International Journal of Pediatrics and Adolescent Medicine (2016) 3, 133–142

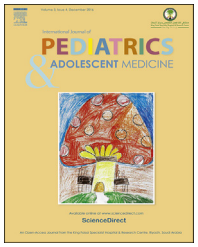
HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/ijpam



Review Article

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

Ihssane El Bouchikhi [a,b,*], Khadija Belhassan [a], Fatima Zohra Moufid [a,b], Mohammed Iraqui Houssaini [b], Laila Bouguenouch [a], Imane Samri [a], Samir Atmani [c], Karim Ouldim [a]

[a] *Medical Genetics and Oncogenetics Laboratory, HASSAN II University Hospital, BP 1835, Atlas, Fez 30000, Morocco*
[b] *Laboratory of Microbial Biotechnology, Faculty of Sciences and Techniques, University of Sidi Mohammed Ben Abdellah, B.P. 2202, Route d'Imouzzer, Fez 30000, Morocco*
[c] *Medico-Surgical Unit of Cardio-pediatrics, Department of Pediatrics, HASSAN II University Hospital, BP 1835, Atlas, Fez 30000, Morocco*

Received 15 April 2016; accepted 14 June 2016
Available online 18 August 2016

KEYWORDS
Molecular etiology;
MAP kinase signaling pathways;
Mutation rate;
Noonan syndrome;
PTPN11;
RAS family

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

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.

* Corresponding author. Medical Genetics and Oncogenetics Unit, Hassan II University Hospital, Fez 30000, Morocco. Tel.:(+212) 610 36 75 09.
E-mail address: ihssane.elbouchikhi@usmba.ac.ma (I. El Bouchikhi).
Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

http://dx.doi.org/10.1016/j.ijpam.2016.06.003
2352-6467/Copyright © 2016, King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

syndrome and the authentic prevalence of the mutational events of its causing-genes. It will also facilitate laying the groundwork for future molecular diagnosis research, and the development of novel treatment strategies.
Copyright © 2016, King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Noonan syndrome ([NS1, OMIM 163950]) is a common autosomal dominant disorder characterized by short stature, congenital heart disease, 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].

2.1.6. Genito-urinary

Altered spermatogenesis and cryptorchidism are observed in 60—80% of patients [13]. Ten percent of patients have renal abnormalities that often include renal pelvis dilatation [3].

2.1.7. Ophthalmological features

Approximately 55% of Noonan syndrome patients have an abnormal ophthalmological test [3]. The frequent abnormalities are refractive errors (61—70%), strabismus (48—63%), amblyopia (33%) and anterior segment changes (63%) [14,15].

2.1.8. Other features

Other features have also been reported, including lymphatic abnormalities, hematological malignancy, giant cell lesions and cognitive disability, among others [16—19].

2.2. Genetic diagnosis and molecular etiology

As shown above, Noonan syndrome is a heterogeneous disorder with various clinical features ranging from facial dysmorphology to short stature and bleeding defects up to congenital heart disease. Those features have been demonstrated by several studies to be the yield of diverse molecular and physiological mechanisms, some of which are well known, while others need to be further elucidated.

The molecular etiology of Noonan syndrome has been established first by the study of two large Noonan syndrome families using linkage analysis [20—22]. These studies suggested that the concerned locus is located in the 12q24 region. Based on these data, and the data suggesting the involvement of SHP-2 in the signaling pathways that control semilunar valvulogenesis [23], and by means of a positional candidacy approach, Tartaglia et al [24] suggested *PTPN11* to be a Noonan syndrome candidate gene, and confirmed this hypothesis by bidirectionally sequencing the fifteen exons of *PTPN11*, which have shown mutations in 50% of the studied cohort.

2.2.1. *PTPN11* (protein-tyrosine phosphatase, nonreceptor-type 11)

The *PTPN11* gene ([OMIM 176876]) (Fig. 1A) is organized into three domains: the N-amino terminal src-homology 2 domain (N-SH2) and the phosphotyrosine phosphatase (PTP)

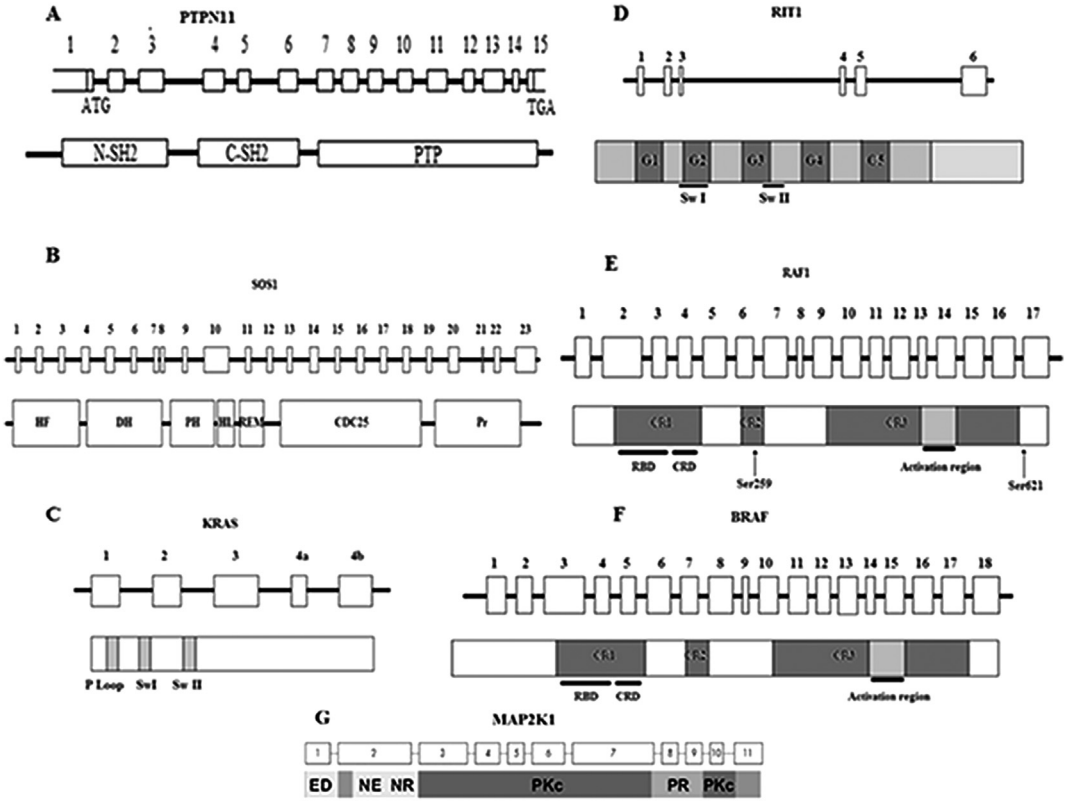


Figure 1 Organization of Noonan syndrome causing genes and domains, **A**. PTPN11 exons and SHP-2 domains, **B**. SOS1 exons and domains, **C**. KRAS coding exons and domains. In most cases, the exon 4a is spliced out. **D**. RIT1 coding exons and domains. **E**. RAF1 coding exons and domains with the localization of Ser259 and Ser621 residues that is critical for RAF1 auto-inhibition. **F**. BRAF coding exons and domains. **G**. MAP2K1 coding exons and domains. C-SH2: C-amino-terminal src-homology 2, CR: Conserved Region, CRD: Cysteine-Rich Domain, DH: Dbl Homology, HF: Histone-like Fold, HL: Helical Linker, N-SH2: N- amino-terminal src-homology 2, PH: Pleckstrin Homology, Pr: Proline-riche motif, PTP: protein-tyrosine phosphatase, RBD: RAS binding domain, REM: RAS Exchange Motif, Sw: Switch.

domain, which are the most commonly mutated domains; and the C-amino terminal src-homology 2 domain (C-SH2) and carboxy-terminal tail [25,26].

Protein SHP-2 coded by *PTPN11* was demonstrated to be involved in several developmental processes such as limb development, semilunar valvulogenesis, hemopoietic cell differentiation and mesodermal patterning [23,27—29], and is widely expressed in several tissues such as the heart, muscles, and brain, in which SHP-2 modulates the cellular proliferation, migration or differentiation processes during the developmental stage [30]. SHP-2 is a key element of the signaling molecular RAS-MAP Kinase cascade (Fig. 2). The latter is triggered when cytokines, hormones or growth factors bind to membrane receptors [25,26,31]. Therefore, its disturbance may cause alterations of these tissues that lead to the aberrant phenotype shown in Noonan syndrome patients. This fact has been confirmed by De Rocca et al, has confirmed that the SHP-2 mutations in Noonan syndrome were associated with the inhibition of GH-induced IGF-1 via the hyperactivation of RAS/ERK1/2 in a mouse model, which lead to the short stature observed in Noonan syndrome [32].

On the molecular level, SHP-2 is a cytosolic phosphatase protein activated by the binding of a N-SH2 domain to phosphotyrosyl residue, which leads to the conformational change making the catalytic site (PTP) available to the phosphotyrosyl residue. In the absence of substrate, SHP-2 regains its inactive form in which N-SH2 interacts with PTP to hide the catalytic site [33].

Most of the *PTPN11* mutations causing Noonan syndrome manifestations cluster in these two domains. The energy-based structured analysis suggests that *PTPN11* mutations disrupt the inactive conformation, resulting in the emergence of the catalytic site which triggers the phosphotyrosyl phosphatase activity in the absence of the ligand [24].

Additionally, several screening studies were carried out to define *PTPN11* mutations in other populations and to highlight putative novel mutations. *PTPN11* mutations were significantly correlated to the manifestation of pulmonary stenosis observed in 45—70% of cases [34,35].

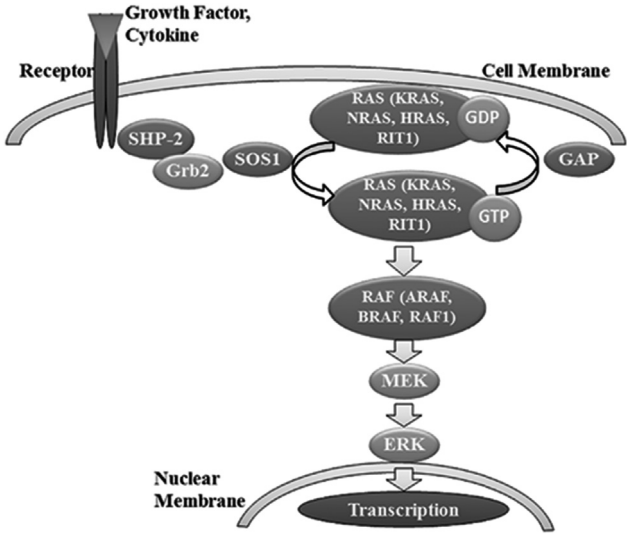


Figure 2 Localization of Noonan syndrome causing genes into the RAS-MAP kinase signal transduction pathway.

Seven other genes from the RAS-MAP kinase pathway (Fig. 2) were demonstrated to be mutated and to cause Noonan syndrome.

2.2.2. *SOS1* (Son of Sevenless homolog 1)

At present, *SOS1* ([OMIM 182530]) is considered the second molecular cause of Noonan syndrome. Roberts et al reported that *SOS1* is responsible for approximately 20% of Noonan syndrome patients in the absence of *PTPN11* mutations [36].

SOS1 is a guanine exchange factor (GEF) with a major role in the RAS-MAP kinase pathway. It is mapped on the 2p22-p21 region and consists of 23 exons (Fig. 1B) [37,38] coding for multiple domains containing: histone-like folds domain (HF), Dbl homology domains (DH) and Pleckstrin homology domains (PH) with the following regulatory function; RAS exchanging motif (REM) and Cdc25 domains with catalytic function; helical linker (HL) relating PH and REM, and the PolyProline region [36,39].

It was reported that Noonan syndrome-causing *SOS1* was associated with a high prevalence of ectodermal abnormalities [36,39—41].

In the RAS-MAP kinase molecular cascade, RAS protein is inactivated by hydrolyzing GTP to GDP via GTPase Activating Protein (GAP). To be reactivated, RAS protein needs to exchange bound GDP for GTP via *SOS1*.

It was suggested that the Dbl homology domain inhibits RAS-GEF activity by competing with RAS for binding to the REM-Cdc25 complex designated as an allosteric site, which stabilizes the inactive conformation [42].

Most mutations cluster in these domains and lead to gain-of-function in the RAS-MAP kinase pathway by disrupting the auto-inhibition of *SOS1* RAS-GEF activity [36,39,43].

Pulmonic stenosis was more frequently observed in patients with *SOS1* mutations (83.3%) than in those with *PTPN11* mutations [34].

The RAS family (*KRAS*, *HRAS*, *NRAS* and *RIT1*) is a small GTPase protein family responsible of signal propagation through the RAS-MAP kinase cascade. It acts as a molecular switch cycling between an inactive GDP bound conformation and an active GTP bound conformation (Fig. 2) [44,45].

2.2.3. *KRAS* (kirsten rat sarcoma viral oncogene homolog)

The *KRAS* ([OMIM 190070]) gene is mapped to the 12p12 region, and consists of 6 exons coding for the P loop, and switch I and switch II domains (Fig. 1C) [46]. In response to a transduction signal generated from membrane receptor binding, *KRAS* regains its active bound GTP conformation via the guanine nucleotide exchange factor, and entails an activation cascade through the downstream effectors of RAS-MAP kinase (such as *RAF1*). *KRAS* has intrinsic GTPase activity, which, supported by RAS-GAPs (RAS-GTPase activating protein), hydrolyzes bound GTP to GDP to inactive itself [44,45].

Lee et al and Schubbert et al have reported that *KRAS* mutations cause approximately 5% of Noonan syndrome cases in the absence of *PTPN11* mutations [34,47]. These mutations lead to a gain in the function effect through the RAS-MAP kinase pathway by altering the intrinsic GTPase activity of *KRAS* and creating insensitivity to RAS-GAPs [46,47].

Noonan syndrome patients with *KRAS* mutations were reported to have severe phenotypes with severe mental retardation [46—48].

2.2.4. *NRAS* (neuroblastoma RAS viral oncogene homolog)

The *NRAS* ([OMIM 164790]) gene mapped on 1p13.2 comprises 6 coding exons [49]. Cirstea et al have reported that *NRAS* mutations are involved in less than 1% of Noonan syndrome cases [50].

2.2.5. *RIT1*(Ric-like protein without Caax motif 1)

Interestingly, in 2013, Aoki et al reported that mutations in *RIT1* ([OMIM 609591]) cause Noonan syndrome [51]. *RIT1* is a member of the RAS subfamily of small GTPases (Fig. 2) [52], and consists of 6 exons and is located in the 1q22 region (Fig. 1D).

Aoki et al identified nine missense mutations in seventeen individuals from 180 patients (9%) with Noonan syndrome or related disorders and without mutations in known Noonan syndrome-causing genes, and observed that the frequency of *RIT* mutations in the Noonan syndrome cohort was seemingly similar to the frequency of *RAF1* mutations. This finding was subsequently confirmed by Bertola et al, in 2014, who found the same prevalence (9%), and Gos et al, in 2014, who found a lower mutation rate (3.8%). Those mutation clusters in the G1, Switch I, and more frequently in Switch II domains, were proven to entail a significant activation of the RAS MAPK pathway by hyper-activating transcription factor *ELK1*. [51,53,54].

Noonan syndrome patients with *RIT1* mutations were characterized by a high incidence of congenital heart disease (94%), especially hypertrophic cardiomyopathy (71%) and pulmonic stenosis (65%). The frequency of hypertrophic cardiomyopathy among *RIT1* mutation-positive patients is similar to that of *RAF1* mutation-positive subjects with Noonan syndrome, which leads to the conclusion that *RIT1* and *RAF1* interact with each other and have the same effect on cardiac development [51,55,56].

The RAF family (*ARAF*, *BRAF* and *RAF1*) has an activation role upstream of the MEK-ERK cascade into the RAS-MAPK pathway (Fig. 2).

2.2.6. *RAF1* (v-raf-1 murine leukemia viral oncogene homolog 1)

RAF1 ([OMIM 164760]) mutations cause 3—17% of Noonan syndrome cases. *RAF1* consists of 17 exons coding for multidomain protein that act as a serine—threonine kinase (Fig. 1E) [55,57,58]. This protein comprises three conserved regions (CR): CR1 that contains the RAS binding domain (RBD) and cysteine-rich domain (CRD), which are both suggested to be involved in the negative regulation of *RAF1* by direct physical interaction [59]; CR2, which is an important region where many *RAF1*-activating mutations and clusters lie. Eighty percent (80%) *RAF1* mutations in Noonan syndrome have HCM. It contains *Ser259* residue, which is critical to *RAF1* auto-inhibition [55]; and the third conserved region (CR3) in the C-terminal region of *RAF1* that is responsible for catalytic activity [55,57]. The *RAF1* inactive conformation is maintained via 14-3-3 protein dimers that bind to phosphorylated *Ser259* and *Ser621* in such a way that the catalytic site remains hidden [60]. Mutations in these conserved residues or in its flanking residues (such as *Arg256* and *Pro261*, among others) prevent the 14-3-3 binding leading to an auto-inhibition fail and the activation of the RAS-MAP kinase cascade [57].

Noonan syndrome-causing *RAF1* mutations were strongly correlated to hypertrophic cardiomyopathy. The latter was observed in 95% of Noonan syndrome patients, and seems to have an allele specificity that is associated with *Ser259* and *Ser612* mutations ($P < .0001$) [57].

In 2015, De Iriarte Rodrıguez et al proved that reduced levels of *RAF1* in mice may lead to hearing impairments [61].

2.2.7. *BRAF* (V-Raf murine sarcoma viral oncogene homolog B1)

BRAF ([OMIM 164757]), a member of the RAF family, was proven to be involved in Noonan syndrome pathogenesis by enhancing *ERK* activation [55,62]. However, the frequency of these mutations reported in a large cohort screening of Noonan syndrome patients were lower than those observed in *RAF1*, approximately 1.7—1.9%. These mutations cluster predominantly in conserved regions of CR1 and CR3 (Fig. 1F), but modestly increase kinase activity compared to *RAF1* [34,63].

2.2.8. *MAP2K1* (mitogen activated protein kinase 1)

MAP2K1 ([OMIM 176872]) is mapped to the 15q22 region and comprises 11 exons encoding the MEK protein, which is a dual-specificity kinase with a major protein kinase domain that activates the extracellular-signal-regulated (Erk) mitogen-activated protein (MAP) kinases (Fig. 1G) [64].

Previous studies confirmed that MEK plays a crucial role in the embryonic developmental process, especially in cell migration and placental development [64]. In 2007, Nava et al identified *MAP2K1* mutations in 4.2% of Noonan syndrome patients who are negative for *PTPN11* and *SO1* mutations [65]. This finding proved that mutations in the MEK protein kinase domain increase MEK basal kinase activity. This hyperactivity entails an increased phosphorylation of the downstream targets (such as ERK1 and ERK2) [66].

Recently, with the progress of molecular screening tools, whole genome sequencing (WGS) and whole exome sequencing (WES) have become increasingly used in the screening of developmental diseases. As a result, several novel Noonan syndrome-causing genes were highlighted in the last two years.

2.2.9. *SOS2* (Son of Sevenless homolog 2)

In 2015, Yamamoto et al reported that *SOS2* ([OMIM 601247]), the homolog of *SOS1*, is responsible of 4% of Noonan syndrome cases with no mutation in the genes previously associated with Noonan syndrome. *SOS1* and *SOS2* are 70% homologous. The reported mutations cluster in the DH domain, which plays a pivotal role in the stabilization of inactive conformation. Similar to *SOS1*, these mutations were associated with ectodermal defects [67].

2.2.10. *LZTR1* (leucine-zipper-like transcription regulator 1)

In the same study, Yamamoto et al identified pathogenic mutations in a candidate gene not associated with the RAS/MAPK pathway, the *LZTR1* gene ([OMIM 600574]). The

prevalence of these mutations in the same studied cohort was 8% [67].

The *LZTR1* gene is located in 22q11.21 and consists of 21 exons and encodes a protein member of the BTB-kelch superfamily. It was suggested that this gene may have a crucial role in the control of fundamental cellular processes (such as the cell cycle and the regulation of chromatin conformation) [68,69].

However, it is worth mentioning that *LZTR1* is already known to be associated with the Schwannomatosis, a form of neurofibromatosis [70].

2.2.11. *A2ML1* (α-2-macroglobulin (A2M)-like-1)

Vissers et al carried out exome sequencing in one Noonan syndrome case-parent trio and found a *de novo* mutation affecting a highly conserved residue of *A2ML1* ([OMIM 610627]), encouraging them to screen an additional cohort of 155 Noonan syndrome patients. This study showed the involvement of *A2ML1* mutations in approximately 1% of Noonan syndrome subjects negative for the other NS major genes [71]. *A2ML1* is a member of the α-macroglobulin superfamily, localized in 12p13 region with 35 coding exons. It acts as a protease inhibitor upstream of the MAPK pathway [72]. Mutations in *A2ML1* are said to cause developmental defects, but the ways in which mutation affects the MAP kinase pathway needs to be further elucidated [71].

Other genes carrying rare variants in a Noonan syndrome population were also highlighted recently, in particular, *RASA2*, *MAP3K8* and *SPRY* [73].

2.2.12. Other causes

Some studies have suggested other causes of some Noonan syndrome manifestations that are not related to a particular gene. For instance, wide-spaced nipples, cryptorchidism and some traits of facial dysmorphia such as hypertelorism, down slanting palpebral fissures, ptosis and low-set posteriorly rotated ears are suggested to be the result of tissue migration disruption or organ displacement caused by lymphedema at the intrauterine stage. Webbing of the neck and prominence of the trapezius may result from cystic hygroma at early intrauterine stages [74].

Recently, it was suggested that the impairment of testicular function responsible for delayed puberty or infertility is due to Sertoli and Leydig cell dysfunction rather than cryptorchidism [75].

The coagulation defect in Noonan syndrome was explained by the fact that the genes causing Noonan syndrome interact with the regulation process of the genes involved in the coagulation pathway [76].

2.3. Assessment of the mutation rate

In the second part of this review, we gathered and discussed mutational screening data reported in previous studies, to produce valid frequencies and authentic conclusions about mutational rates in Noonan syndrome ([NS, OMIM 163950]).

2.3.1. Search strategy

The data gathered were extracted from original articles published up to now (December 2015) in the "PubMed", "ScienceDirect" and "Wiley Online Library" databases using the following key words:

- "Noonan" in ([Abstract]).
- "Noonan" in ([Title/Abstract]) AND "*PTPN11*" in ([Title]),
- "Noonan" in ([Title/Abstract]) AND "*SOS1*" in ([Title]), and the same goes for the other genes (*RAF1*, *KRAS*, *BRAF*, *NRAS* and *RIT1*).

2.3.2. Inclusion criteria

From all of the articles gathered, we considered only studies comprising genetic screening of patient's series. We also considered clinical or endocrinological Noonan syndrome studies based initially on genetic screening. The genes considered in this part of the paper should have been screened by at least 3 studies meeting the inclusion criteria.

On the other hand, to determine the exact frequency of Noonan syndrome mutations, we excluded all data obtained from the screening of cohorts initially presenting with a particular condition (i.e., the mutational screening of Noonan syndrome patients with cardiac hypertrophy). The data gathered from the 82 included studies are summarized in Table 1 [77—108].

2.3.3. Mutational rate of Noonan syndrome-causing genes

Through the analyzed data (Table 1), we found that *PTPN11* is the most studied gene in Noonan syndrome populations (29 studies vs. 16 studies or less for other genes). This may be because *PTPN11* was the first gene of the RAS MAPK pathway to be highlighted in 2001, whereas the second gene involved (*KRAS*) was found 5 years later, followed by SHP-2. Indeed, the second gene, *KRAS*, was known beforehand to be involved in malignancy disorders through somatic mutations, while its germline mutations were associated for the first time with Noonan syndrome in 2006.

Then, in 2007, three genes were highlighted, (*SOS1*, *RAF1* and *MAP2K1*), after which the other RAS/MAP kinase genes, *BRAF*, *NRAS* and *RIT1*, were proven to be involved in Noonan syndrome in more recent, in 2009, 2010 and 2013, respectively.

It should be noted that the chronology of the gene identification does not consistently occur in the "more involved" to "less involved" direction. Indeed, *RIT1*, which was discovered in 2013, was proven to be involved in 8% of cases. This frequency is much higher than the frequency of some genes (*BRAF*, *KRAS* and *NRAS*) that were found first, while their incidences do not exceed 3% (2.3%, 2.8% and 0.8%, respectively).

The first most common genetic cause of Noonan syndrome is still *PTPN11* mutations that are observed in 42.5% of Noonan syndrome patients. Those mutations constitute 52.6% of all mutations detected up to now (Table 1).

The second most-involved gene is *SOS1*, which is altered in 16.4% of patients. On the other hand, we found that *RIT1* and *RAF1* have the same prevalence (8%) and are the third most-involved genes.

Table 1 Summary of the prevalence of Noonan syndrome-causing genes through previous studies.

Genes	N° of mutated subjects/total of subjects (% of mutations)	% of gene in genetic etiology	First year of gene study	N° of studies	References
PTPN11	814/1917 (42.5%)	52.6	2001	29	[19,24,34,35,58,77,83—105]
SOS1	242/1472 (16.4%)	20.3	2007	16	[19,34,36,39,43,58,78,79,97,98,102—107]
RIT1	31/383 (8%)	10	2013	4	[51,53,54,73]
RAF1	76/961 (8%)	10	2007	11	[34,55—58,78,79,98,103,105,107]
KRAS	31/1087 (2.8%)	3.4	2006	11	[46—48,58,65,79,89,98,102,103,105]
BRAF	19/815 (2.3%)	2.8	2009	7	[34,63,78,98,103,105,108]
NRAS	10/1213 (0.8%)	1	2010	4	[50,80—82]

Taken together, *PTPN11*, *SOS1*, *RAF1* and *RIT1* cover 93% of reported mutations (Table 1). Therefore, these genes should be systematically considered in the genetic diagnosis of Noonan syndrome.

Among the RAS subfamily members of the RAS/MAP kinase pathway reported in Noonan syndrome, *RIT1* seems to be the most involved gene compared with *KRAS* and *NRAS*, which have the lowest frequency among all reported cases (2.8% and 0.8%, respectively); however, among RAF family members, *RAF1* is the most involved gene compared to *BRAF* (8% versus 2.3%, respectively). Among these two families, neither *HRAS* nor *ARAF* were reported to cause Noonan syndrome. These divergences should attract more attention from researchers.

It is worth mentioning that there were no mutations in the *SHOC2*, *RRAS* and *CBL* genes in Noonan syndrome patients. These genes were reported to be involved in Noonan-like syndrome (NLS) only.

2.4. Inheritance and genetic counseling

Noonan syndrome is a common disorder that could occur as a sporadic condition or can be inherited in an autosomal dominant pattern. In the latter case, the affected parent who transmits the disorder is predominantly the mother. This may be explained by the adverse impact of Noonan syndrome on male fertility [7,13,108]. However, rare autosomal recessive cases of Noonan syndrome with consanguineous parents have also been reported [109].

When there is molecular evidence in one Noonan syndrome child, the clinical and molecular evaluation of parents becomes primordial in the determination of recurrence risks. In Noonan syndrome-causing genes with heterozygous mutations, the recurrence risk in one genetically affected parent is 50% per each pregnancy, while in an unaffected parent with Noonan syndrome child, the recurrence risk in subsequent pregnancies is very low, approximately 1—5% owing to putative germline mosaicism.

The Noonan syndrome patient and their family should be made aware of the consequences of some Noonan syndrome features that may arise or complicate with adulthood, such as fertility problems in cryptorchidism cases and cardiac and hematological complications, which need rigorous follow-up [110].

The de-novo *PTPN11* mutations are known to be more recurrent in Noonan syndrome. Tartaglia et al suggested that de-novo mutations have a predominantly paternal origin. They also demonstrated that the paternal average age in sporadic Noonan cases was significantly higher than that of the general population [111].

3. Conclusion

Noonan syndrome is a common multigenic disease. Its clinical side has been profoundly discussed by several researchers and diagnostic guides as support has been developed. This review completes the efforts of researchers focusing on the genetic etiology side of this syndrome and explains the physiopathological intervention of different genes in the manifestation of Noonan syndrome traits. In the second part, this paper provides pediatricians and geneticists with the mutational prevalence of genes involved in Noonan syndrome, which was deduced from the analysis of most studies carried out so far.

The result of this prevalence analysis leads to interesting conclusions, in particular, the high mutation rates observed in *PTPN11*, *SOS1*, *RAF1* and *RIT1*, which cover 93% of reported mutations, suggesting that those genes should be systematically considered in the genetic diagnosis of Noonan syndrome. Secondly, we draw attention to the significant differences observed between mutational rates in genes of the same family (genes of the same level of the cascade). The explanation of this divergence and the other points discussed in this review may lead to new insights in the genetic research field of Noonan syndrome.

Conflict of interest

The authors have no conflict of interest to report.

References

[1] Duncan WJ, Fowler RS, Farkas LG, Ross RB, Wright AW, Bloom KR, et al. A comprehensive scoring system for evaluating Noonan syndrome. Am J Med Genet 1981;10:37—50.
[2] Mendez HM, Opitz JM. Noonan syndrome: a review. Am J Med Genet 1985;21:493—506.
[3] Sharland M, Burch M, McKenna WM, Paton MA. A clinical study of Noonan syndrome. Arch Dis Child 1992;67:178—83.
[4] Allanson JE. Noonan syndrome. In: Cassidy SB, Allanson JE, editors. Management of genetic syndromes. Wiley-Blackwell; 2010. p. 569—86.

[5] Allanson JE, Hall JG, Hughes HE, Preus M, Witt RD. Noonan syndrome: the changing phenotype. Am J Med Genet 1985; 21:507—14.
[6] Patton MA. Noonan syndrome: a review. Growth Genet Horm 1994;33(10):1—3.
[7] Allanson JE. Noonan syndrome. J Med Genet 1987;24:9—13.
[8] Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. Arch Dis Child 2007;92:128—32.
[9] Pernot C, Marcon F, Worms AM, Cloez JL, Gilgenkrantz S, Marios L. La dysplasie cardio-vasculaire du syndrome de Noonan. Arch Mal Coeur 1987;80:434—43.
[10] Lin AE. Noonan syndrome. J Med Genet 1988;25:64—5.
[11] Sanchez-Cascos A. The Noonan syndrome. Eur Heart J 1983; 4:223—9.
[12] Nora JJ, Nora AH, Sinha AK, Spangler RD, Lubs HA. The Ullrich-Noonan syndrome (Turner phenotype). Am J Dis Child 1974;127:48—55.
[13] Marcus KA, Sweep CGJ, van der Burgt I, Noordam C. Impaired Sertoli cell function in males diagnosed with Noonan syndrome. J Pediatr Endocrinol Metab 2008;21:1079—84.
[14] Lee NB, Kelly L, Sharland M. Ocular manifestations of Noonan syndrome. Eye 1992;6:328—34.
[15] Reynolds DJ, Rubin SE, Fox J, Kodsi SR. Ocular manifestations of Noonan syndrome in the pediatric patient. J AAPOS 2004; 8:282—3.
[16] White SW. Lymphedema in Noonan's syndrome. Int J Dermatol 1984;23:656—7.
[17] Bader-Meunier B, Tchernia G, Mielot F, Fontaine JL, Thomas C, Lyonnet S, et al. Occurrence of myeloproliferative disorder in patients with Noonan syndrome. J Pediatr 1997; 130:885—9.
[18] Cohen MM, Gorlin RJ. Noonan-like/multiple giant cell lesion syndrome. Am J Med Genet 1991;40:159—66.
[19] Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, Seidenberg MS. Genotype differences in cognitive functioning in Noonan syndrome. Genes Brain Behav 2009;8:275—82.
[20] Jamieson CR, van der Burgt I, Brady AF, van Reen M, Elsawi MM, Hol F, et al. Mapping a gene for Noonan syndrome to the long arm of chromosome 12. Nat Gene 1994;8: 357—60.
[21] Brady AF, Jamieson CR, van der Burgt I, Crosby A, van Reen M, Kremer H, et al. Further delineation of the critical region for Noonan syndrome on the long arm of chromosome 12. Eur J Hum Genet 1997;5:336—7.
[22] Legius E, Schollen E, Matthijs G, Fryns JP. Fine mapping of Noonan/cardio-facio cutaneous syndrome in a large family. Eur J Hum Genet 1998;6:32—7.
[23] Chen B, Bronson RT, Klaman LD, Hampton TG, Wang JF, Green PJ, et al. Mice mutants for Egfr and Shp2 have defective cardiac semilunar valvulogenesis. Nat Genet 2000; 24:296—9.
[24] Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 2001;29:465—8.
[25] Feng GS. Shp-2 tyrosine phosphatase: signaling one cell or many. Exp Cell Res 1999;253:47—54.
[26] Stein-Gerlach M, Wallasch C, Ullrich A. SHP-2, SH2-containing protein tyrosine phosphatase-2. Int J Biochem Cell Biol 1998; 30:559—66.
[27] Saxton TM, Ciruna BG, Holmyard D, Kulkarni S, Harpal K, Rossant J, et al. The SH2 tyrosine phosphatase shp2 is required for mammalian limb development. Nat Genet 2000; 24:420—3.
[28] Qu CK, Yu WM, Azzarelli B, Cooper S, Broxmeyer HE, Feng GS. Biased suppression of hematopoiesis and multiple developmental defects in chimeric mice containing Shp-2 mutant cells. Mol Cell Biol 1998;18:6075—82.
[29] Tang TL, Freeman Jr RM, O'Reilly AM, Neel BG, Sokol SY. The SH2-containing protein-tyrosine phosphatase SH-PTP2 is required upstream of MAP kinase for early Xenopus development. Cell 1995;80:473—83.
[30] Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. Trends Biochem Sci 2003;28:284—93.
[31] Tamir I, Dal Porto JM, Cambier JC. Cytoplasmic protein tyrosine phosphatase SHP-1 and SHP-2: regulators of B cell signal transduction. Curr Opin Immunol 2000;12:307—15.
[32] De Rocca SNA, Edouard T, Tréguer K, Tajan M, Araki T, Dance M, et al. Noonan syndrome-causing SHP2 mutants inhibit insulin-like growth factor 1 release via growth hormone-induced ERK hyperactivation, which contributes to short stature. Proc Natl Acad Sci U S A 2012;109:4257—62.
[33] Hof P, Pluskey S, Dhe-Paganon S, Eck MJ, Shoelson SE. Crystal structure of the tyrosine phosphatase SHP-2. Cell 1998;92: 441—50.
[34] Lee BH, Kim JM, Jin HY, Kim GH, Choi JH, Yoo HW. Spectrum of mutations in Noonan syndrome and their correlation with phenotypes. J Pediatr 2011;159:1029—35.
[35] Tartaglia M, Kalidas K, Shaw A, Song X, Musat DL, van der Burgt I, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet 2002;70: 1555—63.
[36] Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, et al. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet 2007;39: 70—4.
[37] Hart TC, Zhang Y, Gorry MC, Hart PS, Cooper M, Marazita ML, et al. A mutation in the SOS1 gene causes hereditary gingival fibromatosis type 1. Am J Hum Genet 2002;70:943—54.
[38] Webb GC, Jenkins NA, Largaespada DA, Copeland NG, Fernandez CS, Bowtell DD. Mammalian homologues of the Drosophila Son of sevenless gene map to murine chromosomes 17 and 12 and to human chromosomes 2 and 14. Genomics 1993;18:14—9.
[39] Lepri F, De Luca A, Stella L, Rossi C, Baldassarre G, Pantaleoni F, et al. SOS1 mutations in Noonan syndrome: molecular spectrum, structural insights on pathogenic effects, and genotype-phenotype correlations. Hum Mut 2011; 32:760—72.
[40] Zenker M, Horn D, Wieczorek D, Allanson J, Pauli S, van der Burgt I, et al. SOS1 is the second most common Noonan gene but plays no major role in cardio-facio-cutaneous syndrome. J Med Genet 2007;44:651—6.
[41] Nimnual A, Bar-Sagi D. The two hats of SOS. Sci STKE 2002; 145:36.
[42] Sondermann H, Soisson SM, Boykevisch S, Yang SS, Bar-Sagi D, Kuriyan J. Structural analysis of autoinhibition in the Ras activator Son of Sevenless. Cell 2004;119:393—405.
[43] Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, et al. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet 2007;39: 75—9.
[44] Donovan S, Shannon KM, Bollag G. GTPase activating proteins: critical regulators of intracellular signaling. Biochim Biophys Acta 2002;1602:23—45.
[45] Vetter IR, Wittinghofer A. The guanine nucleotide-binding switch in three dimensions. Science 2001;294:1299—304.
[46] Carta C, Pantaleoni F, Bocchinfuso G, Stella L, Vasta I, Sarkozy A, et al. Germline missense mutations affecting KRAS isoform B are associated with a severe Noonan syndrome phenotype. Am J Hum Genet 2006;79:129—35.

[47] Schubbert S, Zenker M, Rowe SL, Böll S, Klein C, Bollag G, et al. Germline KRAS mutations cause Noonan syndrome. Nat Genet 2006;38:331—6.
[48] Zenker M, Lehmann K, Schulz AL, Barth H, Hansmann D, Koenig R, et al. Expansion of the genotypic and phenotypic spectrum in patients with KRAS germline mutations. J Med Genet 2007;44:131—5.
[49] Mitchell EL, Jones D, White GR, Varley JM, Santibanez Koref MF. Determination of the gene order of the three loci CD2, NGFB, and NRAS at human chromosome band 1p13 and refinement of their localisation at the subband level by fluorescence in situ hybridization. Cytogenet Cell Genet 1995;70:183—5.
[50] Cirstea IC, Kutsche K, Dvorsky R, Gremer L, Carta C, Horn D, et al. A restricted spectrum of NRAS mutations causes Noonan syndrome. Nat Genet 2010;42:27—9.
[51] Aoki Y, Niihori T, Banjo T, Okamoto N, Mizuno S, Kurosawa K, et al. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. Am J Hum Genet 2013;93:173—80.
[52] Hynds DL, Spencer ML, Andres DA, Snow DM. Rit promotes MEK-independent neurite branching in human neuroblastoma cells. J Cell Sci 2003;116:1925—35.
[53] Bertola DR, Yamamoto GL, Almeida TF, Buscarilli M, Jorge AAL, Malaquias AC, et al. Further evidence of the importance of RIT1 in noonan syndrome. Am J Med Genet Part A 2014;9999:1—6.
[54] Gos M, Fahiminiya S, Poznański J, Klapecki J, Obersztyn E, Piotrowicz M, et al. Contribution of RIT1 mutations to the pathogenesis of Noonan syndrome: four new cases and further evidence of heterogeneity. Am J Med Genet Part A 2014;9999:1—7.
[55] Razzaque MA, Nishizawa T, Komoike Y, Yagi H, Furutani M, Amo R, et al. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. Nat Genet 2007;39:1013—7.
[56] Kobayashi T, Aoki Y, Niihori T, Cavé H, Verloes A, Okamoto N, et al. Molecular and clinical analysis of RAF1 in Noonan syndrome and related disorders: dephosphorylation of serine 259 as the essential mechanism for mutant activation. Hum Mutat 2010;31:284—94.
[57] Pandit B, Sarkozy A, Pennacchio LA, Carta C, Oishi K, Martinelli S, et al. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. Nat Genet 2007;39:1007—12.
[58] Ko JM, Kim JM, Kim GH, Yoo HW. PTPN11, SOS1, KRAS, and RAF1 gene analysis, and genotype-phenotype correlation in Korean patients with Noonan syndrome. J Hum Genet 2008;53:999—1006.
[59] Cutler RE, Stephens RM, Saracino MR, Morrison DK. Autoregulation of the Raf-1 serine/threonine kinase. Proc Natl Acad Sci U S A 1998;95(16):9209—14.
[60] Fischer A, Baljuls A, Reinders J, Nekhoroshkova E, Sibilski C, Metz R, et al. Regulation of RAF activity by 14-3-3 proteins: RAF kinases associate functionally with both homo- and heterodimeric forms of 14-3-3 proteins. J Biol Chem 2009;284(5):3183—94.
[61] de Iriarte Rodriguez R, Magarinos M, Pfeiffer V, Rapp UR. Varela-Nieto I.C-Raf deficiency leads to hearing loss and increased noise susceptibility. Cell Mol Life Sci 2015;72(20):3983—98.
[62] Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004;116:855—67.
[63] Sarkozy A, Carta C, Moretti S, Zampino G, Digilio MC, Pantaleoni F, et al. Germline BRAF mutations in Noonan, LEOPARD, and cardiofaciocutaneous syndromes: molecular diversity and associated phenotypic spectrum. Hum Mutat 2009;30:695—702.
[64] Giroux S, Tremblay M, Bernard D, Cardin-Girard JF, Aubry S, Larouche L, et al. Embryonic death of Mek1-deficient mice reveals a role for this kinase in angiogenesis in the labyrinthine region of the placenta. Curr Biol 1999;9(7):369—76.
[65] Nava C, Hanna N, Michot C, Pereira S, Pouvreau N, Niihori T, et al. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationships and overlap with Costello syndrome. J Med Genet 2007;44:763—71.
[66] Delaney AM, Printen JA, Chen H, Fauman EB, Dudley DT. Identification of a novel mitogen-activated protein kinase kinase activation domain recognized by the inhibitor PD 184352. Mol Cell Biol 2002;22:7593—602.
[67] Yamamoto GL, Aguena M, Gos M, Hung C, Pilch J, Fahiminiya S, et al. Rare variants in SOS2 and LZTR1 are associated with Noonan syndrome. J Med Genet 2015;52(6):413—21.
[68] Perez-Torrado R, Yamada D, Defossez PA. Born to bind the BTB protein-protein interaction domain. Bioessays 2006;28:1194—202.
[69] Nacak TG, Leptien K, Fellner D, Augustin HG, Kroll J. The BTB-kelch protein LZTR-1 is a novel Golgi protein that is degraded upon induction of apoptosis. J Biol Chem 2006;281:5065—71.
[70] Piotrowski A, Xie J, Liu YF, Poplawski AB, Gomes AR, Madanecki P, et al. Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas. Nat Genet 2014;46:182—7.
[71] Vissers LE, Bonetti M, Paardekooper OJ, Nillesen WM, Frints SG, de Ligt J, et al. Heterozygous germline mutations in A2ML1 are associated with a disorder clinically related to Noonan syndrome. Eur J Hum Genet 2015;23(3):317—24.
[72] Galliano MF, Toulza E, Gallinaro H, Jonca N, Ishida-Yamamoto A, Serre G, et al. A novel protease inhibitor of the alpha2-macroglobulin family expressed in the human epidermis. J Biol Chem 2006;281:5780—9.
[73] Chen PC, Yin J, Yu HW, Yuan T, Fernandez M, Yung CK, et al. Next-generation sequencing identifies rare variants associated with Noonan syndrome. Proc Natl Acad Sci U S A 2014;111:11473—8.
[74] Witt DR, Hoyme HE, Zonana J, Manchester DK, Fryns JP, Stevenson JG, et al. Clues to pathogenesis and prenatal diagnosis and review of the literature. Am J Med Genet 1987;27(4):841—56.
[75] Ankarberg-Lindgren C, Westphal O, Dahlgren J. Testicular size development and reproductive hormones in boys and adult males with Noonan syndrome: a longitudinal study. Eur J Endocrinol 2011;165:137—44.
[76] Bertola DR, Carneiro JD, D'Amico EA, Kim CA, Albano LM, Sugayama SM, et al. Hematological findings in Noonan syndrome. Rev Hosp Clin Fac Med Sao Paulo 2003;58(1):5—8.
[77] Sznajer Y, Keren B, Baumann C, Pereira S, Alberti C, Elion J, et al. The spectrum of cardiac anomalies in noonan syndrome as a result of mutations in the PTPN11 gene. Pediatrics 2007;119(6):1325—31.
[78] Denayer E, Devriendt K, de Ravel T, Van Buggenhout G, Smeets E, Francois I, et al. Tumor spectrum in children with Noonan syndrome and SOS1 or RAF1 mutations. Genes Chromosomes Cancer 2010;49(3):242—52.
[79] Croonen EA, Nillesen W, Schrander C, Jongmans M, Scheffer H, Noordam C, et al. Comparing mutation-positive with mutation-negative Dutch patients. Mol Syndromol 2013;4:227—34.
[80] Runtuwene V, van Eekelen M, Overvoorde J, Rehmann H, Yntema HG, Nillesen WM, et al. Noonan syndrome gain-of-function mutations in NRAS cause zebrafish gastrulation defects. Dis Model Mech 2011;4:393—9.

[81] Denayer E, Peeters H, Sevenants L, Derbent M, Fryns JP, Legius E. NRAS mutations in Noonan syndrome. Mol Syndromol 2012;3:34—8.
[82] Kraoua L, Journel H, Bonnet P, Amiel J, Pouvreau N, Baumann C, et al. Constitutional NRAS mutations are rare among patients with Noonan syndrome or juvenile myelomonocytic leukemia. Am J Med Genet Part A 2012;158A: 2407—11.
[83] Kosaki K, Suzuki T, Muroya K, Hasegawa T, Sato S, Matsuo N, et al. PTPN11 (proteintyrosine phosphatase, nonreceptor-type 11) mutations in seven Japanese patients with Noonan syndrome. J Clin Endocrinol Metab 2002;87:3529—33.
[84] Musante L, Kehl HG, Majewski F, Meinecke P, Schweiger S, Gillessen-Kaesbach G, et al. Spectrum of mutations in PTPN11 and genotype-phenotype correlation in 96 patients with Noonan syndrome and five patients with cardio-facio-cutaneous syndrome. Eur J Hum Genet 2003;11:201—6.
[85] Sarkozy A, Conti E, Seripa D, Digilio MC, Grifone N, Tandoi C, et al. Correlation between PTPN11 gene mutations and congenital heart defects in Noonan and LEOPARD syndromes. J Med Genet 2003;40:704—8.
[86] Zenker M, Buheitel G, Rauch R, Koenig R, Bosse K, Kress W, et al. Genotype-phenotype correlations in Noonan syndrome. J Pediatr 2004;144:368—74.
[87] Yoshida R, Hasegawa T, Hasegawa Y, Nagai T, Kinoshita E, Tanaka Y, et al. Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. J Clin Endocrinol Metab 2004; 89:3359—64.
[88] Niihori T, Aoki Y, Ohashi H, Kurosawa K, Kondoh T, Ishikiriyama S, et al. Functional analysis of PTPN11/SHP-2 mutants identified in Noonan syndrome and childhood leukemia. J Hum Genet 2005;50(4):192—202.
[89] Ferreira LV, Souza SA, Arnhold IJ, Mendonca BB, Jorge AA. PTPN11 (protein tyrosine phosphatase, nonreceptor type 11) mutations and response to growth hormone therapy in children with Noonan syndrome. J Clin Endocrinol Metab 2005; 90:5156—60.
[90] Binder G, Neuer K, Ranke MB, Wittekindt NE. PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. J Clin Endocrinol Metab 2005;90:5377—81.
[91] Jongmans M, Sistermans EA, Rikken A, Nillesen WM, Tamminga R, Patton M, et al. Genotypic and phenotypic characterization of Noonan syndrome: new data and review of the literature. Am J Med Genet Part A 2005;134A:165—70.
[92] Bertola DR, Pereira AC, Albano LMJ, De Oliveira PSL, Kim CA, Krieger JE. PTPN11 gene analysis in 74 Brazilian patients with Noonan syndrome or Noonan-like phenotype. Genet Test 2006;10:186—91.
[93] Lee ST, Ki CS, Lee HJ. Mutation analysis of the genes involved in the Ras-mitogen-activated protein kinase (MAPK) pathway in Korean patients with Noonan syndrome. Clin Genet 2007; 72:150—5.
[94] Hung CS, Lin JL, Lee YJ, Lin SP, Chao MC, Lo FS. Mutational analysis of PTPN11 gene in Taiwanese children with Noonan syndrome. J Formos Med Assoc 2007;106(2):169—72.
[95] Ferreira LV, Souza SA, Montenegro LR, Arnhold IJ, Pasqualini T, Heinrich JJ, et al. Variabilidade do fenótipo de pacientes com síndrome de Noonan com e sem mutações no gene PTPN11. Arq Bras Endocrinol Metab 2007;51(3):450—6.
[96] Croonen EA, van der Burgt I, Kapusta L, Draaisma JMT. Electrocardiography in Noonan syndrome PTPN11 gene mutation-phenotype characterization. Am J Med Genet Part A 2008;146A:350—3.
[97] Ferrero GB, Baldassarre G, Delmonaco AG, Biamino E, Banaudi E, Carta C, et al. Clinical and molecular characterization of 40 patients with Noonan syndrome. Eur J Med Genet 2008;51:566—72.
[98] Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, Rauen KA, et al. Effects of germline mutations in the Ras/MAPK signaling pathway on adaptive behavior: cardiofaciocutaneous syndrome and Noonan syndrome. Am J Med Genet Part A 2010;152A:591—600.
[99] Brasil AS, Pereira AC, Wanderley LT, Kim CA, Malaquias AC, Jorge AA, et al. PTPN11 and KRAS gene analysis in patients with Noonan and Noonan-like syndromes. Gent Test Mol Biomark 2010;14(3):425—32.
[100] Derbent M, Oncel Y, Tokel K, Varan B, Haberal A, Yazıcı AC, et al. Clinical and hematologic findings in Noonan syndrome patients with PTPN11 gene mutations. Am J Med Genet Part A 2010;152A:2768—74.
[101] Papadopoulou A, Issakidis M, Gole E, Kosma K, Fryssira H, Fretzayas A, et al. Phenotypic spectrum of 80 Greek patients referred as Noonan syndrome and PTPN11 mutation analysis: the value of initial clinical assessment. Eur J Pediatr 2012; 171:51—8.
[102] Choi JH, Lee BH, Jung CW, Kim YM, Jin HY, Kim JM, et al. Response to growth hormone therapy in children with noonan syndrome: correlation with or without PTPN11 gene mutation. Horm Res Paediatr 2012;77:388—93.
[103] Razzaque MA, Komoike Y, Nishizawa T, Inai K, Furutani M, Higashinakagawa, et al. Characterization of a novel KRAS mutation identified in Noonan syndrome. Am J Med Genet Part A 2012;158A:524—32.
[104] Şimşek-Kiper PÖ, Alanay Y, Gülhan B, Lissewski C, Türkyilmaz D, Alehan D, et al. Clinical and molecular analysis of RASopathies in a group of Turkish patients. Clin Genet 2013;83(2):181—6.
[105] Prendiville TW, Gauvreau K, Tworog-Dube E, Patkin L, Kucherlapati RS, Roberts AE, et al. Cardiovascular disease in Noonan syndrome. Arch Dis Child 2014;99(7):629—34.
[106] Narumi Y, Aoki Y, Niihori T, Sakurai M, Cavé H, Verloes A, et al. Clinical manifestations in patients with SOS1 mutations range from Noonan syndrome to CFC syndrome. J Hum Genet 2008;53:834—41.
[107] Longoni M, Moncini S, Cisternino M, Morella IM, Ferraiuolo S, Russo S, et al. Noonan syndrome associated with both a new Jnk-activating familial SOS1 and a de novo RAF1 mutations. Am J Med Genet Part A 2010;152A:2176—84.
[108] Elsawi MM, Pryor JP, Klufio G, Barnes C, Patton MA. Genital-tract function in men with Noonan syndrome. J Med Genet 1994;31:468—70.
[109] van der Burgt I, Brunner H. Genetic heterogeneity in Noonan syndrome: evidence for an autosomal recessive form. Am J Med Genet 2000;94:46—51.
[110] van der Burgt I. Noonan syndrome. Orphanet J Rare Dis 2007; 14:2—4.
[111] Tartaglia M, Cordeddu V, Chang H, Shaw A, Kalidas K, Crosby A, et al. Paternal germline origin and sex-ratio distortion in transmission of PTPN11 mutations in Noonan syndrome. Am J Hum Genet 2004;75:492—7.