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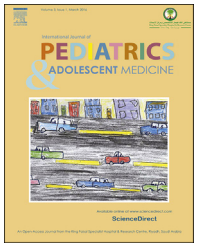

REVIEW ARTICLE

Noonan syndrome-causing genes: Molecular update and an assessment of the mutation rate

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Abstract Noonan syndrome is a common autosomal dominant disorder characterized by short stature, congenital heart disease and facial dysmorphia with an incidence of 1/1000 to 2500 live births. Up to now, several genes have been proven to be involved in the disturbance of the transduction signal through the RAS-MAP Kinase pathway and the manifestation of Noonan syndrome. The first gene described was *PTPN11*, followed by *SOS1*, *RAF1*, *KRAS*, *BRAF*, *NRAS*, *MAP2K1*, and *RIT1*, and recently *SOS2*, *LZTR1*, and *A2ML1*, among others. Progressively, the physiopathology and molecular etiology of most signs of Noonan syndrome have been demonstrated, and inheritance patterns as well as genetic counseling have been established. In this review, we summarize the data concerning clinical features frequently observed in Noonan syndrome, and then, we describe the molecular etiology as well as the physiopathology of most Noonan syndrome-causing genes. In the second part of this review, we assess the mutational rate of Noonan syndrome-causing genes reported up to now in most screening studies. This review should give clinicians as well as geneticists a full view of the molecular aspects of Noonan syndrome and the authentic prevalence of the mutational events of its causing-genes. It will

Abbreviations: CDC25, cell division cycle 25; CHD, congenital heart defects; CR, conserved region; CRD, cysteine-rich domain; GAP, GTPase activating protein; GDP, guanosine-DiPhosphate; GEF, guanine exchange factor; GTP, guanosine-TriPhosphate; GH, growth hormone; HCM, hypertrophic cardiomyopathy; IGF-1, insulin-like growth factor I; RBD, RAS binding domain; REM, RAS exchange motif.

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also facilitate lay the groundwork for future molecular diagnosis research, and the development of novel treatment strategies.

1. Introduction

Noonan syndrome ([NS1, OMIM 163950]) is a common autosomal dominant disorder characterized by short stature, congenital heart disease and facial dysmorphia and other features such as cryptorchidism, bleeding diathesis, skeletal malformations and mild cognitive delays with variable expressivity. The prevalence of this disorder is estimated to be 1/1000–2500 live births [1–3]. The varied clinical manifestations observed in Noonan syndrome patients (facial, skeletal cardiac, and hematological, among others) are a result of the involvement of the RAS MAP kinase molecular signaling pathway, as will be shown below.

The previous updates and reviews in the literature have thoroughly discussed Noonan syndrome, often focusing on diagnostic evaluations, clinical guidelines, and management with treatment options, which have amply helped clinicians provide the best care for Noonan syndrome children. The molecular aspects of this disorder have been approached in these reviews progressively with genetic advances. However, considering the fast advances and consecutive progress being made in the physiopathology and genetic studies of Noonan syndrome, it seems important to gather these findings in one paper to help the audience of clinicians and geneticists have a full view of recent advances in the molecular etiology of Noonan syndrome, as well as an authentic prevalence of the mutational rates of its causing-genes. Therefore, this review provides, in the first part, an update on the molecular aspect of the disease, in which we summarize the data concerning clinical features frequently observed, then focus on the molecular etiology, the inheritance pattern and the genetic counseling that should be given to patients. In the second part of this review, we establish and discuss the mutational rate reported up to now in most genes involved in Noonan syndrome.

2. Review

2.1. Clinical features and diagnosis

The diagnosis of Noonan syndrome is based primarily on the clinical features that have been established from the very beginning through several clinical studies that have meticulously defined the criteria and signs of diagnosis [1–3].

2.1.1. Dysmorphic face

The extreme variability of facial traits in Noonan syndrome from one individual to another makes the assessment of frequency difficult and not very meaningful. Furthermore, the dysmorphic signs could change within the same patient depending on his/her age, to be less perceptible in adulthood than earlier in childhood. The dysmorphology is characterized during the postnatal period by a tall forehead, low-set-posteriorly-rotated ears, a thickened helix, nerve deafness, hypertelorism, ptosis, down slanting palpebral fissures, epicanthal folds, deeply grooved philtrum, a high arched palate and triangular face, with a low posterior hairline and webbed neck. In adulthood, the facial features become more subtle, the eyes are less prominent, with a slightly elongated neck, wrinkled skin and high anterior hairline [3–5].

2.1.2. Congenital heart defect

The cardiac features are well delineated and are estimated to be present in 50% up to 90% of Noonan syndrome patients [6–8]. The most common congenital heart defects (CHD) are pulmonic stenosis (50–60%), hypertrophic cardiomyopathy (HCM) (20%) and atrial septal defect (6–10%) [9,10]. The other CHDs such as ventricular septal defect, atrioventricular canal defect, and aortic coarctation are observed less frequently [6,8,11]. Electrocardiographic abnormalities were reported in 87% of patients [3]. Electrocardiograms display wide QRS complexes with a predominant negative pattern in the left precordial leads, a left axis deviation and giant Q waves [9–11].

2.1.3. Growth/short stature

Weight and height are normal at birth. However, during childhood and at puberty, short stature becomes a prominent common sign of Noonan syndrome. In one series reported by Nora et al, the prevalence of Noonan children with height below the 3rd percentile is approximately 83% [12]. In another study, pubertal growth was found to be delayed by almost two years and the mean height was in the 3rd percentile, with female and male average heights of 151 cm and 161 cm, respectively, and the average bone age delayed by two years [8].

2.1.4. Skeletal defects

A chest deformity characterized by superior pectus carinatum and inferior pectus excavatum is observed in up to 95% of Noonan syndrome patients. Half (50%) have cubitus valgus and 30% have a clinobrachydactyly. The other orthopedic features, such as thoracic scoliosis, talipes equinovarus or radiolunar synostosis, are observed less often [3,7].

2.1.5. Bleeding defect

The coagulation defect is the most common hematologic disorder in Noonan syndrome patients. Approximately 55% of patients have mild to moderate abnormal bleeding, whereas only 3% have major abnormal bleeding [3].

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