# *163950 NOONAN SYNDROME

*Alternative titles; symbols*

NOONAN SYNDROME 1; NS1
MALE TURNER SYNDROME
FEMALE PSEUDO-TURNER SYNDROME
TURNER PHENOTYPE WITH NORMAL KARYOTYPE
PTERYGIUM COLLI SYNDROME, INCLUDED

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Gene Map Locus: 12q22-qter

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## TEXT

The disorder now known as Noonan syndrome bears similarities to the disorder described by Turner (1939) and shown by Ford et al. (1959) to have its basis in a 45,X chromosomal aberration. (With considerable justification, Ullrich's name is combined with that of Turner as the designation for the 45,X syndrome. Ullrich described the disorder 8 years before Turner. Wiedemann and Glatzl (1991) provided a follow-up

of Ullrich's original patient with Ullrich-Turner syndrome and demonstrated that the restudy in 1987, when the patient was 66 years old, confirmed the 45,X chromosome constitution.)

Noonan (1968) reported 19 cases of whom 17 had pulmonary stenosis and 2 had patent ductus arteriosus. Twelve were males and 7 were females. Deformity of the sternum with precocious closure of sutures was a frequent feature. Kaplan et al. (1968) described 2 brothers with elevated alkaline phosphatase levels, one of whom also had malignant schwannoma of the forearm. Nora and Sinha (1968) observed mother-to-offspring transmission in 3 families; in 1 family, transmission was through 3 generations. They suggested X-linked dominant inheritance of either a single mutant gene or a submicroscopic deletion. Among 95 male patients with pulmonary stenosis, Celermajer et al. (1968) found the Turner phenotype in 8. In 5 of these, karyotyping was performed. In 4 the chromosomes were normal. In one an extra acrocentric chromosome was present. Abdel-Salem and Temtamy (1969) reported 2 affected sibs from a first-cousin marriage. A deceased female sib may have been affected also. They suggested autosomal recessive inheritance. Baird and De Jong (1972) described 7 cases in 3 generations. One affected woman had 5 affected children (out of 6) with 2 different husbands. Seizures and anomalous upper lateral incisors may have been coincidental. Diekmann et al. (1967) described 2 brothers and a sister, with normal and unrelated parents, who had somatic characteristics of the Noonan syndrome, particularly pterygium colli and deformed sternum, and had myocardiopathy leading to death at ages 12 and 10 in two of them. Migeon and Whitehouse (1967) described 2 families, each with 2 sibs with somatic features of the Turner syndrome. In 1 family, 2 brothers had webbing of the neck, coarctation of the aorta and cryptorchidism. In the second, a brother and sister were affected. Simpson et al. (1969) reported experiences suggesting that rubella embryopathy may result in the Turner phenotype, thereby accounting for either the male Turner syndrome or the female pseudo-Turner syndrome. A particularly convincing pedigree for autosomal dominant inheritance was reported by Bolton et al. (1974), who found the condition in a man and 4 sons (in a sibship of 10). Four of the 5 affected persons had pulmonic stenosis. Father-to-son transmission was reported by Qazi et al. (1974).

Cole (1980) pointed out that the blacksmith in the famous painting 'Among Those Left' by Ivan Le Lorraine Albright appears to have had Noonan syndrome. The contour of the sternum, the low-set ears, and

the short stature are suggestive. Genetic confirmation was provided by studies of a great-grandson with general features of the Noonan syndrome and cardiac abnormalities consistent with that diagnosis (pulmonic stenosis and regurgitation, abnormal architecture of the left ventricular musculature). Opitz and Pallister (1979) reproduced the first published illustration of the Noonan syndrome by Kobylinski (1883), and Opitz (1985) republished the photograph of Rickey E., the first patient with 'her' syndrome studied at the State University of Iowa by Jacqueline A. Noonan.

Koretzky et al. (1969) described an unusual type of pulmonary valvular dysplasia which showed a familial tendency with either affected parent and offspring or affected sibs. Although some relatives had pulmonary valvular stenosis of the standard dome-shaped variety, the valvular dysplasia in others was characterized by the presence of three distinct cusps and no commissural fusion. The obstructive mechanism was related to markedly thickened, immobile cusps, with disorganized myxomatous tissue. Other features were retarded growth, abnormal facies (triangular face, hypertelorism, low-set ears and ptosis of the eyelids), absence of ejection click, and unusually marked right axis deviation by electrocardiogram. It now seems clear that the patients of Koretzky et al. (1969) had the Noonan syndrome. Mendez and Opitz (1985) stated that the Watson syndrome (193520) and the LEOPARD syndrome (151100) 'are essentially indistinguishable from the Noonan syndrome.' Witt et al. (1987) reviewed the occurrence of lymphedema in Noonan syndrome. When it does occur, it opens the possibility of prenatal diagnosis by imaging methods or by AFP level. Noonan syndrome was one of the causes found for posterior cervical hygroma in a series of previable fetuses studied by Kalousek and Seller (1987). The authors found, furthermore, that 45,X Turner syndrome lethal in the fetal period showed a constant association of 3 defects, posterior cervical cystic hygroma, generalized subcutaneous edema, and preductal aortic coarctation. Evans et al. (1991) found a large cutaneous lymphangioma of the right cheek and amegakaryocytic thrombocytopenia in a male infant with Noonan syndrome. Donnenfeld et al. (1991) presented a case of Noonan syndrome in which posterior nuchal cystic hygroma was diagnosed at 13 to 14 weeks of gestation by ultrasonography. The hygroma had regressed by the time of birth leaving nuchal skin fold redundancy and pterygium colli. On the basis of studies of genital tract function in 11 adult males with Noonan syndrome, Elsawi et al. (1994) concluded that bilateral testicular

Four of the 11 men had fathered children.

Thrombocytopenia occurs in some cases of the Noonan syndrome (Goldstein, 1979). Partial deficiency of factor XI was described by Kitchens and Alexander (1983). Out of 9 patients with Noonan syndrome, de Haan et al. (1988) found 4 with partial deficiency of factor XI (30-65% of normal). They reviewed the other reports of bleeding tendency associated with thrombocytopenia or with abnormal platelet function. Witt et al. (1988) described bleeding diathesis in 19 patients with Noonan syndrome. Several different defects were identified in the coagulation and platelet systems, occurring singly or in combination; for example, 2 patients had factor XI deficiency, 3 had presumptive von Willebrand disease, and 1 had thrombocytopenia. In 5 of the patients an unusually pungent odor of urine and sweat was noted by parents. One of these patients was reported by Humbert et al. (1970) as a case of trimethylaminuria (136131) and another patient was suspected of having this condition. Sharland et al. (1990) also described a variety of coagulation factor deficiencies. The most common abnormality was a partial factor XI deficiency in the heterozygote range, found in 21 of 31 patients. Of 72 patients studied (37 male, 35 female, mean age 11.4 years) by Sharland et al. (1992), 47 (65%) had a history of abnormal bruising or bleeding. In 29 patients (40%), prolonged activated partial thromboplastin time was found. In 36 patients (50%) specific abnormalities were found in the intrinsic pathway of coagulation, i.e., partial deficiency of factor XI:C, XII:C, and VIII:C. Multiple abnormalities among these 36 patients included combined deficiencies of factors XI and XII (4 patients), of factors XI and VIII (4 patients), and of factors VIII, XI, and XII (1 patient). In 5 families, similar coagulation-factor deficiencies were present in first-degree relatives. Sharland et al. (1992) suggested that because of the involvement of several factors, either singly or in combination, there are likely to be regulatory factors that control the intrinsic (contact activation) system; that these factors are under chromosomal genetic control; and that abnormalities of this regulation occur in Noonan syndrome.

Allanson et al. (1985) studied the changes in facial appearance with age. They pointed out that the manifestations may be subtle in adults. Ranke et al. (1988) analyzed the clinical features of 144 patients from 2 West German centers. The size at birth was normal in both sexes. In both males and females, the mean height followed along the 3rd percentile until puberty, but decreased transiently due to an

the lower limits of normal at the end of the second decade of life. The mean adult height was 162.5 cm in males and 152.7 cm in females, respectively. Allanson (1987) provided a useful review. The fetal phenytoin syndrome, occurring in the offspring of mothers taking this anticonvulsant, closely simulates the Noonan syndrome. Baraitser and Patton (1986) reported 4 unrelated children (2 boys, 2 girls) with a Noonan-like syndrome associated with sparse hair as a conspicuous feature.

Using a number of probes at the neurofibromatosis type I locus (NF1; 162200) in the study of 11 families with Noonan syndrome in 2 or 3 generations, Sharland et al. (1992) excluded proximal 17q as the location of the gene. Studying six 2-generation families with classic Noonan syndrome, Flintoff et al. (1993) could find no evidence of linkage of this disorder to NF1 on 17q or to NF2 (101000) on 22q. Edman Ahlbom et al. (1995) likewise could find no evidence of linkage between NF1 and Noonan syndrome with cafe-au-lait spots. By means of a genome-wide linkage analysis in a large Dutch kindred with autosomal dominant Noonan syndrome, Jamieson et al. (1994) localized the gene to chromosome 12; maximum lod = 4.04 at theta = 0.0. Linkage analysis using chromosome 12 markers in 20 smaller, 2-generation families gave a maximum lod of 2.89 at theta = 0.07, but haplotype analysis showed nonlinkage in 1 family. These data implied that a gene for Noonan syndrome is located on 12q between D12S84 and D12S366. This is in the distal part of 12q, 12q22-qter.

## SEE ALSO

Alslev and Reinwein (1958) ; Char et al. (1972) ; Duncan et al. (1981) ; Fisher et al. (1982) ; Golabi et al. (1985) ; Hall et al. (1982) ; Levy et al. (1970) ; Linde et al. (1973) ; Miller and Motulsky (1978) ; Nora et al. (1974) ; Pierini and Pierini (1979) ; Sharland et al. (1992) ; Wiedemann (1991) ; Witt et al. (1985)

## REFERENCES



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