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The Face of Noonan Syndrome: Does Phenotype Predict Genotype

Judith E. Allanson[1,2,*], **Axel Bohring**[3], **Helmuth-Guenther Dorr**[4], **Andreas Dufke**[5], **Gabrielle Gillessen-Kaesbach**[6], **Denise Horn**[7], **Rainer König**[8], **Christian P. Kratz**[9], **Kerstin Kutsche**[10], **Silke Pauli**[11], **Salmo Raskin**[12], **Anita Rauch**[13], **Anne Turner**[14], **Dagmar Wieczorek**[15], and **Martin Zenker**[16]

[1]Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada [2]University of Ottawa, Ottawa, Ontario, Canada [3]Institut für Humangenetik, Westfälische Wilhelms-Universität Münster, Münster, Germany [4]Department of Pediatric Endocrinology and Pediatric Cardiology, University Children's Hospital, Erlangen, Germany [5]Department of Medical Genetics, University Hospital Tuebingen, Tuebingen, Germany [6]Institut für Humangenetik Lübeck, Universität zu Lübeck, Lübeck, Germany [7]Institute of Medical Genetics, Charité – University Medicine of Berlin, Berlin, Germany [8]Institute of Human Genetics, University of Frankfurt, Frankfurt, Germany [9]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland [10]Institut für Humangenetik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany [11]Institute of Human Genetics, University of Göttingen, Göttingen, Germany [12]Laboratorio Genetika, Alameda Augusto Stellfeld, Curitiba Parana, Brazil [13]University of Zurich, Institute of Medical Genetics, Zurich, Switzerland [14]Department of Medical Genetics, Sydney Children's Hospital, Randwick, NSW, Australia [15]Institut für Humangenetik, Universität Duisburg-Essen, Essen, Germany [16]Institute of Human Genetics, University Hospital, Magdeburg, Germany

Abstract

The facial photographs of 81 individuals with Noonan syndrome, from infancy to adulthood, have been evaluated by two dysmorphologists (JA and MZ), each of whom has considerable experience with disorders of the Ras/MAPK pathway. Thirty-two of this cohort have *PTPN11* mutations, 21 *SOS1* mutations, 11 *RAF1* mutations, and 17 *KRAS* mutations. The facial appearance of each person was judged to be typical of Noonan syndrome or atypical. In each gene category both typical and unusual faces were found. We determined that some individuals with mutations in the most commonly affected gene, *PTPN11*, which is correlated with the cardinal physical features, may have a quite atypical face. Conversely, some individuals with *KRAS* mutations, which may be associated with a less characteristic intellectual phenotype and a resemblance to Costello and cardio-facio-cutaneous syndromes, can have a very typical face. Thus, the facial phenotype, alone, is insufficient to predict the genotype, but certain facial features may facilitate an educated guess in some cases.

Keywords

*Correspondence to: Dr. Judith E. Allanson, Department of Genetics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, Canada K1H 8L1. allanson@cheo.on.ca.

INTRODUCTION

One of the most intriguing stories in developmental biology today is that of the Ras/MAPK pathway, a pathway critical for cell growth, differentiation, senescence, and death. Genes in this pathway are frequently mutated in cancer and germline mutations have been linked to Noonan syndrome (NS), cardio-facio-cutaneous syndrome (CFC), Costello syndrome (CS) and Legius syndromes, multiple lentigines or LEOPARD syndrome, and neurofibromatosis type 1. Mutations in *PTPN11* were the first to be described in NS [Tartaglia et al., 2001]. Almost half of all individuals with NS will have a *PTPN11* mutation, and hotspots are reported. In 2007, mutations in *SOS1* were shown to cause NS in about 20% of affected persons without a *PTPN11* mutation [Roberts et al., 2007; Tartaglia et al., 2007]. Mutations in *KRAS* only occasionally cause NS (1–3%) [Carta et al., 2006; Schubbert et al., 2006]. In 2007, a fourth gene responsible for causing NS was reported [Pandit et al., 2007; Razzaque et al., 2007]. Mutations in *RAF1* are found in just 3–10% of affected individuals. The mutations causing NS are supposed to have gain-of-function effects on Ras/MAPK signaling. Two individuals have been reported with NS and mutations in MEK2; however, this genotype–phenotype correlation has yet to be reproduced [Nava et al., 2007]. Recently, a recurrent mutation in *SHOC2* was demonstrated in 25 individuals with NS, all occurring de novo where parental samples were available for testing [Cordeddu et al., 2009]. Subsequently, five individuals with NS, three sporadic and a mother–son dyad, were found to have mutations in *NRAS* [Cirstea et al., 2010]. Nyström et al. [2008] reported an individual with NS and a *BRAF* mutation, however, the clinical diagnosis may be more in keeping with CFC syndrome [Neri et al., 2008]. Another individual with NS and a *BRAF* mutation is known to the authors. *PTPN11* and *RAF1* mutations also cause multiple lentigines syndrome [Legius et al., 2002]. Over 95% of individuals with CS have a mutation in *HRAS*, with the majority in codon 12 [Aoki et al., 2005]. CFC syndrome is associated with mutations in *BRAF, MEK1, MEK2*, and *KRAS* [Niihori et al., 2006; Rodriguez-Viciana et al., 2006; Narumi et al., 2007; Zenker et al., 2007a].

Knowledge of the phenotype can help to predict the likely causative gene. For example, *PTPN11* mutations are more likely to be found in persons with pulmonary stenosis than those with hypertrophic cardiomyopathy [Tartaglia et al., 2002; Zenker et al., 2004]. They are positively correlated with short stature, pectus deformity, and factor VIII deficiency, and negatively correlated with hypertrophic cardiomyopathy and factor XI deficiency [Sarkozy et al., 2003; Yoshida et al., 2004; Limal et al., 2006]. The presence of florid ectodermal features is suggestive of *SOS1* mutations [Roberts et al., 2007; Tartaglia et al., 2007]. These mutations also are associated with normal stature and intellectual functioning. Mutations in *RAF1* show a very strong correlation with hypertrophic cardiomyopathy, present in 95% [Pandit et al., 2007; Razzaque et al., 2007]. *KRAS* mutations seem to cause a more severe intellectual handicap and may predispose to a phenotype similar to CFC syndrome or CS [Zenker et al., 2004]. The majority has short stature, webbed neck, pectus deformity, and few skin problems. Individuals with *SHOC2* mutations have a distinctive hair phenotype described as loose anagen hair [Cordeddu et al., 2009]. We have carried out this study to determine if there are clues to mutation status in the face.

METHODS AND RESULTS

We have evaluated the facial photographs of 81 individuals with NS, from infancy to adulthood. Thirty-two have *PTPN11* mutations, 21 *SOS1* mutations, 11 *RAF1* mutations, and 17 *KRAS* mutations. In each mutation category more than half of the individuals have classical facial features of NS [Allanson et al., 1985; Allanson, 1987]. The faces of children and adults with *PTPN11* mutations and a typical gestalt are illustrated in Figure 1. However,

many faces of individuals with *PTPN11* mutations are unusual and diagnosis would be challenging (Fig. 2). Some faces are broader and coarser, reminiscent of CFC syndrome. Others have a long nose with low-hanging columella. Occasional individuals lack wide-spaced eyes and show close-spaced features and a narrow face. Coarseness of facial features is also seen in infants with *SOS1* mutations, and ptosis is very common. In some infants, the face is similar to the face of CS or CFC syndrome (Fig. 3A,B). Later in life, the lips are often full and the nose fleshy. Curly or sparse hair may be present. In other individuals, facial features are quite characteristic of NS (Fig. 4). Two brothers with *RAF1* mutations have unremarkable features (Fig. 5), while other children have quite a characteristic appearance of NS (Fig. 6). A few individuals have facial or cranial asymmetry that would be unusual for NS (Fig. 7). Lastly, those with mutations in *KRAS* can have a very typical NS face (Fig. 8). However, there are some individuals with *KRAS* mutations and coarser features, or a markedly prominent and wide nasal root and base, in whom diagnosis would be challenging (Fig. 9).

DISCUSSION

The classical facial features of NS change with age [Allanson et al., 1985]. In the newborn, typical features include tall forehead, hypertelorism, downslanting palpebral fissures, epicanthal folds, a short and broad nose with a depressed root with upturned tip, deeply grooved philtrum with high, wide peaks of the vermilion, high palate, micrognathia, low-set and posteriorly angulated ears with thick helices, and excessive nuchal skin with low posterior hairline. During infancy, the head is relatively large with a tall and prominent forehead. Hypertelorism, ptosis, or thick hooded eyelids are characteristics. The nose is short and wide with a depressed root. During childhood, the face may appear coarse or myopathic. Facial contour becomes more triangular with age, as the face lengthens. The upper face is broad while the chin is narrow and pointed. During adolescence and young adulthood, the nose has a thin, high bridge and a wide base. The neck is longer with accentuated webbing (pterygium colli) or prominent trapezius. In older adults, the nasolabial folds are prominent and the skin appears thin and transparent [Allanson et al., 1985; Allanson, 1987]. Features present regardless of age include blue-green irides, arched and diamond-shaped eyebrows, and low-set posteriorly angulated ears with thickened helices [Allanson, 1987; Sharland et al., 1992]. The hair may be wispy during infancy and curly or woolly in later childhood and adolescence.

In this study, we demonstrate that some individuals with mutations in the most commonly affected gene, *PTPN11*, which is correlated with the cardinal physical features, including the characteristic facial phenotype, can have a quite atypical face. There is no one alternate gestalt, and several atypical features may be found, including a broader face and coarser appearance, reminiscent of the face in CFC syndrome, which is characterized by rounder and more bulbous nasal tip with wider nasal base, and fuller lips. Other atypical faces demonstrate a long nose with low-hanging columella. Occasional individuals lack the typical wide-spaced eyes and show close-spaced features and a narrow face. At the other end of the spectrum, some individuals with *KRAS* mutations, which may be associated with a more severe intellectual disability with severe and longstanding feeding problems and failure to thrive, resembling Costello and CFC syndromes, can have a very typical NS facial appearance. In each gene category, as reviewed in the Methods and Results Section, both typical and unusual faces may be found.

This study was carried out before knowledge of causative mutations in *SHOC2* and *NRAS* was available. However, review of facial appearance in illustrations that are part of the supplemental information accompanying the publication of *NRAS* mutations suggests that both typical and atypical facial appearance may be found in this cohort as well [Cirstea et

al., 2010]. The single recurrent *SHOC2* mutation was found to be associated with a characteristic hair phenotype [Cordeddu et al., 2009].

If one considers the question posed by the title: "Does phenotype predict genotype?" the answer is a clear "No." Characteristic NS facial appearance does not point to a specific genotype. It would be most useful to know how often a particular genotype is found with an atypical face; however, it is only reasonable to expect that level of detail by studying a cohort with *PTPN11* mutations as each of the other causative genes is responsible for such a small proportion of affected individuals that any one study is likely to be biased by small numbers. Such a study of *PTPN11*-mutation-positive individuals has not been carried out to date.

However, it may be possible to "make an educated guess" about genotype based on clues present in the face. The child with rounded features, sparse eyebrows and eyelashes, curly or sparse hair, and skin erythema may have a higher likelihood of a *SOS1* mutation. Loose anagen hair makes a *SHOC2* mutation more likely. Cranial or facial asymmetry may point to higher odds of a *RAF1* mutation, while coarse features or a markedly prominent and wide nasal root and base may suggest a *KRAS* mutation. In reality, one is more likely to make a correct prediction of genotype if other factors, such as height, IQ, and type of cardiac defect are added to impressions of facial gestalt. Fortunately, with the advent of newer molecular approaches using a combination of DNA sequencing techniques to evaluate the coding regions and splice sites of all known genes, a cost-efficient testing approach does not require the physician managing the patient to predict which gene to evaluate first.

Acknowledgments

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FIG. 1.
Individuals with *PTPN11* mutations, from infancy to adolescence, and a typical face of Noonan syndrome.

FIG. 2.
PTPN11 mutations and a facial gestalt uncharacteristic of Noonan syndrome.

FIG. 3.
Individuals with *SOS1* mutations and a coarse appearance, which, in infancy, can resemble the face of Costello syndrome (A,B). Reproduced from Zenker et al. [2007b] with permission from BMJ Publishing Group Ltd.

FIG. 4.
Very typical features of Noonan syndrome, seen from early childhood to adulthood, in individuals with *SOS1* mutations.

FIG. 5.
Brothers with a *RAF1* mutation and essentially unremarkable facial features.

FIG. 6.
Typical facial features of Noonan syndrome in four children of varying ages, each with a *RAF1* mutation.

FIG. 7.
RAF1 mutations and cranial asymmetry, a long narrow nose, and markedly downslanting palpebral fissures.

FIG. 8.
KRAS mutations associated with typical facies of Noonan syndrome. Reproduced from Zenker et al. [2007a] with permission from BMJ Publishing Group Ltd.

FIG. 9.
KRAS mutations and unusual facial features: in childhood a coarseness suggestive of Costello syndrome; in adulthood a broadening of features with marked widespacing of eyes and broad nasal root and tip somewhat reminiscent of G/BBB and Teebi hypertelorism syndromes. Reproduced from Zenker et al. [2007a] with permission from BMJ Publishing Group Ltd.