Journal of Paediatrics and Child Health

doi:10.1111/j.1440-1754.2010.01970.x

REVIEW ARTICLE

# Noonan syndrome

Anne M Turner

Department of Medical Genetics, Sydney Children's Hospital, Randwick, New South Wales, Australia

**Abstract:** Noonan syndrome is a common autosomal dominant condition, readily recognisable in childhood. It is characterised by a pattern of typical facial dysmorphism and malformations including congenital cardiac defects, short stature, abnormal chest shape, broad or webbed neck, and a variable learning disability. Mildly affected adults may not be diagnosed until the birth of a more obviously affected child. The phenotype is highly variable. Important progress in understanding the molecular basis of this and other related conditions was made in 2001 when germline mutations in the *PTPN11* gene were found to account for ~50% of cases. Since then, mutations in additional genes in the rat sarcoma (RAS) pathway have been identified in a proportion of the remainder. Molecular confirmation of diagnosis is now possible for many families and has become increasingly important in guiding management. Increased awareness by paediatricians will lead to earlier diagnosis, and provide patients and their families with accurate genetic counselling, including options when planning pregnancy.

**Key words:** autosomal dominant; congenital heart defect; Noonan syndrome; *PTPN11*; short stature.

Noonan syndrome (NS) is a common autosomal dominant multiple congenital anomaly disorder. The prevalence is said to be 1 in 1000 to 1 in 2500,[1] but mild cases may be even more common.[2] Many adults are healthy individuals. A true prevalence figure must await some form of population screening (for multiple genes). Despite this, many clinicians consider NS to be quite rare and that an affected child would be easy to spot. However, making the diagnosis of NS is not always straightforward, especially in adulthood as the features are often quite subtle. It is sometimes difficult in the newborn period too, especially in the presence of oedema. The advent of genetic testing to confirm the diagnosis has meant that the wide spectrum of the disorder has only recently become apparent. This phenomenon is seen regularly when a diagnostic test for a genetic condition first becomes available. The condition is still sometimes referred to as 'male Turner syndrome', implying that the condition is not seen in females. This term is misleading, incorrect and should not be used.

**Key Points**

1. Noonan syndrome is a common and under-diagnosed condition.
2. Molecular testing can confirm most cases and may have important implications for management.
3. Correct early diagnosis is important for optimal management of the child and family. Where the diagnosis is suspected, early referral to a clinical genetics service is advised.

**Correspondence:** Dr Anne M Turner, Department of Medical Genetics, Sydney Children's Hospital, High Street, Randwick, NSW 2031, Australia. Fax: +02 93821711; email: A.Turner@unsw.edu.au

Accepted for publication 1 July 2010.

NS should be considered in any child who presents with a combination of two or more of the following:

- A learning disability however mild
- A cardiac defect especially pulmonary valve stenosis
- A typical chest deformity (pectus carinatum and/or excavatum)
- Short stature
- Cryptorchidism
- A family history of any of the above.

These features should trigger a specific history and examination looking for characteristic features of the condition. However, it is important to appreciate that the condition can be present in the absence of any one single feature as listed above.

In particular, although most affected individuals have a congenital heart defect (CHD), some do not.[3]

Clinicians may sometimes consider that only a child who looks exceedingly unusual and has a significant learning disability could have a 'syndromal' diagnosis. This is a possible barrier to making the diagnosis in this condition as the young child with Noonan is often quite attractive, with prominent eyes and a cute uptilted nose. In addition, it is characteristic of these children that they often have a cheerful personality and frequently 'aim to please'. Individuals with Noonan can have normal learning, and most attend mainstream school.[3] These may be some of the reasons that many, possibly most cases of NS, are diagnosed late, if at all. A characteristic of the condition is that the phenotype changes considerably with age.[4] If the diagnosis is missed in childhood, then it may be more difficult to recognise later on. The older literature reports average age at diagnosis as 9 years.[5]

There are a number of disorders that have long been recognised to share clinical features with NS, including cardiofaciocutaneous (CFC), LEOPARD and Costello syndromes. Recent research has shown that they are indeed biologically related disorders, all being because of mutations in genes involved in

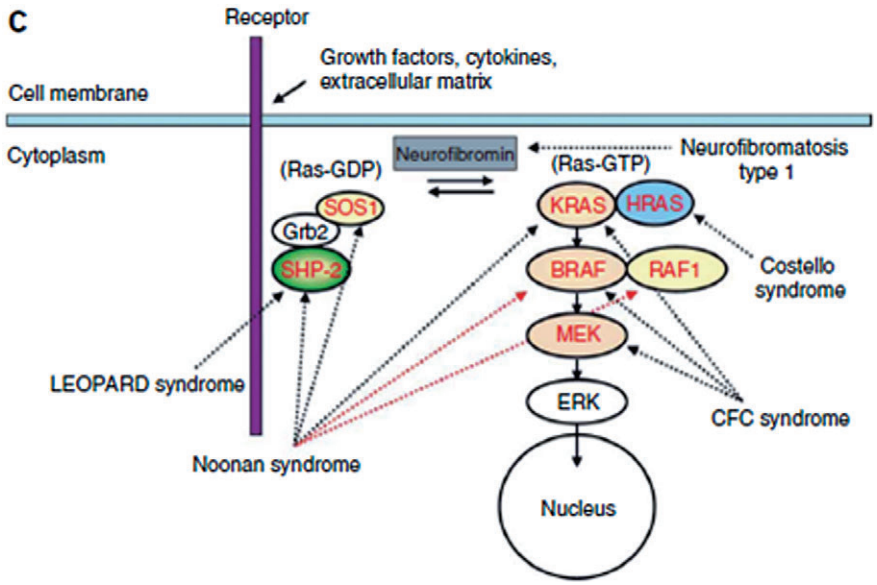


**Fig. 1** RAS–MAPK signal transduction pathway with associated developmental disorders (reproduced with permission from *Nature Genetics*). CFC, cardiofaciocutaneous.

the RAS–MAPK (mitogen activated protein kinase) pathway (Fig. 1). However, a detailed discussion of these conditions is beyond the scope of this review.

## The Genes

From a genetic point of view, NS was poorly understood until quite recently. NS is genetically heterogeneous. Approximately half the cases are caused by activating germline mutations in the *PTPN11*[1] gene, but other cases have since been shown to be because of gain-of-function mutations in *KRAS*,[6] *SOS1*,[7,8] and *RAF1*.[9] The phenotypically similar condition, LEOPARD syndrome, is now recognised to be allelic and due to specific mutations in *PTPN11*[10] and, in some cases, *RAF1*.[10] Even in the past year, two more NS genes have been recognised – *SHOC2*[11] and *NRAS*,[12] – but only *PTPN11*, and to a lesser extent *SOS1*, account for more than a few per cent of NS cases. At the time of writing, a proportion of NS cases do not appear to be caused by mutations in any of the currently identified NS genes, suggesting that there may be other genes yet to be identified.

The phenotype of Noonan–neurofibromatosis has been shown to be because of mutations in the neurofibromin (*NF1*) gene[13] – also within the same pathway – and mutations in yet another RAS pathway gene, *SPRED1*, have been shown to cause a neurofibromatosis-like disorder.[14]

The Noonan-related disorders CFC syndrome and Costello syndrome were also found to result from mutations in other genes coding for transducers of the RAS–MAPK signalling pathway. These include *BRAF*, *MEK1*, *MEK2*, *KRAS* (CFC) and *HRAS* (Costello syndrome). This finding explains the numerous overlapping phenotypic features previously noted between these conditions.

Molecular testing of the four best recognised NS genes is available and identifies mutations in *PTPN11* in about 50%, *KRAS* in <5%, *SOS1* in about 15% and *RAF1* in 3–17%.

Some genotype–phenotype correlations have already been recognised. Pulmonary stenosis is more common,[1] and hypertrophic cardiomyopathy is less common in NS patients with *PTPN11* mutations. Short stature, chest deformity, easy bruising, characteristic face and undescended testes are all more common with *PTPN11* mutations.[15–17] One common mutation in this gene (p.Asn308Asp) has been shown to be associated with a better than average educational outcome, with affected individuals being more likely to attend mainstream school than other NS children.[16] This information could be reassuring for parents. Some specific mutations identify a group at risk for juvenile myelomonocytic leukaemia.[18]

Individuals with *KRAS* mutations are said to have an atypical phenotype and be more likely to have more significant learning problems.[19]

A recent study of 22 individuals with *SOS1* mutations[7] found more ectodermal abnormalities. These children had less severe short stature and fewer learning problems, but another study did not confirm this.[8]

For those with changes in *RAF1*, there is a markedly increased risk of hypertrophic cardiomyopathy, with most (95%) showing this feature.[9]

As with many autosomal dominant disorders, a significant percentage of cases result from *de novo* mutations. When the disorder is transmitted by an affected parent, that parent is much more often the mother, rather than the father,[20] an observation that is likely to be related to reduced fertility in many males with NS. Most familial cases are because of *PTPN11* mutations.[21]

## Clinical Features – How to Recognise the Child with NS

The diagnosis is made on clinical grounds by observation of key features. Affected individuals have normal chromosomes. The characteristic facial appearance is the key to diagnosis in this condition. Rather than the presence of any single feature, it is the 'gestalt' (all the features seen at once) that is diagnostic.


Journal of Paediatrics and Child Health (2011)

These facial features can be subtle and change with age.[4]

In some cases, it may be difficult to recognise the appearance in infancy, especially when complicated by neonatal oedema. In the newborn, the forehead is tall. There is hypertelorism (widely spaced eyes) and downslanting palpebral fissures. The lids may be ptosed or thickened. There may be epicanthic folds and low-set ears.

Although these features remain throughout childhood, the features are easiest to recognise in the infant or young child. The combination of the high forehead and prominent widow's peak with low posterior hairline, a relatively large head and short uptilted nose is quite characteristic. The nasal root is flat, and the nasal tip is broad. The pillars of the philtrum (between mouth and nose) are prominent, and there are wide peaks to the vermillion border of the upper lip (cupid's bow appearance). The ears are not only low set but also often prominent, posteriorly rotated and characterised by a thickened upper helix.[5,22]

The neck is short, and there may be redundant skin in infancy. This can be seen at older ages as webbing of the neck. An enlarged nuchal translucency may be noted on first trimester scans prenatally. The posterior hairline is low.

The chest is broad with widely set nipples and a specific chest shape – a pectus carinatum superiorly and excavatum deformity inferiorly[22] (see Fig. 4). The hands show brachydactyly and persistence of fetal finger tip pads. An additional clue in boys is the presence of undescended testes.

Many children will have strikingly blue/green irides (see Fig. 3), depending on ethnicity (Fig. 8), often out of keeping with the family colouring (see Fig. 5). The hair can be sparse in the baby but is often curly or woolly in the older child.

By adolescence, the facial shape becomes triangular – wide at the forehead and tapering to a pointed chin. There is often an expressionless quality – almost a myopathic appearance. The neck lengthens, and any webbing is accentuated.[4]

In the adult, the features are often quite subtle, and the diagnosis can be more difficult. Nasolabial folds are prominent, and the skin is thin, transparent and wrinkled.[4,22]

## Cardiovascular Features

Most NS children will have CHD, but the condition can occur with a structurally normal heart. The frequency of CHD is estimated to be between 50%[22] and 90%.[23] These estimates vary as the presence of CHD will often lead to consideration of this diagnosis. In a recent survey, over 80% of NS individuals had some kind of a cardiac malformation.[3] In this study, prenatal anomalies had been present in 25%.

The commonest abnormality, seen in up to a half, is valvular pulmonary stenosis, often with dysplasia of the valve. This can be isolated or associated with other cardiac defects. Other structural defects include atrial and ventricular septal defects, and Tetralogy of Fallot. Coarctation of the aorta is more common in NS than previously thought.[24] Hypertrophic cardiomyopathy is found in 20–30% and may present at birth, infancy or during childhood.[25] (Fig. 6) The electrocardiogram is abnormal in 90%, with left axis deviation being the most common abnormality. This feature can be an important pointer to the diagnosis.[26] Whenever NS is considered, a cardiological opinion can be very valuable.

## Growth and Feeding

Problems with feeding and growth are common and may lead to paediatric referral, although birthweight and length are usually normal. Feeding problems occur in 77%,[25,27] with failure to thrive in 40%, but this usually resolves by 18 months. In one study where a large cohort was followed over many years, a strong association was noted between significant feeding difficulties in infancy and later requirement for special education.[25]

Childhood growth follows the normal values, but most are quite short. Height centres around the third percentile. The pubertal growth spurt is often delayed. Final adult height is reduced with an average of 161 cm in males and 150–152 cm in females.[25] Specific growth charts are available. The role of growth hormone in these children is still under study.[28,29] There is evidence of growth hormone resistance in individuals with NS because of mutations in *PTPN11*. There is some evidence that this treatment may still be safe even in the presence of hypertrophic cardiomyopathy.[30]

## Development and Learning

Learning disability is common in this condition but may have been overestimated. In fact, the majority do not have any significant problems in this area. Normal learning may be more common with certain genotypes.

Early milestones are often delayed, with hypotonia and joint laxity responsible for some of the motor delay that is frequently seen in this condition. Joint hyperextensibility occurs in 30%.[25,31] Most children are educated in mainstream schools. An estimated 15–35% have mental retardation, but this is usually mild.[21] Verbal performance is often reduced compared with non-verbal. Speech therapy is frequently required as most children have a degree of articulation difficulty. A survey of 48 children[32] found that two of three did not have a learning disability but that a proportion of the remainder had significant disability. Mean IQ was 85–90. The distribution of scores did not follow the classic bell curve as more children than predicted fell into the low average or mentally retarded range (Wecshler Intelligence Scale for Children, WISC-R). Severe learning disability was rare, but as many as half of the children showed some evidence of impairment.[32] Levels of self-esteem were comparable to that of a standardised population. A more recent study of adults with the condition confirmed the wide spread of intellectual ability with IQ scores ranging from 65 to 121. They found a moderate level of impairment of social cognition and highlighted a particular problem in emotion recognition (alexithymia).[33] They confirmed the observation made by many, that these individuals are remarkably friendly, co-operative and willing to please. Importantly, for parents, Noonan is not regularly associated with any behavioural or psychiatric phenotype,[32] unlike other conditions such as Williams or fragile X syndromes.

## Bleeding Diathesis

About a third have some kind of coagulation defect.[31,34] Most have a history of easy bruising or bleeding. Clotting factor deficiencies, platelet dysfunction and other coagulopathies have

been described. Aspirin should be avoided if abnormalities are found, and coagulation profile should be performed at time of diagnosis.[35]

## Genitourinary

About 10% will have renal abnormalities, mostly commonly renal pelvis dilatation. A renal ultrasound should be considered at the time of diagnosis. In males, even in the absence of cryptorchidism at birth, puberty can be delayed and fertility reduced.[20,21,25,36] Deficient spermatogenesis is seen in 60–80%.[37] Most females are fertile, but delayed menarche is common.

## Ophthalmological Features

The eyes are frequently affected in NS. One study found that over 70% had a refractive error, mostly myopia.[38] Anterior segment changes such as coloboma can also occur.[25] Early ophthalmological examination of children with NS is recommended.[38]

## Skin

Follicular keratoses over the extensor surfaces and face are a marker for the condition[39] (see Fig. 7), but extensive skin changes (and more severe learning problems) are more characteristic of CFC syndrome. Cafe au lait spots, pigmented naevi and lentigines are more frequent than in other children,[40] but Noonan features with extensive lentigines and deafness might suggest the related condition, LEOPARD syndrome (**l**entigines, **E**CG (electrocardiogram) abnormalities, **o**cular hypertelorism, **p**ulmonary stenosis, **a**bnormalities of genitalia, **r**etardation of growth, **d**eafness).

## Leukaemia and Solid Tumours

A low-frequency association with myeloproliferative disorders exists, particularly for juvenile myelomonocytic leukaemia. One specific *PTPN11* mutation (p.The73Ile) is seen in many who develop this rare complication.[41] A large long-term follow-up study of 151 NS cases[25] found no cases of myeloproliferative disorders.

## Prenatal Period

Features on prenatal ultrasound that might raise the possibility of NS are polyhydramnios, seen in one of three,[42] increased nuchal translucency and cystic hygroma. Other lymphatic features that may be noted are scalp oedema, ascites or hydrops. As these features are non-specific, they may not assist in making the diagnosis prenatally, unless there is a family history, but a recent retrospective study[43] showed that in 11% of pregnancies with isolated cystic hygroma, the fetus had a *PTPN11* mutation. In pregnancies with increased nuchal translucency, rates were lower. Ultrasound may provide important information where a parent is affected. Prenatal diagnosis can be offered where there is an affected parent and the mutation is known. The presence of these prenatal features on history may provide important clues to the diagnosis. (Fig. 2)

## Conclusion

NS is a condition commonly seen by paediatricians. The diagnosis may not be straightforward, especially in infancy or later in childhood. NS can exist in the absence of typical cardiac defects such as pulmonary valve stenosis, but the ECG is almost always abnormal. Learning disability in the condition is quite variable, but most attend mainstream school. Paediatricians should consider this diagnosis and have a high index of suspicion when a child shows characteristic features. Referral of possible cases to a clinical genetics service is the best way to confirm the diagnosis and access molecular testing. The genes involved in this group of disorders are newly recognised to be related at the cellular level and are now sometimes termed the 'RASopathies'.[44] Early accurate diagnosis is important, not only for the management of the index case throughout life, but also for appropriate genetic counselling for family members and for the patient him/herself (Figs 2–8).

**Fig. 2** The blacksmith pictured in the painting 'Among those left' by Albright almost certainly had Noonan syndrome. The features depicted are consistent with the diagnosis, and one of his descendants has Noonan syndrome, confirmed on molecular testing.[45]

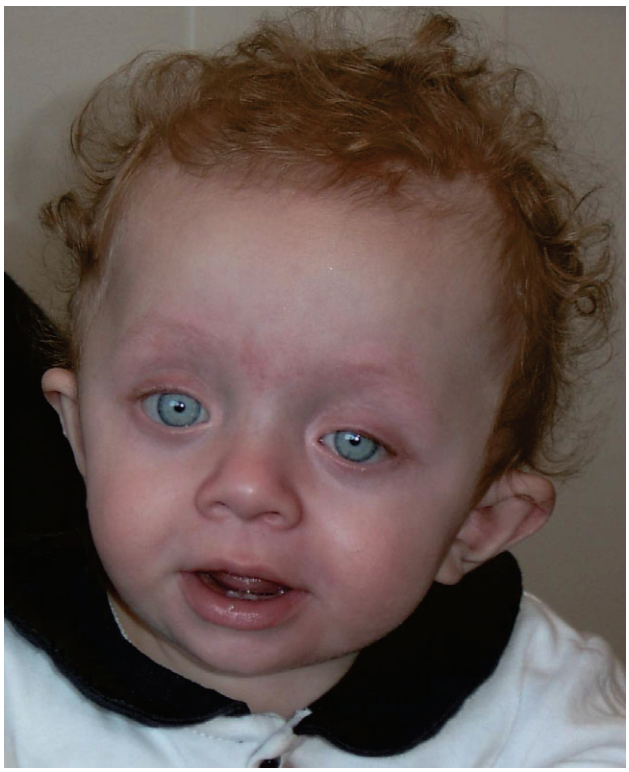

**Fig. 3** The infant face showing the high forehead, ptosis and striking blue eyes often seen in Noonan syndrome. Also note the low-set ears with thickened helices. Patient with a *PTPN11* mutation.

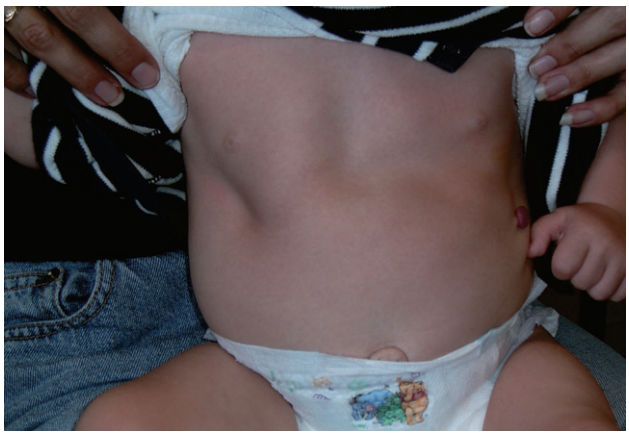

**Fig. 4** Same patient showing typical pectus excavatum deformity.

## Multiple Choice Questions

1 Which feature is present in about 50% of individuals with Noonan syndrome:

A Coarctation of the aorta
B Moderate intellectual handicap
C Significant behaviour problems
D A mutation in *PTPN11* gene
E Undescended testes

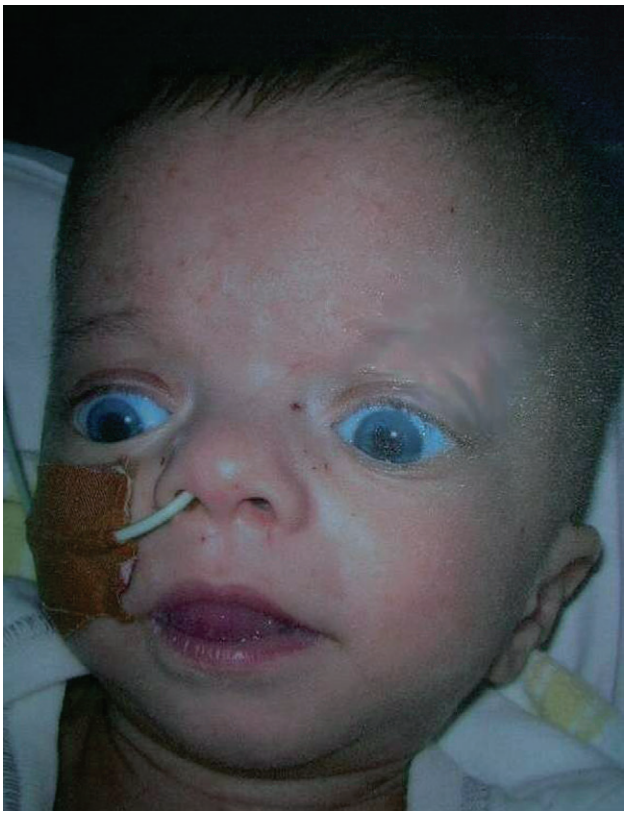

**Fig. 5** Patient of Middle Eastern descent. Parents are both brown eyed. Patient has *PTPN11* mutation.

**Fig. 6** Older child that has *RAF1* mutation and hypertrophic cardiomyopathy.

Correct answer: D

2 Concerning the psychological profile in Noonan syndrome:

A There is a fairly narrow range of intellectual ability
B A deficiency in emotion recognition has been identified

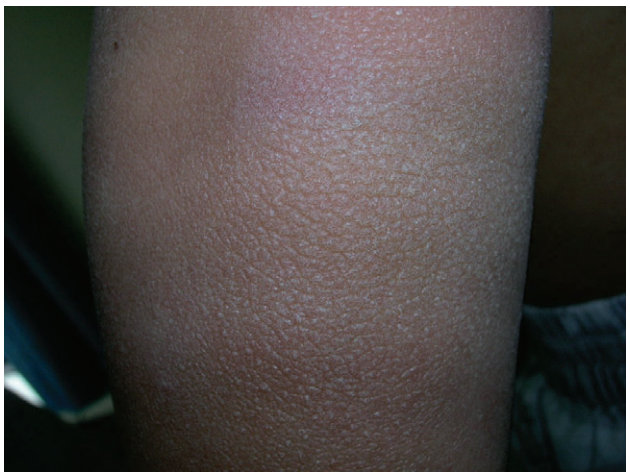

**Fig. 7** Same patient showing keratosis pilaris often seen in Noonan syndrome.

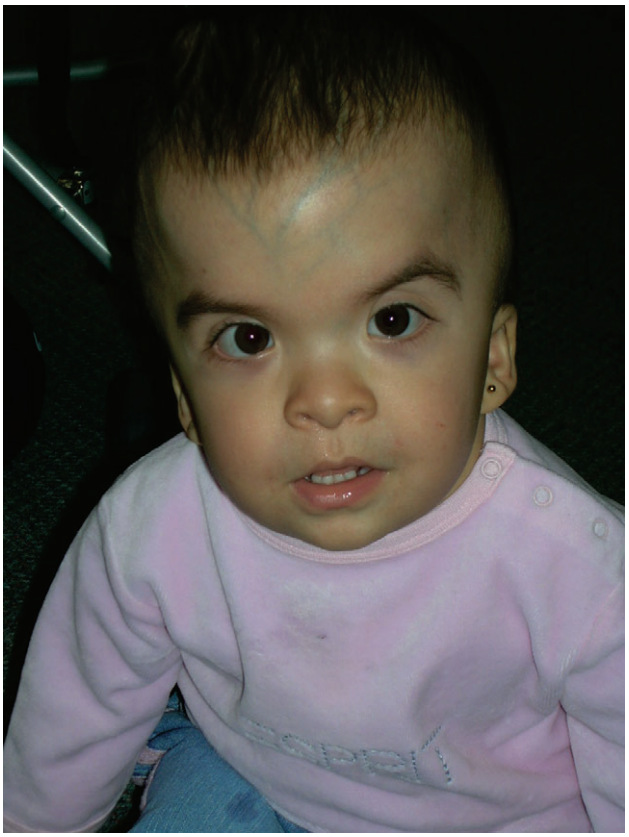

**Fig. 8** Girl with *KRAS* mutation and moderate mental retardation. South American parents.

C There is a significant risk of schizophrenia in teenage years
D Over 60% require special schooling
E Self-esteem is low in most

Correct answer: B

The finding of a causative mutation in Noonan syndrome:
A Confirms the clinical diagnosis in 100% of cases
B Intellectual ability can be predicted from mutation type
C Will show that most also have an affected parent
D Will distinguish the condition from Turner syndrome
E Is important for management and accurate genetic counselling

Correct answer: E

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