Review Article

J Genet Med 2019;16(1):1-9
https://doi.org/10.5734/JGM.2019.16.1.1
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

Noonan syndrome and RASopathies: Clinical features, diagnosis and management

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Noonan syndrome (NS) and NS-related disorders (cardio-facio-cutaneous syndrome, Costello syndrome, NS with multiple lentigines, or LEOPARD [lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth and sensory neural deafness] syndrome) are collectively named as RASopathies. Clinical presentations are similar, featured with typical facial features, short stature, intellectual disability, ectodermal abnormalities, congenital heart diseases, chest & skeletal deformity and delayed puberty. During past decades, molecular etiologies of RASopathies have been growingly discovered. The functional perturbations of the RAS-mitogen-activated protein kinase pathway are resulted from the mutation of more than 20 genes (*PTPN11, SOS1, RAF1, SHOC2, BRAF, KRAS, NRAS, HRAS, MEK1, MEK2, CBL, SOS2, RIT, RRAS, RASA2, SPRY1, LZTR1, MAP3K8, MYST4, A2ML1, RRAS2*). The *PTPN11* (40-50%), *SOS1* (10-20%), *RAF1* (3-17%), and *RIT1* (5-9%) mutations are common in NS patients. In this review, the constellation of overlapping clinical features of RASopathies will be described based on genotype as well as their differential diagnostic points and management.

Key words: Noonan syndrome, Noonan syndrome related disorders, Genes.

Introduction

Noonan syndrome (NS; OMIM 163950) is one of the most common syndromes inherited in autosomal dominant manner. The patients display typical face, cardiac abnormalities, chest deformities and short stature. It was originally described by Jacquelin Noonan, a pediatric cardiologist in 1962 [1]. Positive family history is documented in 14-75% of cases. The incidence of NS is known to be one out of 1,000-2,000 [2]. In Korea, more than 250 clinically diagnosed Noonan patients are enrolled in registry. NS with multiple lentigines (NSML), previously called LEOPARD (lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth and sensory neural deafness) syndrome (OMIM 151100), cardio-facio-cutaneous syndrome (CFC; OMIM 115150), and Costello syndrome (CS; OMIM 218040) display similar phenotypes with NS and are classified as NS-related disorders [3,4]. They are all clinically overlapped by the common features of dysmorphic face, congenital heart disease, proportionate post-natal short stature, chest deformity, delayed puberty, short neck, dermatological abnormalities, and hematological abnormalities. During past 20 years, many genes responsible for NS are discovered since Tartaglia et al. [5] identified the heterozygous mutation in *PTPN11* in 2001. As of 2019, more

Received: 15 May 2019, Revised: 31 May 2019, Accepted: 31 May 2019, Published: 30 June 2019
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Conflict of interest: The authors declare that they do not have any conflicts of interest.

than 20 genes (*PTPN11, SOS1, RAF1, SHOC2, BRAF, KRAS, NRAS, HRAS, MEK1, MEK2, CBL, SOS2, RIT, RRAS, RASA2, SPRY1, LZTR1, MAP3K8, MYST4, A2ML1, RRAS2*) were known to cause NS and its related disorders [6-8]. Since the consequences of genetic defect of these genes are the gain of function in the rat sarcoma viral oncogene (RAS) /mitogen-activated protein kinase (MAPK) pathway, Noonan syndrome and its related disorders (LEOPARD, CFC, CSs, and neurofibromatosis type I) are named as RASopathies [7,9]. Owing to the phenotypic and genotypic similarities, the differential diagnosis of these syndromes is challenging. However, precise diagnosis is important to provide appropriate clinical management and genetic counseling at risk family.

Genetic Heterogeneity and Molecular Genetics of Noonan Syndrome and RASopathies

The molecular pathogenesis behind RASopathies is now increasingly understood. It is commonly resulted from gain of function of the RAS-MAPK signaling pathway. The MAPK signaling pathway plays a bio-functional role of growth factor-mediated cell proliferation, differentiation, and apoptosis. The MAPK signaling pathway involves guanosine binding RAS proteins (HRAS, NRAS and KRAS), functioning as a signal switch. They are critical for both integration of extracellular stimuli and activation of downstream effectors. The guanosine triposphate (GTP)-bound form of RAS is able to stimulate several intracellular pathways including MAPK pathway. The RAF (murine sarcoma viral oncogene homolog)-MEK (mitogen-activated kinase kinase)-ERK (mitogen-activated kinase) pathway is RAS downstream effector pathway. There are three RAF serine/threonine kinase (ARAF, BRAF, and RAF1), activating the MEK-ERK kinase cascade. The proteins, PTPN11 (protein tyrosine phosphatase, non-receptor type 11) and SOS1 (son of sevenless 1) are in the upstream of RAS. Most patients carrying the mutation in these genes are Noonan or NSML syndrome phenotypes. The germline mutations enhancing the function of the RAS-MAPK pathway components are underlying molecular mechanism for the development of NS and NS-related disorders [10]. *PTPN11* (40-50%), *SOS1* (10-20%), and *RAF1* (3-17%) mutations are relatively common in NS patients [10-13]. A small number of NS patients also carry *KRAS* [14], *BRAF* [15], *MEK1* [4], or *NRAS* mutations [16]. The *SHOC2* mutation was reported in NS-like patients with loose anagen hair [17]. So far, the causative genes are still elusive in 20% of patients with NS [7,8,10,12]. The *BRAF* (~50%), *MEK1* and *MEK2* mutations are found in 60-80% of CFC patients [4,15,18-21]. The *PTPN11*, *RAF1* and *BRAF* mutations were reported in NSML patients (mostly *PTPN11* mutation), and vast majority of CS patients carry *HRAS* mutations [2,15,22,23]. Both *PTPN11* (~45%) and *SOS1* mutations (~15%) are prevalent mutations in Korean NS patients. The *BRAF* (41.2%) and *SHOC2* (23.5%) mutations are common in Korean CFC patients. Other mutations are found in *MEK1, MEK2, KRAS*, and *SOS1* in a few CFC patients [13,24]. But in our study on Korean patients [24], *SHOC2* mutation was in a substantial number of CFC patients, not in NS patients same as in other report [25]. It suggests that *SHOC2* mutations are causative in CFC as well as NS. The mutation spectrum of CS and NSML are unique, mostly found in *HRAS* and *PTPN11* genes respectively. Still, there are phenotypic heterogeneities even in patients with identical genotypes. The p.G464R mutation of *BRAF* was previously reported both in a CFC patient [3], and in NS patients [24]. The clinical overlapping features are described in other patients with *MEK1, MEK2*, and *KRAS* mutations [4]. The functional alteration of the three variants were verified by exploring the downstream effectors in the RAS-MAPK pathway [13,24]. The RAF1 activity is enhanced by GTP-bounded RAS, subsequently phosphorylating serine residues of MEK. During the cascade process, the conserved region 2 (CR2) domain of RAF1 plays a major role with the dephosphorylated status of p.S259 in the CR2 domain, which is crucial for the activation of RAF1. Vast majority of *RAF1* mutations are located in the CR2 domain [13,22,24,26]. Especially, novel p.S259T and p.P261T mutation are located at or near the p.S259 amino acid residue. Functional assay using these mutant constructs demonstrated that *in vitro* activities were higher than those of wild-type RAF1 in the presence of growth factor [24]. The p.K170E mutation of *SOS1* is located in the histone fold (HF) domain, where mutations were rarely reported. The HF domain is important to maintain the stabilization of the auto-inhibitory conformation of SOS1 by the inhibition of allosteric RAS-binding site, thereby interfering the RAS activation by SOS1 at basal state. In the presence of a growth stimulus, this blocking is uninhibited, allowing RAS to bind to SOS1, leading to the activation of down-stream singnaling [27,28]. Despite extensive efforts utilizing single gene, targeted panel, and whole exome sequencing in order to discover reponsible genes of RASopathies, around 20% of patients with RASopathies remain genetically undiagnosed [4,8-12], as in our studies [13,24] (Fig. 1).

Genotype-Phenotype Correlation

Precise clinical delineation of RASopathies is important for the prediction of prognosis and optimal management. Short stat-

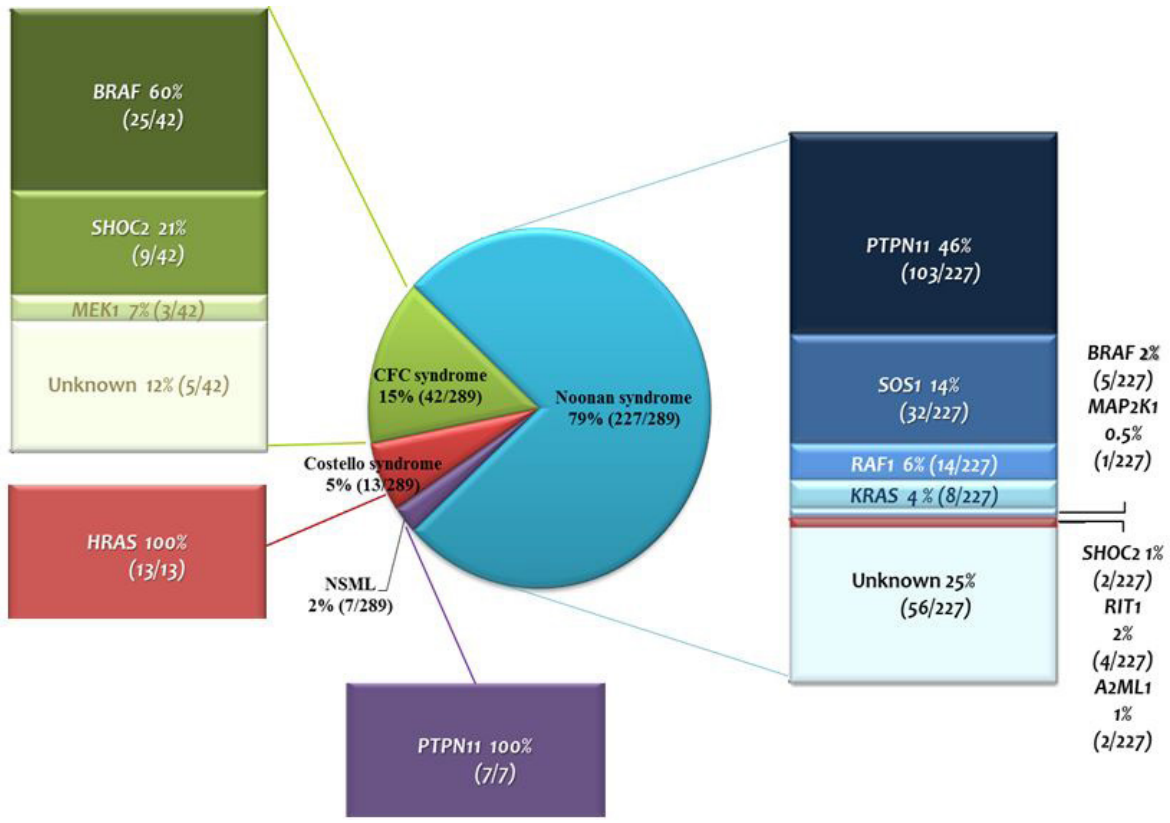

Fig. 1. Distribution of genetic locus where the mutation is present in Korean patients with RASopathies.

ure and global developmental delay or intellectual disabilities are more common in patients with NS-related disorders than in patients with NS. The early diagnosis is often problematic in infants and toddlers. Dermatological features (skin, hair) and size of head will help to differentiate the disease. Understanding of correlations between phenotypes and genotypes is able to make genotype-based surveillance and management possible. For instances, the *PTPN11* mutations are commonly associated with pulmonary stenosis, pectus deformity easy bruising and hematological malignancies [5,29], while hypertrophic cardiomyopathy is often correlated with *RAF1* and *RIT1* mutations [8,13,22]. In Korean NS patients, pulmonary stenosis is prevalent in *SOS1* mutation carrying patients (~80%), as in other reports (~70%) [24,30]. The patients with *HRAS* mutations have a highly likelihood of developing genitourinary tract solid tumors, necessitating tumor surveillance [23]. Korean patients with *SOS1* mutation are not that short as in other reports [24,27,31]. NS patients carrying *SOS1* mutation are more likely to present similar skin findings with CFC syndrome and less likely to show short stature and impaired cognitive function. The JAK (Janus kinase)-STAT (signal transducers and activators of transcription) pathway is not directly linked to SOS1. The JAK-STAT signaling pathway is one of major signaling pathways induced by growth hormone (GH) linked to PTPN11. The PTPN11 inhibits it [32]. NS patients with *SHOC2* gene mutation tend to have higher frequency of mitral valve prolapse and septal defects. They are more likely to have growth hormone deficiency (GHD). Also, they have easily pluckable, sparse, thin, slow growing hair, darkly pigmented skin eczema, and ichthyosis . They frequently present with hypernasal voice. *RIT1* is one of the major genes for NS (5-10% of NS). The clinical features of *RIT1* carrying NS patients are distinct from NS with other genotypes, with a high incidence of cardiovascular involvements, such as hypertrophic cardiomyopathy, and lymphovascular anomalies [33].

The RASopathies patients carrying the mutation in *SHOC2, BRAF, KRAS*, and *HRAS* mutations show higher incidence of intellectual disability than *PTPN11* and *SOS1* mutation carrying patients. It indicates that intellectual disability is caused by different biological functions of causative genes of the RAS-MAPK pathway [6,7] (Fig. 2).

Clinical Features, Differential Diagnosis and Management

1. Noonan syndrome

Conventionally, van der Burgt et al.'s criteria [1] are utilized

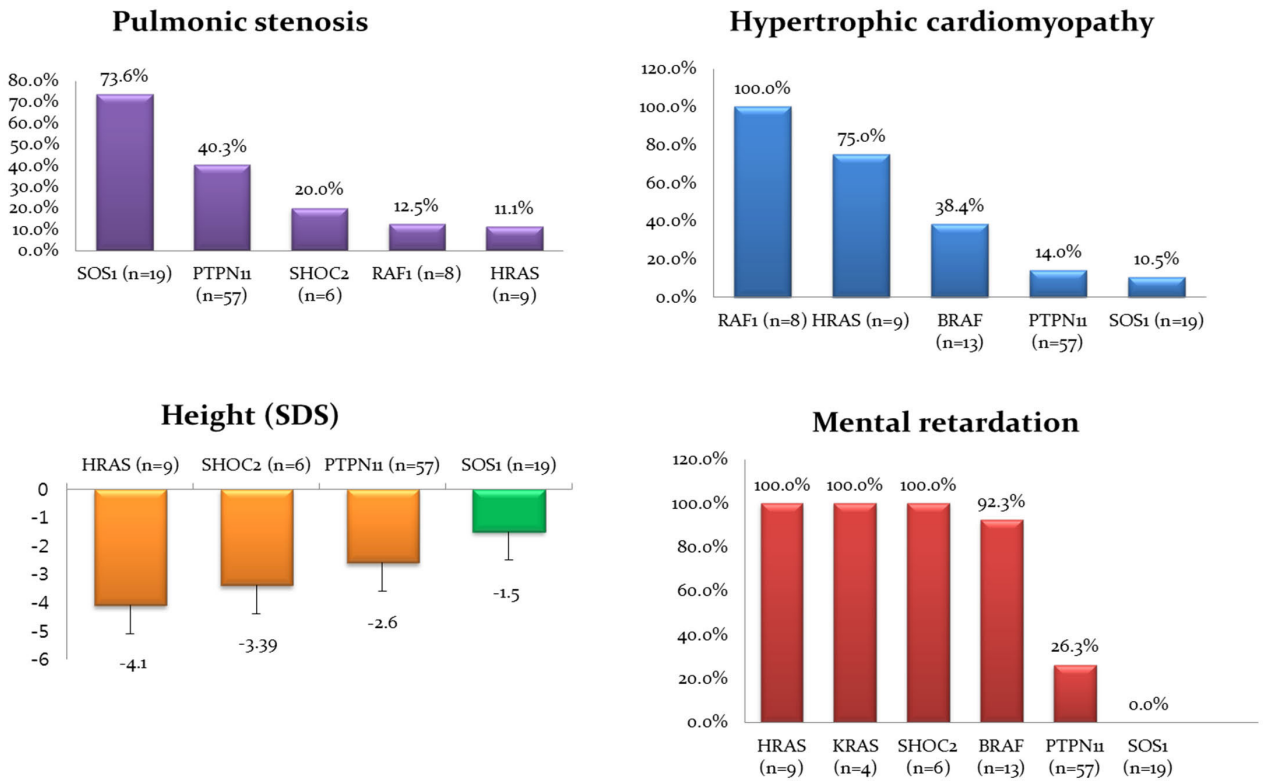

Fig. 2. Genotype and phenotype correlations of Korean patients with RASopathies.

to make the clinical diagnosis of NS. The characteristic facial morphology with one or two major clinical characteristics or suggestive face with two major or three minor clinical features is required to make the diagnosis. Short stature (postnatal onset) is usually observed in 50-80% of patients. Birth weight and height are typically normal, but there is a substantial deceleration of growth velocity during 2-4 years after birth with more than 2 year delayed bone age for chronological age. Final adult height of NS reaches the lower limit of normal at the end of the second decade of life, 160 to 162 cm in males, and 150 to 152 cm in females in non-Asians. Head and neck abnormalities are often prominent, displaying typical face with small chin, ear abnormalities (44-90%) with low-set posteriorly rotated ears with thick helix, sensory neural hearing loss, ophthalmological problems (95%) with ptosis, hypertelorism, down-slanting palpebral fissures, strabismus, proptosis, myopia and nystagmus, deeply grooved philtrum with high peaks of upper lip vermillion border (95%), neck abnormalities (95%) with short or webbed neck, high arched palate (34-45%), dental malocclusion (35%), low posterior hair line (32%), and micrognathia (22%). Congenital heart defects are frequently accompanied in 50-75% of patients, most commonly pulmonic valve stenosis (50%). Other cardiovascular abnormalities are hypertrophic cardiomyopathy (10%), atrial septal defect (10%), and others (aortic stenosis, ventricular septal defect and mitral insufficiency). Those with cardiac problems need regular follow-up on a regular interval. Some will require treatment such as balloon valvuloplasty or surgery. Long-term follow-up is essential (specifically, after successful cardiac surgery, cardiac care should not be discontinued). Individuals without heart disease at initial evaluation also need cardiac assessment every 5 years. Adults should not discontinue periodic cardiac evaluations even if their evaluations in childhood or adolescence were normal because unexpected cardiac findings can occur at any point in time [6,7]. Chest deformities are one of the major criteria for the diagnosis, observed in 53-70% of patients; flat, funnel, shield or deformed chest, pectus carinatum superiorly and/or pectus excavatum inferiorly. Undescended testes in males and delayed puberty are common clinical issues in 60-80% of patients. The mean age of pubertal onset is 13.5 to 14.5 years in boys and 13 to 14 years in girls. Skeletal abnormalities are cubitus valgus (47%), hand abnormalities including clinodactyly, brachydactyly and blunt fingertips (30%), and vertebral abnormalities (25%). Neurological involvements are featured by motor developmental delay (26%), language delay (20%), learning disability (15%), recurrent seizure (13%), peripheral neuropathy (3%), and mild intellectual disability (25-

35%). Hematological problems are noted in NS patients; bleeding diathesis (20%) including factor XI or XII deficiencies, von Willebrand's disease, platelet dysfunction and leukemia, especially juvenile myelomonocytic leukemia (JMML) [34].

The diagnosis of NS is primarily based on clinical features aforementioned. Therefore, high clinical suspicion should be a prerequisite for the diagnosis. Mutation analysis of 20 genes (*PTPN11, SOS1, RAF1, SHOC2, RIT, KRAS, NRAS, MRAS, BRAF, MEK1, MEK2, CBL, SOS2, SPRY1, LZTR1, A2ML1, RRAS, RRAS2, RASA2, PPP1CB*) makes the diagnosis confirmatory in about 80%. In female patients, karyotype should be done to exclude Turner syndrome [6-8,24,34].

Management of NS patients is entirely dependent on its individual manifestation. Cautious physical examinations are mandatory to delineate the presence of congenital defects in cardiovascular, genitourinary, skeletal, and other birth defects. Documentation of past growth history is helpful to understand growth problem. Regular audiometric and ophthalmologic evaluations are needed. Surgical intervention is required for congenital heart defects and undescended testes. *RAF1* mutation positive phenotype is frequently associated with hypertrophic cardiomyopathy. Bleeding diathesis is common in NS patients. It should be tested using bleeding time, coagulation profiles analyses before surgery. Malignant hyperthermia risk is considered during the process of anesthesia. Mild myeloproliferative disorder occurring in 10% of NS infants, mimicking JMML is usually self-limited by one year of age without specific therapy. The risk of cancer development in NS patients is 3.5 fold higher than normal population, especially hematological malignancies and solid tumors [35]. Special education is needed in 10-40% of NS patients because of learning difficulty. However, NS patients with mutations in the *SOS1* gene and N380D or N380S mutation in the *PTPN11* gene show relatively normal cognitive function. Most NS infants have feeding difficulties with poor suck and prolonged feeding time and may require tube feeding. This period of failure to thrive usually ends by the age of 2. Oral and dental problems often draw a medical attention. Particularly, dental malocclusion due to small chin commonly develops, necessitating orthodontics intervention. Articulation difficulty is common (72%), but responds well to intervention therapy. Language delay may be derived from hearing defect, perceptual motor disabilities or articulation deficiencies [2,6]. Growth evaluation is important in individuals with postnatal growth failure or delayed puberty. Insulin-like growth factor (IGF)-1 and insulin-like growth factor-binding protein 3 (IGF-BP3) levels are assayed with thyroid function test. Most NS patients show normal IGF-1 and IGF-BP3 levels, indicating GHD is not a major cause of postnatal growth failure. However, some studies reported subnormal overnight mean GH concentration, suggestive of blunted GH secretion. There are several studies regarding the efficacy of recombinant human growth hormone (rhGH) on the final adult height outcome in subjects with NS from a rhGH registry, the KIGS International Growth Database [36,37], to several, observational studies [38-40]. Both the height velocity and the final adult height are improved by rhGH therapy in NS patients, despite small numbers of patients, varying age at start of rhGH therapy, treatment durations, and rhGH doses. The National Cooperative Growth Study, a post-marketing observational study of rhGH-treated children, showed that rhGH significantly improved height standard deviation score (SDS) in relatively large numbers of children with NS [41]. In May 2007, Novo Nordisk obtained FDA (Food and Drug Administration) approval for the treatment of NS with their rhGH preparation, Norditropin using a dose of 66 μg/kg/day [42]. It has been suggested that there may be a genotype-phenotype correlation with respect to spontaneous growth, IGF-1 and IGF-BP3 levels, and response to GH therapy [5,27]. *PTPN11* mutation carrying NS patients tend to be born with shorter birth length, lower IGF-1 and IGF-BP3, higher resting and stimulated GH levels, and poorer response to GH therapy. These phenomena are hypothetically explained by post-receptor signaling defect. The frequently detected upstream defects of this pathway are gain-of-function mutations of *PTPN11*, leading to a mild form of GH resistance and IGF-1 deficiency, presumably due to interference with the JAK2-STAT 5b signaling of the GH receptor. In about 50% of with NS, the cytoplasmic tyrosine phosphatase SHP2 encoded by *PTPN11* is mutated [34]. The longer-term data regarding adult heights for those treated with GH show no difference between mutation-positive and negative patients. Several studies have reported final adult height outcome after rhGH treatment in NS [38-41]. However, these studies were conducted in relatively small cohort, often lacking the matched or randomized control. The height gain is varying in these studies (0.6-1.8 SDS; mean height gain: 9.5-13 cm for boys and 9.0-9.8 cm for girls), with the best results in younger age groups at the start of treatment. The results were better in both groups of the younger age of initiating rhGH therapy and the more delayed age of pubertal onset [38-40]. Our group has published a result of short-term efficacy of GH therapy in *PTPN11* mutation positive or negative Korean Noonan patients, demonstrating short-term growth promotion efficacy in both groups [43]. Other endocrine issues are delayed puberty and autoimmune thyroid disorder. Pubertal induction

with low dose estrogen or androgen may be instituted in case of no secondary sex characteristics in girls by 13 years or boys by14 years [2].

2. Noonan syndrome with multiple lentigines (NSML, LEOPARD syndrome)

Acronym LEOPARD denotes the Lentigines, electrocardiogram (EKG) abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness. The syndrome shares with NS clinical features; hypertelorism, pulmonic valve stenosis, hypertrophic cardiomyopathy, and short stature. More striking features of NSML are multiple skin lentigines, especially on neck and trunk, sensory neural hearing loss, conduction abnormalities on EKG (prolonged PR, QRS intervals and abnormal P waves). Intellectual disability is common. Delayed puberty and hypogonadotrophic hypogonadism may require sex hormone therapy. Less commonly, there are cleft palate, renal agenesis, and kyphoscoliosis. From the molecular point of view, NSML is allelic with NS in the *PTPN11*, more than 90% of NSML patients carry Y259C and T468M of *PTPN11* gene, usually not found in NS patients [2,6,24,34].

3. Cardio-facio-cutaneous syndrome

Main clinical features of CFC syndrome overlap with NS; they include hypertelorism with down-slanting palpebral fissures, epicanthic folds, and eyelid ptosis, depressed nasal root, short stature, relative macrocephaly, and cardiovascular anomalies (pulmonic valve stenosis, hypertrophic cardiomyopathy, atrial septal defect). However, they manifest with relatively coarse face with high forehead and bitemporal depression, failure to gain weight and constipation, and moderate to severe developmental delay. Most distinct features are present in ectoderm, consisting of dry, hyperkeratotic, scaly skin, sparse and curly hair; absent or sparse eyebrows and eye lashes, and keratosis pilaris. The clinical diagnosis is based on typical clinical features including ectodermal abnormalities. DNA testing offers a confirmatory diagnosis in 70% of patients; two thirds of patients carry a mutation in *BRAF* gene, and the others in *MEK1* and *MEK2* genes. Prematurity is common, often with polyhydramnios. Prenatal ultrasonogram may demonstrate the fetus with macrosomia, ventriculomegaly, increased nuchal fold thickness, or evident hydrops fetalis. Specific management is focused on each clinical issue. Feeding and gastrointestinal problems are common, necessitating nasogastric tube feeding in infancy. Postnatal growth failure is found in most patients (>70%), where GH therapy is not justified at the present. Congenital heart diseases requiring surgical intervention are found in 75% of patients; pulmonic valve stenosis is most common, followed by atrial septal defect, ventricular septal defect. Hypertrophic cardiomyopathy is frequently associated in 40% of patients. The medication of β-blocker or calcium channel blockers will help in severe, progressive cases. Nutritional education is important to alleviate chronic constipation. Topical emollient and keratolytic preparations are useful for the amelioration of skin problems. Eye evaluation must be conducted periodically. Myopic, optic nerve hypotrophy, and nystagmus are common symptoms. Genitourinary problems are clinical challenges (cryptorchidism and renal/bladder abnormalities) in 20-38%, requiring genital evaluation and renal sonogram [44]. Musculoskeletal system is also examined because kyphoscoliosis and joint contractures are often associated [6,24,34,44].

4. Costello syndrome

CS is a unique from both clinical and molecular points of view. It is caused by a gain of function mutation in the oncogene, *HRAS* gene with high risk for various benign and malignant tumors, especially rhabdomyosarcoma. Clinical features are very diverse and characteristic; coarse facial features, relative macrocephaly, wide nasal bridges, deep palmar and plantar creases with hyperkeratosis, loose skin with increased pigmentation with age, premature aging and hair loss, papillomata of the face or perianal region, hypertrophic cardiomyopathy, pulmonic valve stenosis, multifocal atrial tachycardia, short stature, and intellectual disability. Skeletal abnormalities are chest deformity, cervical kyphosis, joint laxity, ulnar deviation at wrist, and hyperextensibility of small finger joints. Polyhydramnios, large birth weight for gestational age, and failure to thrive in infancy are additional features. The diagnosis is usually made on the recognition of distinctive features. DNA testing is able to offer confirmatory diagnosis. The vast majority mutation is most commonly (80-90%) present in the *HRAS* gene. Growth failure is grave. Adult height ranges 122-154 cm in females, 124-153 cm in males. The pathophysiology behind growth failure is not clearly elucidated. GH secretion is reduced in some cases. Both feeding difficulty and nutritional issues contribute to failure to thrive. It is unclear whether or not GH therapy is efficacious in CS. Even if GHD is present, GH therapy must be cautiously prescribed. Other endocrine problems are abnormal glucose homeostasis leading to hypoglycemia, and delayed onset of puberty. Hypertrophic cardiomyopathy might be aggravated. Malignancy (e.g. bladder carcinoma) has been reported with GH therapy. High prevalence of intellectual disability needs special education and early

intervention. Hypertrophic cardiomyopathy is most prevalent (60%), with other congenital heart defects such as pulmonic or mitral valve problems or polyvalves. Respiratory tract anomalies such as laryngomalacia, tracheomalacia, and bronchomalacia are common. Orthopedic issues are feet problems and kyphoscoliosis, often necessitating surgical intervention. Electroencephalography abnormalities are documented in three fourth of patients and seizure occurs in about 10% of patients with CS. Other endocrine issues are abnormal glucose homeostasis leading to hypoglycemia, and delayed puberty. Ophthalmologic examination should be done to evaluate visual acuity and the presence of strabismus or astigmatism. Tumor surveillance is critical in CS patients. Abdominal ultrasound evaluation is necessary every 3 to 6 months until age 8 to 10 years to identify rhabdomyosarcoma and abdominal neuroblastoma [43]. Urine analysis is simple test to screen bladder carcinoma. Dermatologic examination is needed to evaluate skin tags, warts, dry skin and acanthosis nigricans. Recurrent papilloma can be removed by dry ice [6,24,34,45].

Conclusion

Noonan syndrome and its related disorders (RASopathies) are not rare as a whole. Because the natural course and management of each disease is different, it is important to recognize RASopathies and differentiate them primarily by examining typical clinical feature. Gene panel testing offers confirmatory diagnosis in about 80% of patients. RASopathies require multidisciplinary team approach to provide the best medical cares for each particular clinical issue. However, further research on molecular defects of the disease and optimal care guidelines for patients with RASopathies remain to be developed.

Acknowledgements

This study was partly supported by a grant from the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (Grant No. 2011-0019674).

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