

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.

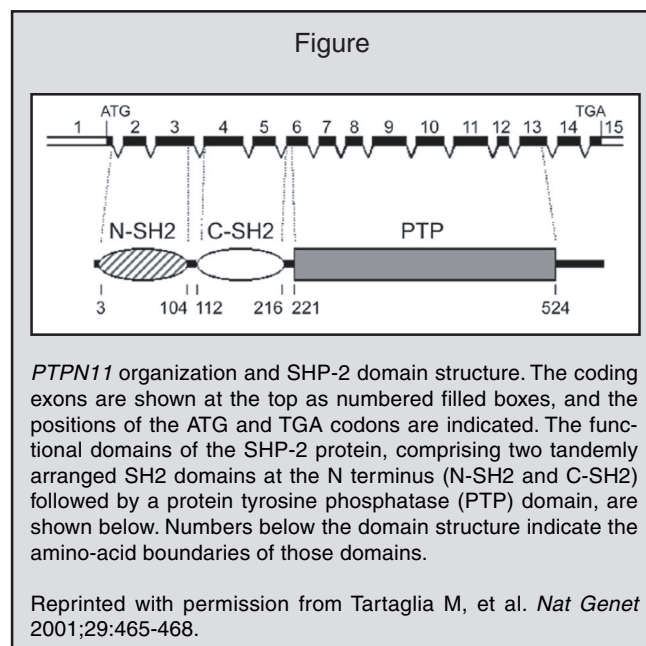
Editor's Comment: Noonan syndrome (OMIM 163950) is characterized by "Turner-like" facial features, short stature, webbed neck, cubitus valgus, pulmonic stenosis (rather than coarctation of the aorta which is frequent in Turner syndrome), developmental delay, and bleeding diathesis. Since the Noonan phenotype 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.^{1,2} 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

age. One developed an intracerebral hemorrhage. An additional patient was microcephalic at birth. None of the 18 female offspring had malformation of the external genitalia. Follow-up of the 31 offspring, 6 of whom were less than 5 years of age, 7 of whom were between 5-10 years, and 18 who were older than 10 years of age at the time of evaluation, revealed that all were growing, maturing, and developing normally.

Krone N, et al. *Clin Endocrinol* 2001;55:523-529.

First Editor's Comment: *These data are encouraging in that women with simple virilizing and non-classical CAH are often able to conceive and deliver healthy children, thus confirming previous reports. More data on the degree of adrenal suppression during pregnancy, and knowing post-natal neonatal adrenal function would have been of interest.*

That only one of 48 women with salt-losing CAH had an infant illustrates the difficulties still encountered in the management of many of these patients. As Krone et al discuss, the relative infertility of women with CAH may be due to hormonal (hyperandrogenism), anatomic (inadequate reconstruction of the vagina), or psychosocial factors (behavioral masculinization, low marriage rate, and/or sexual preference). It is anticipated that prenatal detection and treatment of females with CAH and establishing neonatal screening programs for this disorder will change substantially the "natural history" of pregnancy in females with CAH.

Regarding surgical reconstruction of the external genitalia in the virilized female, while clitoroplasty may be appropriate in the neonatal period, vaginoplasty

should be deferred until the peri menarchal period, as earlier reconstructive surgery is usually inadequate.¹ In 39 adolescent phenotypic females (20 with CAH) (mean age at examination 15 years) who underwent vaginal surgery in infancy at a median age of 10 months, Creighton et al found that approximately 60% had a good or satisfactory cosmetic appearance of the external genitalia, but almost all required further surgery to permit use of tampons during menses and, presumably, sexual relations in adulthood.

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Second Editor's Comment: *Much is being discussed and written in 2002 regarding surgery on the genitalia of patients with enlarged clitorises. The current recommendation of many surgeons and pediatric endocrinologists is that surgery on the clitoris be delayed in most cases in the newborn period. For more details the reader is referred to references 1, 2, and 3 below. A lead article concerning the dilemmas of gender assignment and surgery will be published soon in GGH to provide up-to-date considerations for you our reader.*

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References

1. Creighton SM, et al. *Lancet* 2001;358:124-125.
2. Creighton S and Minto C. *Brit Med J.* 2001;323:1264-1265.
3. Ramecroft L and Members of the Working Party of the British Association of Pediatric Surgeons on the Surgical Management of Ambiguous Genitalia. Available from: <http://www.baps.org.uk/documents/Intersex%20statement.htm>.

Growth Hormone Improves Clinical Status in Prepubertal Children with Cystic Fibrosis: Results of a Randomized Controlled Trial

Hardin and colleagues studied the effects of recombinant GH (0.3 mg/kg/wk) in 10 children with cystic fibrosis (CF) (ages 7-12, Tanner stage I) as compared to a control group of 9 similar children. All children recruited for the study were $\leq 10^{\text{th}}$ percentile for both height and weight and had adequate caloric intake as determined on 2 evaluations. Only one had an abnormal growth hormone stimulation test. Children were excluded from the study if they had been hospitalized within 6 weeks or had been treated with systemic or oral steroids within 6 weeks. Evaluations were made of pulmonary functions including forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV₁). In addition, peak expiratory pressure (PEP) and peak inspiratory pressure (PIP) were measured. Resting energy expenditure, was determined using indirect calorimetry, and lean body mass was determined by

whole body dual energy x-ray absorptiometry. Studies were made at baseline and every 3 months. Data were collected with regard to the number of hospitalizations and antibiotic therapy. All data for both the treatment group and the control group were similar at baseline.

The height and weight Z scores were significantly greater in the treatment group after one year than in the control group; furthermore the treatment group had a significant increase in lean body mass. Additionally, at 12 months the treatment group had a significant improvement in percent FVC, PIP, and PEP. There was no significant change in percent FEV₁. The GH treated group had a significant decrease in the number of hospitalizations, although outpatient antibiotic therapy was not different between the two groups. There was no significant change in resting energy expenditure or nutritional intake during the study and carbohydrate