over 20 years of age at the time of study. Eighteen of the 122 women (15%) had delivered 31 children. The diagnosis of the 18 mothers was as follows: salt-losing, 1 of 48 total (2%); simple virilizing, 12 of 64 total (19%), and non-classical, 5 of 10 total (50%). The woman with

salt-losing CAH had two miscarriages before delivering her child. One woman with non-classical CAH had two tubal pregnancies.

Conception occurred between 18-36 years (mean 28 years). The pregnancies were uneventful with the women receiving hydrocortisone, prednisone, prednisolone, or dexamethasone during gestation. Sixteen pregnancies required cesarean sections, primarily in women not having nonclassical CAH. Five of the 31 offspring were <10th percentile for gestational