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Chapter 2

Learning Disability in RASopathies

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Additional information is available at the end of the chapter

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Abstract

Learning disabilities are relatively common conditions in pediatric population. The incidence of learning disability ranges from 1% to 17%, reflecting that learning disability may be not a single clinical entity but a wide distribution of cognitive traits in the population. As reported by the American Association on Intellectual and Developmental Disabilities (AAIDD), among the prenatal learning disability causes, chromosomal disorders, genetic syndromes, and inborn errors of metabolism must be taken into account. In this chapter, we will focus the attention on RASopathies, genetic disorders characterized by germline mutations in the RAS-MAPK pathway whose role is crucial in the regulation of the cell cycle, differentiation, growth, and cell senescence. This group of disorders includes Noonan syndrome, neurofibromatosis type 1, Costello syndrome (CS), Legius syndrome, Noonan syndrome with multiple lentigines, and cardiofaciocutaneous syndrome. Mutations in RAS-MAPK pathways lead to impairments in synaptic plasticity, necessary for normal brain function, especially for learning and memory. Variation across the RAS/MAPK pathway syndromes suggests that different gene mutations affecting this pathway can have markedly different developmental effects.

Keywords: learning disabilities, RASopathy, long-term potentiation, RAS, ERK, MAPK, neurofibromatosis, Noonan syndrome, Costello syndrome, Legius syndrome, LEOPARD, CFC

1. Introduction

Learning disabilities are relatively common pediatric conditions, and there is no universal consensus establishing what a learning disability represents [1, 2]. The American Pediatrics Association subcategorizes specific learning disorder as reading, written expression, or

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mathematics skills that are substantially lower than expected for the individual's age, measured intelligence, and age-appropriate education level or when achievement falls below a set standard definition [3]. The International Classification of Disease (ICD) identifies learning disability as a condition of arrested or incomplete development in cognitive functioning or in adaptive behavior in the developmental period [4]. It can be evaluated with the general intelligence functioning and supplemented by scales.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) is available from 2013. The DSM-V now indicates a unique new category or diagnosis of "specific learning disorder" for issues previously differentiated as: dyslexia, dyscalculia, dysgraphia, and dysorthography. The change was made because there had been no support for a continued distinction among the terms. The single definition joined the "specifiers," and for each of them, the deficit capacities are mentioned with reference to the reading, calculation, and the written language. The DSM-V state classifies the disorder in mild, moderate, and severe. In addition, the risk factors are confirmed as the disturbance of language, familiarity, co-morbidity [5].

During last decades, many studies have been conducted to understand the basis of these neurodevelopmental disorders, leading to the identification of some altered specific neural networks although the mechanisms are not fully understood [6–9].

In this context, the American Association on Intellectual and Developmental Disabilities (AAIDD) identifies prenatal, perinatal, and postnatal causes. Among the prenatal causes, chromosomal disorders, Syndrome disorders (RASopathies), and inborn errors of metabolism can be taken into account; perinatal and postnatal causes often encompass infectious and traumatic etiologies. Several cognitive deficits may be caused by a single-gene mutation and can be classified into discrete clinical conditions with specific diagnoses [10, 11]. Notwithstanding distinct clinical entities could rise from the interaction between genes and environment.

A better understanding of pathophysiological mechanisms that lead to learning disability could provide new insights in knowledge and therapy of intellectual and learning disabilities.

2. RASopathies

RASopathies are a group of genetic developmental syndromes with phenotypic overlapping features caused by germline mutation in genes that encode components or regulators of RAS/mitogen-activated protein kinase (MAPK) pathway. Approximately, these syndromes affect 1 in 1000 live births, being one of the most common group syndromes. This group includes neurofibromatosis type I (OMIM #162200), Legius syndrome (OMIM #611431), Noonan syndrome (OMIM #163950), Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome, OMIM #151100), Costello syndrome (CS) (OMIM #218040), cardiofaciocutaneous (CFC) syndrome (OMIM #115150), Noonan-like syndrome, hereditary gingival fibromatosis, and capillary malformation-arteriovenous malformation [9–14]. Several functionally related genes, such as *PTPN11* (OMIM *176876, mapped in 12q24.13 region), *SOS1* (OMIM *182530, 2q22.1), *KRAS* (OMIM *190070, 12p12.1), *BRAF* (OMIM *164757, 7q34), *RAF1* (OMIM *164760, 3p25.2), *MAP2K1* (OMIM *176872, 15q22.31), *MAP2K2* (OMIM *601263, 19p13.3), *RIT1* (OMIM

*609591, 1q22), *NRAS* (OMIM *164790, 1p13.2), *RRAS* (OMIM *165090, 19q13.33), *SOS2* (OMIM *601247, 14q21.3), *SHOC2* (OMIM *602775, 10q25.2), *CBL* (OMIM *165360, 11q23.3), *NF1* (OMIM *613113, 17q11.2), *HRAS* (OMIM *190020, 11p15.5), and *SPRED1* (OMIM *609291, 15q14), have been associated to the pathogenesis of these disorders [12–32].

Although clinical presentation can be similar, every disorder has its peculiar features (as shown in **Table 1**). They share common central nervous system dysfunction leading to learning disability-intellectual disability, cardiovascular abnormalities, dismorphic features, short stature, skeletal malformation, coetaneous lesions (tumors, spots, vascular malformation), and increasing risk of benign or malignant tumors (e.g. **Figure 1**).

Syndrome	Gene	Phenotypic features
Neurofibromatosis type I (NF1)	*NF1*	Multiple café-au-lait spots, skin-fold freckling, neurofibromas, short stature, macrocephaly, Lisch nodules, vasculopathy, aneurysm, stenosis, arteriovenous malformation, optic pathway glioma
Noonan syndrome	*PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *RRAS*	Relative macrocephaly, distinctive facial features, short stature, mild developmental/cognitive impairment, webbed neck, cryptorchidism, Pectus excavatum, myeloproliferative disorder, cardiovascular abnormalities (pulmonary stenosis, atrial septal defect and others)
Noonan syndrome with multiple lentigines (LEOPARD)	*PTPN11*, *RAF1*, *BRAF*	Multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and sensorineural deafness, hypertrophic cardiomyopathy
Legius syndrome	*SPRED1*	Multiple café-au-lait spots, skin-fold freckling, macrocephaly, learning disability, lipomas, NS-like face/characteristics
Costello syndrome	*HRAS*	Failure to thrive, distinctive facial features, feeding difficulties, short stature, curly hair, palmar keratosis, increased risk of malignant tumors (~10–15%), congenital heart defects, hypertrophic cardiomyopathy
Cardiofaciocutaneous (CFC) syndrome	*BRAF*, *MAP2K1*, *MAP2K2*, *KRAS*	Failure to thrive, distinctive facial features, skin abnormalities including nevi, lentigines and palmarplantar keratosis, curly hair, severe intellectual disability, seizure, pulmonary valvular stenosis, hypertrophic cardiomyopathy, septal defects, cardiac valve anomalies
Noonan-like syndrome	*SHOC2*, *CBL*	Macrocephaly, short stature with growth hormone deficiency, fine, sparse and easily pluckable hair, mild neurocognitive impairment, hyperpigmented skin lesions, microcephaly, cardiovascular abnormalities
Hereditary gingival fibromatosis	*SOS1*	Gingival fibromatosis
Capillary malformation-arteriovenous malformation	*RASA1*	Capillary malformation, arteriovenous malformation

Table 1. Classification of RASopathies with gene correlation and phenotypic features.

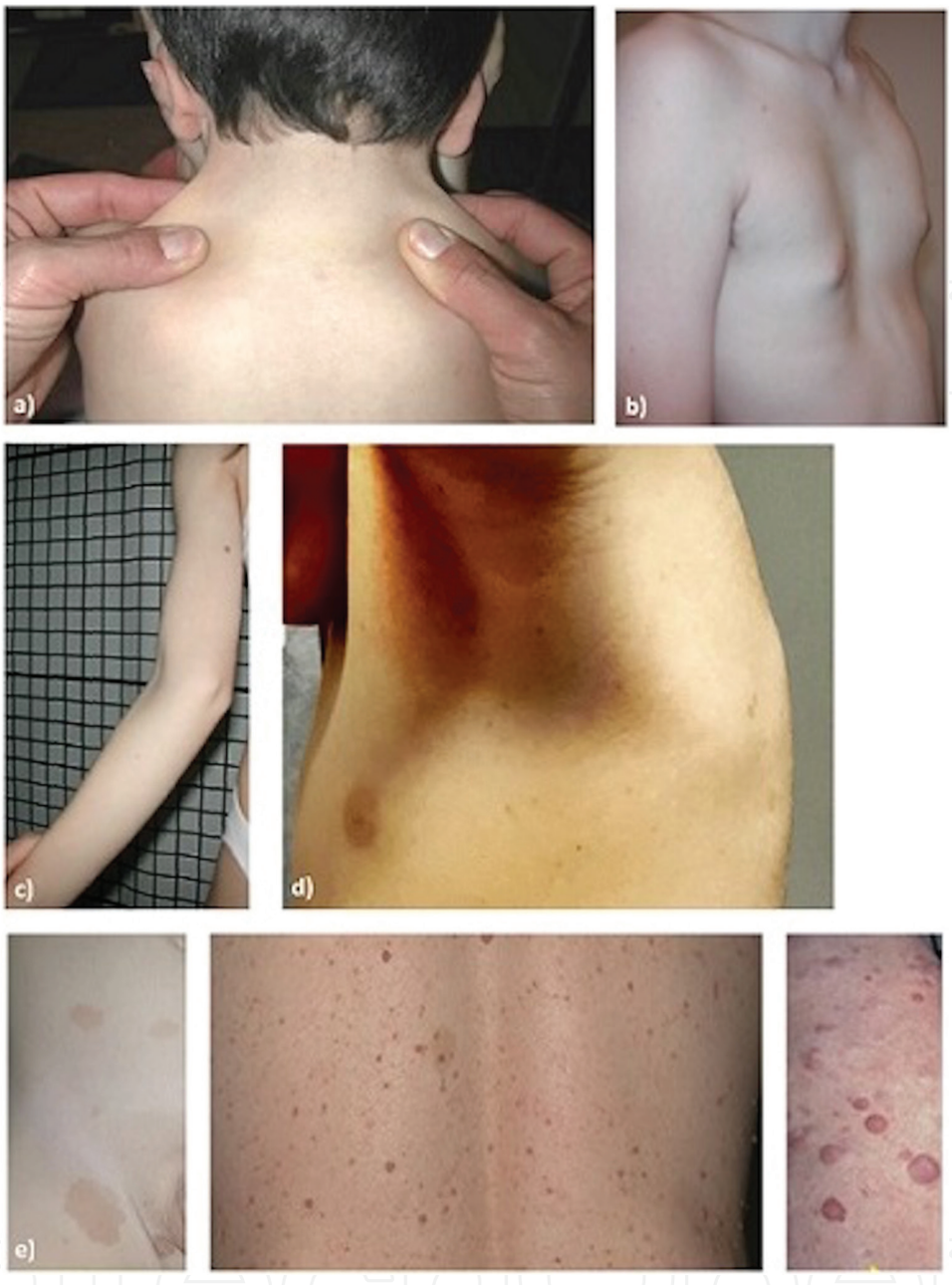


Figure 1. Typical signs of RASopathies: a) Pterigium colli (the clinical signs are wanted); b) Pectus escavatum; c) Cubitius valgus; d) Axillary freckling: a sign which initially show; e) From strains to nodules and fibroids.

Such complex phenotypes derive from mutation in the Ras/mitogen-activated protein kinase (MAPK) pathway which plays an essential role in regulation of cell cycle, differentiation, growth and cell senescence [12, 15, 16]. Focusing on these signaling alterations, there was a hyperactivation of extracellular-regulated kinase 1/2 (ERK1/2; member of the MAPK super-family) in all of these disorders. This kind of signal could be induced by mutations in positive regulators, producing gain-of-function alleles or in negative regulators (neurofibromin 1), loss-of-function alleles, of the RAS/ERK signaling pathway. Oyshi et al. ruled out this mechanism only in Noonan syndrome with multiple lentigines (LEOPARD syndrome), where mutation in the gene *PTPN11* (Y729C and T468M) encoding for protein tyrosine phosphatase SHP-2 results in a loss-of-function and a decrease in the level activity of ERK1/2 [33].

Variation across the Ras/MAPK pathway syndromes suggests that different mutant alleles of gene can have markedly various developmental effects, flowing in several syndromes. At the same time, the same allele mutant can produce different phenotypes because of the interaction with the environment, the epigenetic variation, and the action of others gene.

Recent advances in genetic analysis technologies, including whole-exome sequencing, have identified potential new genes for RASopathies [12].

2.1. The Ras/mitogen-activated protein kinase (MAPK) pathway

The Ras/mitogen-activated protein kinase (MAPK) pathway has a crucial role in regulating cell cycle and development, transducting signals from membrane receptors activated by growth factors to the cytoplasm and nucleus. This cascade is tightly regulated [16, 23, 34, 35]. For a better understanding, see **Figure 2**.

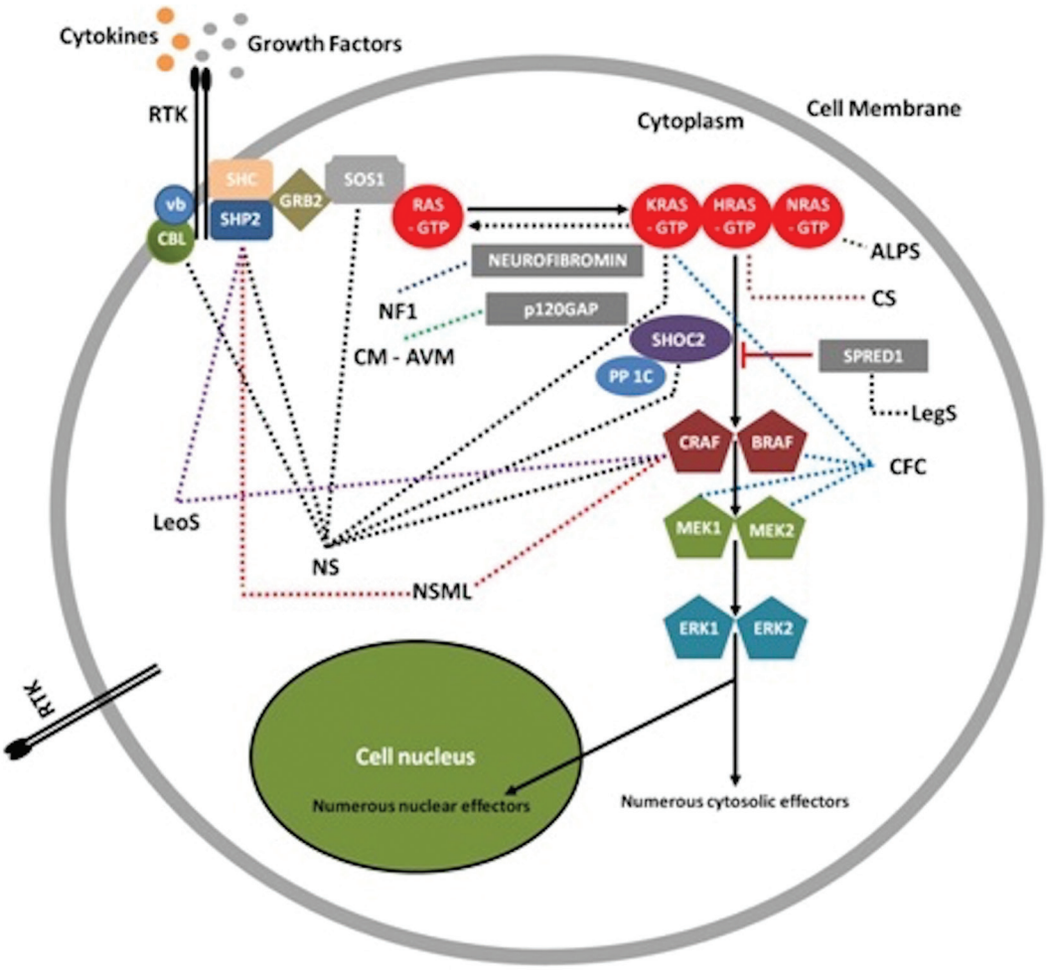


Figure 2. The Ras/MAPK signal transduction pathway of protein kinases is critically involved in cellular proliferation, differentiation, motility, apoptosis, and senescence. Mutation of genes encoding components or regulators of the Ras/MAPK pathway (indicated by *dashed lines*) cause medical genetics syndromes named RASopathies. These disorders include neurofibromatosis type 1 (NF1). Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), capillary malformation-arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC), Leopard syndrome (LeoS), Legius syndrome (Legs), and ALPS (Autoimmune lymphoproliferative syndrome). RTK is the Receptor Tyrosine Kinase.

RAS genes, including *HRAS*, *NRAS* and *KRAS*, encode for small guanosine nucleotide-bound GTPases which are positively matched with different kind of receptors, inducing a transformation in an active GTP-bound form and an inactive Guanosine Diphosphate (GDP) bound form. Activation of RAS through receptor tyrosine kinases (RTKs) occurs thanks to recruitment of the adaptor protein growth factor receptor bound protein 2 (GRB2) and son of sevenless (SOS) which increase the level of active GTP-bound Ras [36–38].

After RAS activation, the signaling cascade is turned on with the activation of RAF (ARAF, BRAF, and/or CRAF), which activates, phosphorylating the MAPK kinases, MEK1 and/or MEK2 and, in turn, ERK1 and ERK2. ERK1 and ERK2 are the effectors of the cascade and control a large number of nuclear and cytosolic molecules owning as target cell cycle progression, cellular differentiation, and cellular growth.

Among the negative regulators of this cascade, neurofibromin 1 (*NF1*) is a GTPase-activating protein that is a negative regulator of RAS (RAS-GAP) and the Sprouty-related protein with an EVH-1 domain *SPRED1* [16, 35–39].

2.2. Basis of learning disability in RASopathies

Since 1997 the central role of RAS-ERK signaling has been identified in long-term potentiation (LTP), in long-term depression (LTD), in synaptic plasticity, in memory formation and learning during the development, including spatial learning and fear conditioning, therefore not only in cell growth, proliferation, migration, and survival [40–45].

So far, many studies have neglected the psychological and psychiatric profile of RASopathies, but new contributions of literature are proving that it is just the tip of the iceberg [46].

In central nervous system (CNS), synaptic plasticity is a prerequisite for learning and memory. First studies in animal models of RASopathies have provided interesting findings on the biological basis of these disabilities, examining the RAS/ERK functions that unfortunately are not completely understood.

The long-term potentiation (LTP) and the long-term depression (LTD) are prerequisite for synaptic plasticity in key areas as hippocampus, amygdala, insular cortex, and prefrontal cortex. N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) are closely related to these mechanisms. After high-frequency release of glutamate and activation of AMPA receptors, NMDA magnesium block is removed resulting in a more sustained excitatory. NMDA receptors lead to intracellular calcium influx and AMPA phosphorylation of AMPA receptors and movement to the cell surface bringing to an increasing answer to glutamate release. Furthermore, calcium influx can promote the transcription of crucial gene for the LTP trough cAMP-dependent signaling cascade involving PKA, mitogen-activated protein kinases (MAPK), and the transcription factor cAMP-responsive element binding protein (CREB). On the other hand, low-frequency stimulation induces LTD through a weak calcium influx inducing dephosphorylation and endocytosis of AMPA receptors [47].

Increased activity of RAS-ERK pathway in keys areas of the brain (as hippocampus, parahippocampus, amygdale, prefrontal) can lead, on the one hand, to an increased activity of

GABAergic interneurons, and on the other hand, to an impaired signaling in glutamatergic synapses and consequently to dysruption of synaptic plasticity through LTP or LTD. In GABAergic synapses, RAS-MAPK pathway regulates the phosphorylation of synapsin I in presynaptic neurons, where it is critically involved in maintaining the vesicle reserve pool and regulating the rate of neurotransmitter vesicle release. Neurofibromin 1 negatively regulates Ras/MAPK signaling pre-synaptically in hippocampal-GABAergic neuron; as a matter of fact, mutations in the gene of NF1 induce an enhanced GABA release. As for glutamatergic synapses, RAS-ERK pathway is activated by tyrosine kinase receptors (TRK) or calcium influx activated through N-methyl-D-aspartate (NMDA) receptors or voltage-gated calcium channels, playing a key role in the transcription of many crucial genes for long-term potentiation. Modulation of glutamatergic synapses is necessary to modify AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) receptor expression on cells surface, enhancing the basal excitatory synaptic transmission, blocking further potentiation of synaptic strength. Consistently, an hyper-activation of RAS-ERK signaling, for example, could be also due to a SHP2 mutation, enhancing the basal excitatory synaptic transmission, facilitating the synaptic trafficking of AMPA receptors to synapses with the subsequent events before described (for more information see: [45, 47–53]).

Recently, the importance of RAS-MAPK pathway has been also revealed in differentiation of neuron progenitor cells. Disruption of this cascade can result in an imbalance between neurogenesis and glycogenesis [35].

Several neurophysiological studies have been conducted in patients with RASopathies by using transcranial magnetic stimulation (TMS), a noninvasive and safe way to investigate neuronal plasticity. Several experimental paradigms applying the so-called paired associative stimulation (PAS) have demonstrated that patients with neurofibromatosis type I and Noonan syndrome have reduced LTP-like synaptic plasticity depending on an increased intracortical inhibition. On the contrary, TMS studies in Costello syndrome (CS) patients have shown enhanced LTP-like synaptic plasticity related to reduced inhibition [51, 54–56].

In summary, there are strong evidences that the deregulation of activity of RAS-MAPK signaling can lead to LTP impairment and altered neuronal plasticity resulting in learning and memory impairment.

3. Focus on learning disability in every RASopathy

3.1. Neurofibromatosis type 1

Neurofibromatosis type I was the first RASopathies identified, it is a genetic disorder caused by mutations in the neurofibromin 1 gene (*NF1*) at locus 17q11.2, resulting in loss-of-function of its protein product. Neurofibromatosis type I has an autosomal dominant inheritance, as homozygous mutations appear to be lethal and has an incidence of approximately 1 in 2600–3000 individuals [39, 57, 58].

This syndrome is characterized by the presence of café-au-lait maculae (spots), (axillary and inguinal) intertriginous freckling, neurofibromas and plexiform neurofibromas, iris Lisch

nodules, osseous dysplasia, optic pathway glioma, and/or a first-degree relative with NF1. Up to 65% of NF1 patients show cognitive impairments which frequently involve executive and higher order cognitive domain [14, 16, 39, 48, 49, 57–59].

Neurofibromin acts as a RAS-GAP (GTPase activating protein) and negatively regulates Ras signaling, also working as an activator of adenylate cyclase. Its mutation brings to a hyperactivation of the RAS-MAPK signaling cascade and to an increased GABA-mediated inhibition of interneurons, significantly reducing long-term potentiation in hippocampus and amygdala. The role of NF1 is crucial in maintaining the balance between RAS- and cAMP-dependent signaling [38, 47, 48, 56–58].

Reading/vocabulary, visuospatial functions, motor coordination, planning, and organizational skills are often impaired. High co-morbidity with attention deficit hyperactivity disorder (ADHD) is explained by frequent impairment of working memory, cognitive flexibility, and inhibitory control. Patients with NF1 show both *nonverbal* (poor performance in tests of visuospatial functioning and spatial learning, impairments in the ability to perceive social cues, poor organizational skills, and increased impulsiveness) and *verbal-type learning disability* (expressive and receptive language, vocabulary, visual naming, and phonologic awareness). A single mutation can give rise to a complex spectrum of learning disabilities [39, 60, 61].

Emerging insights from the pathophysiology of this syndrome have provided new potential targets for learning disability therapy. A randomized, double-blind, placebo-controlled study evaluated the influence of lovastatin on impaired synaptic plasticity in patients with NF1. By decreasing the ERK basal activation, lovastatin reduces RAS-pathway hyperactivity with a significant improvement in verbal and nonverbal memory, visual attention, and efficiency [15, 54, 56, 58, 61].

3.2. Noonan syndrome

Noonan syndrome is an autosomal dominant genetic disorder with a prevalence approximately of 1 every 1000–2500 live births, caused by activating germline mutations in the *PTPN111* gene in 50% of affected individuals, but other cases have shown to be caused by gain-of-function mutations in *KRAS* (fewer than 50%), *SOS1* (approximately in 13%), *RAF1*, and *RIT1* (in 5%). Other genes have been reported in literature which is associated with Noonan syndrome, for example, NRAS, BRAF, and MAP2K1 [14, 55, 62–66].

Mutation in *PTPN11* induces alteration of function in the protein SHP2 (nonreceptor tyrosine phosphatase) which loses its ability to switch from the active to the inactive protein conformation, causing an increased signaling in Ras/MAPK cascade. Its role is crucial in determining neuronal cell fate and regulating the generation of oligodendrocytes. Hyperactivity of Ras/MAPK cascade increases delivery of AMPA receptors to the synapses, enhancing the basal excitatory synaptic transmission. Mutations in SOS1 induce loss-of-function in auto-inhibition and gain-of-function in the protein product RAS-GEF protein which acts as a stimulator of the conversion of RAS from the inactive to the active form. Mutations of KRAS and BRAF also determine RAS/MAPK up-regulation [35, 62–66].

This syndrome is typically characterized by facial anomalies, short stature, family history, chest carinatum/excavatum, congenital heart defects (pulmonary valve stenosis, septal defects and hypertrophic cardiomyopathy, atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot), lymphatic dysplasia, cryptorchidism, varied coagulation defects, and learning disabilities [64, 65].

A wide variability of cognitive complaints has been recognized ranging from absent or mild learning problems to severe intellectual disabilities and depends on type of mutation. Patients with *SOS1* mutations performed significantly higher on both verbal and nonverbal cognitive tests than individuals with PTPN11 and other kinds of mutations. Several studies have demonstrated that these patients have a greater risk to have impaired performance in verbal free recall task than in visual and spatial recognition memory tasks. Furthermore, Pierpont et al. showed that children with Noonan syndrome have different performance on verbal memory tasks, on visual memory, or working memory. Better performances have been obtained in immediate verbal memory than in delayed free recall tasks; a more pronounced hippocampal and prefrontal cortex dysfunction may probably reflect RAS-MAPK aberration in memory formation and consolidation [62, 63, 65–67].

Likewise, NF1 promising studies on the therapeutic effect of lovastatin in mice with mutation in PTPN11 are currently underway thanks to its action in decreasing basal Erk activation and seem to represent a therapeutic strategy for learning deficits Noonan syndrome [68].

3.3. Legius syndrome (NF1 like)

Legius syndrome is an autosomal dominant genetic disorder caused by germline mutations in the SPRED1 which induce loss-of-function in the product protein. It is typically characterized by multiple café au lait macules without neurofibromas or other tumors, intertriginous freckling, lipomas, macrocephaly, and learning disabilities/ADHD/developmental delays [57, 69].

SPRED1 is a negative regulator of the Ras/MAPK pathway, being a substrate of SHP2, and its mutation leads to a hyperactivation of this cascade, and in animal models, it also has been seen that mice have some deficits in hippocampus-dependent spatial learning and in several phases of visual discrimination learning [35, 70].

3.4. LEOPARD syndrome

LEOPARD syndrome (Noonan syndrome with multiple lentigines) is an autosomal dominant genetic disorder, caused by mutation in *PTPN11* (p.Y279C and p.T468P) and *RAF1*. Phenotypically, they have the same features of Noonan syndrome patient but with multiple lentigines, electrocardiogram abnormalities, pulmonary valve stenosis, abnormal genitalia, growth retardation, and ocular hypertelorism [14, 16, 17, 35, 71].

Several studies conducted in vitro have demonstrated that mutation in PTPN11 leads to a reduced catalytic activity in SHP2 causing a loss-of-function, despite studies conducted in animal models have demonstrated that this residual activity is sufficient to generate a gain-of-function like phenotype in the cascade that leads to a hyperactivation of Ras/MAPK pathway [14, 16, 35, 71].

In this syndrome, learning disability are reported in the 30% of cases [54] and are more evident in verbal recall memory performance but relative sparing of visual and spatial recognition memory [16, 66, 71].

3.5. Costello syndrome

Costello syndrome is one of the rare syndromes of the group of RASopathies. It is caused by heterozygous activating germline mutations in *HRAS*. Typically, it is a missense mutation that induced the reduction of the intrinsic GTPase activity of RAS, which remains in the active form facilitating the synaptic trafficking of AMPA receptors. Besides, it has been seen that its action occurs in the spine dendritic structures too, which presents an increased density [14, 16, 35, 72].

This syndrome is phenotypically characterized by failure to thrive; short stature; developmental delay or intellectual disability; coarse facial features, curly, or sparse fine hair; loose, soft skin with deep palmar and plantar creases; papillomatosis of the face and perianal region; diffuse hypotonia and joint laxity; cardiac involvement (cardiac hypertrophy, valvar pulmonic stenosis, arrhythmia); relative or absolute macrocephaly Chiari I malformation with associated anomalies including hydrocephalus or syringomyelia. Moreover, they present an increased risk, approximately 15%, to malignant tumors [14, 16, 72].

Particularly, in these patients, it has been observed that verbal learning and memory are impaired but are better than the nonverbal cognitive abilities, while the visual associative memory is performed in the mildly disabled, but the related data are not completely clear [35, 73].

3.6. CFC syndrome

Cardiofaciocutaneous (CFC) syndrome is a very rare RASopathy. It is caused by heterozygous activating mutations in *BRAF* (~75%), *MAP2K1,* and *MAP2K2* (~25%), *KRAS* (<2%) that cause a deregulation of the RAS-MAPKinase cascade in a positive way. It is inherited in an autosomal dominant manner [14, 16, 74, 75].

CFC is characterized by craniofacial dysmorphology, congenital heart disease (pulmonic stenosis and other valve dysplasias, septal defects, hypertrophic cardiomyopathy, and rhythm disturbances), dermatologic abnormalities (xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema ophryogenes, eczema, pigmented moles, hemangiomas, and palmoplantar hyperkeratosis), growth retardation, and intellectual and learning disability [14, 16, 74, 75].

Assessing the learning ability, CFC patients present significant delay in adaptive skills, impaired spatial learning, and hippocampal long-term potentiation. It has been evidenced disability in verbal skills, especially the communication abilities were more impaired than the comprehension and in spatial learning [35, 75].

Mutations in MAP2K1, which are frequently associated with neurological complications and intellectual disability, can be associated with a milder clinical and neurocognitive profile more typical of individuals with Noonan syndrome. Variability of expression may arise from a complex interplay between RAS/MAPK pathway genotype, epigenetics, medical and obstetric factors, and environmental influences [76].

4. Conclusion

Children with RASopathies show commonly learning disabilities, such as impaired reading/vocabulary, visuospatial functions, motor coordination, planning, and organizational skills. Variability of expression may arise from a complex interplay between RAS/MAPK pathway genotype, epigenetics, medical and obstetric factors, and environmental influences. Emerging insights from the pathophysiology of these different genetic syndromes may facilitate the development of mechanism-based individualized treatment and may provide new potential targets for learning disability therapy in patients with RASopathies.

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