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REVIEW

A Review of Psychological, Social, and Behavioral Functions in the RASopathies

Karin S. Walsh[1,2] · A. del Castillo[1] · T. Kennedy[1] · A. I. Karim[3] · C. Semerjian[4,5]

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Abstract

Aims The aim of this review is to summarize research that has focused on psychological, social, and behavioral functions and outcomes across the RASopathies.

Methods Empirical studies published in peer-reviewed, scientific journals over the past 32 years were identified through searches in PubMed, PsychInfo, and Google Scholar through July 23, 2019. Searches included the names of each of the RASopathies individually with one psychological search term. The authors reviewed all titles and abstracts for relevancy. Full-text articles of abstracts deemed relevant were then fully reviewed by the authors. Case studies were excluded.

Results A total of 718 publications were identified through the initial search. Fifty-nine of these publications (8%) were deemed relevant after initial screening and fully reviewed by the authors.

Interpretation There is a paucity of research on the psychological, social, and behavioral manifestations in children and adults with RASopathies, although an increase in research has emerged over the past 7 years. Dysfunction in these areas can negatively impact the individuals functioning with regard to relationships, education, employment, and quality of life. This review highlights the need for prospective research in these areas of functioning, with the ultimate goal of developing interventions and therapies targeting psychosocial impairments.

Keywords RASopathies · RASopathy · Psychological · Social · Behavioral

Introduction

The RASopathies comprise a group of genetic disorders defined by germline mutations in genes that affect the encoding of regulators and transducers of the RAS/mitogen-activated protein kinase (MAPK) signaling pathway (Rauen 2013). The Ras/MAPK pathway affects the regulation of cell growth and differentiation and plays a fundamental role in development (Tidyman and Rauen 2009). There are multiple syndromes arising from mutations in the Ras/MAPK pathway including cardiofaciocutaneous syndrome (CFCS), Costello syndrome (CS), neurofibromatosis type 1 (NF1), Noonan syndrome (NS), Noonan syndrome with multiple lentigines (previously LEOPARD syndrome), Noonan syndrome-like disorder with loose anagen hair (NSLAH), and Legius syndrome. Although these syndromes result from different mutations along the Ras/MAPK pathway, they share some overlapping clinical features such as craniofacial dysmorphology, cardiac defects, cutaneous and musculoskeletal abnormalities, developmental delays, and neurocognitive deficits (Rauen 2013; Tidyman and Rauen 2009; Magoulas 2013). Noonan syndrome is the result of germline mutations on one of several genes of the Ras/MAPK signaling pathway including *BRAF*, *KRAS*, *MEK1*, *NRAS*, *PTPN11*, *RAF1*, *RIT1*, *SOS1*, and *SOS2*. This syndrome is the most common of the RASopathies, occurring in approximately 1:1000 to 1:2500 individuals (Mendez and Opitz 1985). Cardiofaciocutaneous syndrome may also result from a mutation on genes *BRAF*, *KRAS*, and *MEK1*; however, a mutation on *MEK2* will also

✉ Karin S. Walsh
kwalsh@childrensnational.org

[1] Division of Neuropsychology, Children's National Hospital, 111 Michigan Avenue NW, Washington, DC 20010, USA

[2] Departments of Pediatrics and Psychiatry, George Washington University Medical Center, Washington, DC, USA

[3] Premier Psychological Services, Houston, TX, USA

[4] Department of Neuropsychology, Kennedy Krieger Institute, Baltimore, MD, USA

[5] Johns Hopkins University School of Medicine, Baltimore, MD, USA

result in the syndrome. In contrast, CS, NF1, LS, NSLAH, and Legius syndrome are single-gene disorders involving *HRAS*, *NF1*, *PTPN11*, *SHOC2*, and *SPRED1*, respectively.

Disruptions in typical development across varying domains have been well established in many of the RASopathies, and cognitive deficits are some of the most well-known morbidities in many of these syndromes (Rauen 2013; Axelrad et al. 2011; North et al. 2002; van der Burgt et al. 1999). In a murine model, mutations in the RAS signaling pathway, which plays a vital role in synaptic plasticity, learning, and memory, have been associated with cognitive deficits (Costa et al. 2002; Krab et al. 2008). Studies examining the cognitive deficits across the RASopathies have provided insight on the possibility of genotype-phenotype correlations between the mutated gene and the severity of cognitive difficulties (Alfieri et al. 2014).

Although the RAS/MAPK signaling pathway has been proposed as a key determinant of cognitive and behavioral impairments in the RASopathies (Krab et al. 2008; Packer 2012), research dedicated to understanding the neuropsychiatric profiles and potential phenotypes within and across these syndromes is far less prominent. The research that has focused on neuropsychiatric function and dysfunction in these syndromes has generally revealed that patients with RASopathies experience more behavioral, psychological, and social difficulties than the general population (Alfieri et al. 2014; Pierpont and Wolford 2016). Understanding the full scope of neuropsychiatric disorders and psychosocial deficits is crucial to implementing appropriate clinical care options to ensure positive patient outcomes and the patient's overall well-being, particularly as cognitive and emotional deficits are commonly co-occurring (Jarrett and Ollendick 2008; Garg et al. 2013a).

The purpose of this review is to present a comprehensive description of the existing literature on psychosocial, emotional, and behavioral functioning in the RASopathies and to highlight the importance of psychological function and dysfunction in these syndromes with the goal of increasing awareness and encouraging the development of collaborative research into the manifestations and mechanisms of these problems within and across the RASopathies.

Methods

This comprehensive review includes all empirical studies published in peer-reviewed, scientific journals over the past 32 years, since the first published research on neuropsychiatric, psychological, and emotional functioning in individuals with any of the RASopathies. Articles were identified through searches within electronic literature databases PubMed, PsychInfo, and Google Scholar. The databases were last searched on July 23, 2019. Searches included the names of each of the RASopathies (cardiofaciocutaneous syndrome, Costello syndrome, neurofibromatosis type 1, Noonan syndrome, LEOPARD syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome-like disorder with loose anagen hair, and Legius syndrome). Searches were conducted with one syndrome at a time combined with one psychological search term including the following: anxiety, depression, internalizing, externalizing, behavior, social, social skills, autism, and autism spectrum disorder (ASD). Studies were eligible for inclusion if they were (a) published in a peer-reviewed scientific journal; (b) included psychological, behavioral, or social outcomes in one of the RASopathies; (c) were written in or translated into English; and (d) were not case studies.

The authors reviewed all titles and abstracts of the articles retrieved through the searches for relevancy and exclusion criteria. Full-text articles of selected articles were then obtained and fully reviewed by the authors. Additionally, reference sections of relevant full-text articles were scanned to identify articles not found in original literature searches.

Results

A total of 718 abstracts were obtained based on the initial searches as described above. Of those, 59 were retained as relevant and meeting inclusion criteria. Research on neurofibromatosis type 1 (NF1) was the most prominent, followed by Noonan syndrome (NS), Costello syndrome (CS), cardiofaciocutaneous syndrome (CFCS), and Noonan syndrome with multiple lentigines (NSML). Very little research has been published in this area on Legius syndrome (LS) and Noonan syndrome-like disorder with loose anagen hair (NSLAH). The initial NF1 search yielded 544; 504 were deemed not relevant for the purposes of this review (see the "Methods" section above), and 40 were included. Of the 128 articles found in the NS search, 13 were included in this paper. Ten of the 56 articles found in the CS search were included as well. Half of the 14 articles found in the CFCS search were deemed not relevant. Only two articles were found in each the NSLAH and LS search; one was included for LS, while none were deemed relevant for NSLAH. Of the 718 abstracts reviewed, 30 discussed multiple RASopathies; eight of these articles were included in this paper. Brief summaries of all included and excluded articles are presented in Tables 1 and 2.

Cardiofaciocutaneous Syndrome

Although there have been relatively few studies that have reported on the emotional, behavioral, and social functioning of individuals with CFCS, there is a general consensus in the existing literature that individuals with CFCS experience

Table 1 Results of publication search and review

	Unique Articles (not repeated across more than one RASopathy)							
	Cardiofaciocutaneous syndrome ($n = 5$)	Costello syndrome ($n = 45$)	Noonan syndrome ($n = 100$)	Neurofibromatosis type 1 ($n = 526$)	Noonan syndrome with multiple lentigines ($n = 10$)	Noonan syndrome-like disorder with loose anagen hair ($n = 2$)	Legius syndrome ($n = 0$)	Found in multiple RASopathies (duplicates; $n = 30$)
Total excluded*	$n = 3$	$n = 39$	$n = 93$	$n = 490$	$n = 10$	$n = 2$	$n = 0$	$n = 22$
Total included	$n = 2$	$n = 6$	$n = 7$	$n = 36$	$n = 0$	$n = 0$	$n = 0$	$n = 8$

* See Table 2

difficulties in all of these areas. In recent studies examining social difficulties in multiple RASopathies, it was demonstrated that individuals with CFCS are more likely to exhibit social difficulties and autistic traits than any of the other RASopathies (Alfieri et al. 2014; Adviento et al. 2014).

A higher proportion of individuals with CFCS scored above the threshold suggestive of autism on the Social Communication Questionnaire (SCQ; 54%) and the Modified Checklist for Toddlers/SCQ combined (M-CHAT; 64%) than other RASopathies (including NF1, Noonan syndrome, Costello syndrome, and NSML/LEOPARD syndrome) or non-affected sibling controls (Alfieri et al. 2014; Adviento et al. 2014). In those individuals with CFCS that scored above the threshold for autistic traits, 71% met criteria for ASD based on DSM-IV-TR diagnostic criteria (Adviento et al. 2014). Individuals with CFCS also exhibited significantly higher levels of social impairment on the Child's Behavior Checklist (CBCL) and the Social Responsiveness Scale (SRS) compared with the other RASopathies, but lower levels of impairment on the SRS than individuals with idiopathic ASD (Alfieri et al. 2014; Adviento et al. 2014).

Beyond ASD symptom screening measures, more recent research has taken a more comprehensive diagnostic approach, using the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) in children with CFCS, which are considered the "gold standard" in diagnostic evaluations for autism. Garg and colleagues (Garg et al. 2017) administered the ADOS and the ADI-R to a cohort of nine children with CFCS and their parents, and eight (89%) of those children met criteria for ASD.

Although research indicates that a higher percentage of individuals with CFCS experience social deficits than other RASopathies, there is limited research comparing the emotional and behavioral functioning of CFCS and the other syndromes. Problems in these areas can be described broadly as internalizing or externalizing. Internalizing symptoms are those that do not have obvious outward signs or specifically impact the person's environment (e.g., symptoms of withdrawal, anxiety, depression). In contrast, externalizing symptoms are those that are shown outwardly and can have an impact on the people and things in the person's environment (e.g., oppositional, aggressive, and rule-breaking behaviors). In individuals with CFCS, 29–50% have been described as presenting with internalizing symptoms in the borderline to clinically elevated ranges relative to the normative sample

Table 2 Results of publication search and review, excluded manuscripts by disease and reason

	Unavailable in English	Case study/not a study published in a peer-reviewed journal	Preclinical/ animal study	Author name is RASopathy name (e.g., author Noonan)	Unrelated – NON-RAS (not related to any RASopathy)	Unrelated – RAS (related to a RASopathy, but not related to our topic)
Total Excluded	$n = 54$	$n = 228$	$n = 42$	$n = 33$	$n = 80$	$n = 222$
CFCS	$n = 0$	$n = 1$	$n = 0$	$n = 0$	$n = 1$	$n = 1$
CS	$n = 0$	$n = 5$	$n = 1$	$n = 27$	$n = 3$	$n = 3$
NS	$n = 6$	$n = 34$	$n = 3$	$n = 6$	$n = 24$	$n = 20$
NF1	$n = 47$	$n = 168$	$n = 35$	$n = 0$	$n = 48$	$n = 192$
NSML/Leopard	$n = 0$	$n = 7$	$n = 1$	$n = 0$	$n = 1$	$n = 1$
NSLAH	$n = 0$	$n = 0$	$n = 0$	$n = 0$	$n = 2$	$n = 0$
Legius	$n = 0$	$n = 0$	$n = 0$	$n = 0$	$n = 0$	$n = 0$
Repeats	$n = 1$	$n = 13$	$n = 2$	$n = 0$	$n = 1$	$n = 5$

on the CBCL. Pierpont and Wolford (2016) indicated that withdrawn behaviors were reported more frequently by parents than anxious behaviors in their children with CFCS. Rates of internalizing problems have been reported to be higher than rates of externalizing problems in this group by some (Alfieri et al. 2014; Pierpont and Wolford 2016). However, Garg et al. (2017) reported higher levels of internalizing (78%) and externalizing (89%) behaviors based on a behavioral observation form completed by the researchers (Test Observation Form; TOF). The TOF defines internalizing behaviors by the empirically based withdrawn/depressed and thought problems scales while oppositional behaviors and attention problems scale items make up externalizing behaviors. The elevated externalizing scale in this study may be driven by the inclusion of attention problems in that scale, given the high prevalence of attention deficits in this population (Garg et al. 2017). Attention problems are not included in the CBCL externalizing scale.

There are significant correlations between internalizing behaviors and several modalities of sensory processing, including tactile, visual, or auditory sensitivities, poor auditory filtering, and low energy/stamina in CFCS (Pierpont and Wolford 2016). Greater sensory processing difficulties in these areas are associated with more internalizing behaviors (e.g., anxious, withdrawn). Externalizing behaviors were most closely correlated with the sensation-seeking aspect of sensory processing, and social problems were associated with over- and under-responsiveness to sensory stimuli (Pierpont and Wolford 2016).

The risk for internalizing and externalizing problems in children with CFCS appears to increase with the presence of significant pre- or perinatal complications such as preterm birth and neonatal complications, such that children with such histories demonstrate greater behavioral and emotional problems (Pierpont and Wolford 2016). Quality of life (QoL) may be negatively affected by the level of disability in children with CFCS as well (Johnson et al. 2014). Children with CFCS experienced significantly poorer general quality of life, social functioning, and general happiness as well as greater pain/discomfort than the general population based on child and parent report and performance-based assessment of daily functional abilities (Johnson et al. 2014). However, adolescents with CFCS (ages 11–18) were reported to be significantly happier and have better general QoL than younger children with CFCS (ages 2–10) suggesting that functioning in these areas may improve with age (Johnson et al. 2014).

Costello Syndrome

Costello syndrome is characterized by global developmental delays including feeding problems and growth delays, language, and motor delays, as well as orthopedic impairment, cardiac, and neurological complications (Gripp et al. 2010; Gripp and Lin 2012; Schwartz et al. 2017). An age effect in social-emotional functioning is apparent in CS such that younger children demonstrate greater social-emotional difficulties that appear to become less prevalent as the children age, similar to that demonstrated in CFCS and general quality of life (Schwartz et al. 2017; Galéra et al. 2006; Kawame et al. 2003). There is some indication that social functioning is a relative strength in older children with CS relative to their adaptive and intellectual functioning (Axelrad et al. 2011; Kawame et al. 2003; Axelrad et al. 2004; Axelrad et al. 2007).

In a study conducted by Schwartz et al. (2017), age was significantly associated with exceeding clinical cutoffs for ASD on parent symptom screening report forms (SCQ and M-CHAT). No child in the school-aged group (5–18 years) exceeded the clinical cutoff, whereas 72% of the children in the preschool group (≤ 4 years) met the ASD cutoff on the age appropriate measure (Schwartz et al. 2017). There was a significant correlation between the presence of a gastrostomy tube and meeting symptom criteria for ASD in the preschool aged group (all of the children in the preschool group who met the ASD criteria had a gastrostomy tube). Developmentally, not yet being able to walk, eat solid foods, and not being toilet trained were all associated with meeting ASD criteria in this group. The authors note that in medically complex children, such as these, screening tools can overestimate the prevalence of ASD symptoms, resulting in a high false positive rate (Schwartz et al. 2017; Johnson and Marlow 2009).

These findings support earlier research examining social and emotional behaviors in children with CS. Kawame et al. (2003) retrospectively analyzed medical records of children with CS, and found that in infancy, all of the patients exhibited characteristics of irritability, hypersensitivity to sounds and tactile stimuli, sleep disturbances, and excessive shyness with strangers. During infancy, these children also experienced severe feeding difficulties, and as the feeding problems resolved between two and 4 years of age, the symptoms of irritability also decreased, although sensory hypersensitivity remained until the children were older (Kawame et al. 2003). When these children were four to 5 years of age, they were reported to be generally happy and social per clinician report (Kawame et al. 2003). Although no standardized psychometric tool was used in the Kawame et al. (2003) study, these findings were supported by a study conducted by Galéra et al. (2006). They indicated that children with CS under age four demonstrated significantly greater symptoms of internalizing problems (specifically anxiety and somatic complaints) than typically developing children in that age range, which the authors attributed to feeding problems and hospitalizations (Galéra et al. 2006). When comparing children with CS ages four and older, there was no significant difference in internalizing problems compared with healthy controls (Galéra et al. 2006).

In contrast, a study by Axelrad et al. (2007) suggested that their cohorts of children with CS did not "age out" of emotional and behavioral difficulties. However, methodological issues associated with inconsistent measurement may have affected these findings. At the first time-point, 24% of children ages 2–17 (M = 10 years) exhibited at-risk or clinically significant internalizing symptoms on the CBCL, while only 6% were displaying elevations in externalizing symptoms (Axelrad et al. 2004). In a separate cohort, children ages 4–19 years (M = 10 years) showed a high rate of elevated internalizing symptoms (73%), while only 27% were rated as having elevated externalizing symptoms on the Vineland-II Adaptive Behavior Scales Rating Form Maladaptive Behavior Index (Axelrad et al. 2007).

Gender differences have also been documented in children with CS with regard to social-emotional and behavioral functioning (Axelrad et al. 2011; Axelrad et al. 2009). Using the Vineland-II, caregivers reported significantly more emotional and behavioral concerns in males ($n = 9$), including internalizing problems, externalizing problems, and maladaptive behaviors than females ($n = 9$) between the ages of four and 24 (Axelrad et al. 2009). Using a screener for child anxiety-related disorders, separation anxiety was reported in 39% of the sample, with a greater male prevalence (males 50%, females 33%; 5). This exceeds the prevalence of separation anxiety in the general pediatric population, which ranges from 1.6 to 4% (Kessler et al. 2012; Pine and Klein 2008). The gender effect may be maintained into adulthood as caregiver report of QoL in adults with CS indicates significantly higher QoL in females compared with males (Hopkins et al. 2010).

Noonan Syndrome

In addition to research on cognitive deficits within the NS population, there has been a growing literature on the social difficulties experienced by this group of children. Problems with social skills have been identified as one of the most commonly reported challenges in NS (Alfieri et al. 2014; Wood et al. 1995; Pierpont et al. 2015). To better understand the social functioning of individuals with NS, research has begun to explore social function and ASD symptomatology in children with NS compared with unaffected siblings. Based on this research, children with NS were reported to have significantly more ASD symptoms and social problems than their unaffected siblings (Adviento et al. 2014; Pierpont et al. 2015; Pierpont et al. 2018). Elevated ASD symptomatology and social dysfunction has been reported ranging from 15 to 21% in children with NS, which was consistent with ratings reported in NF1, but higher than unaffected siblings (Adviento et al. 2014; Pierpont et al. 2018). Pragmatic language deficits and elevated ADHD symptoms were predictive of greater social deficits for all groups (Pierpont et al. 2018). Using gold standard ASD diagnostic approaches (e.g., ADOS and ADI-R), Garg and colleagues (Garg et al. 2017) assessed 40 children with NS and reported that 30% met criteria for ASD, while an additional 30% showed partial features of ASD. These symptoms were not explained by intellectual function (Garg et al. 2017). There are similarities in social dysfunction between children with NS and children with NF1, and the presence of ADHD and social pragmatic deficits predict social skill deficits in both groups (Pierpont et al. 2018). Although much of the research suggests social difficulties within this population, a study examining a small sample of children with NS ($n = 22$) found no significant differences in social skills on the Vineland-II compared with children in the normative population (Pierpont et al. 2009). Similarly, another study examining a small sample of children with NS ($n = 19$) and their siblings ($n = 10$) did not find significant differences in reported social problems on the CBCL between the two groups (Wood et al. 1995).

Research has suggested specific genotype-phenotype patterns in NS with regard to social dysfunction. Alfieri and colleagues (Alfieri et al. 2014) demonstrated that patients with NS who had the SOS1 heterozygous mutation were more commonly rated as having social deficits compared with patients with the PTPN11 mutation (50% and 22% respectively); however, a statistically significant difference was not found likely due to a relatively small sample size (Alfieri et al. 2014). In a small study of adult patients with NS, emotion recognition in social situations was moderately impaired. It is reported that there is an increased incidence of alexithymia in adults with NS (Verhoeven et al. 2007). Alexithymia refers to an impairment of the ability to identify and communicate one's emotional state (Sifneos 1973). In this small sample, there was a tendency for participants to exhibit an indirect expression of emotions during social interactions resulting in deficiencies of social and emotional recognition and expression (Verhoeven et al. 2007). Wingbermuhle and colleagues (Wingbermühle et al. 2009) explained that these symptoms closely align with type II alexithymia, which is characterized by sparing affective experience and a normal physiological reaction (Vorst and Bermond 2001). It is hypothesized that because individuals with NS are likely to have observable amiable personality traits (such as agreeableness, friendliness, confidence, and happiness), symptoms of alexithymia and psychopathology may be underreported (Verhoeven et al. 2007; Wingbermühle et al. 2009).

The literature examining the emotional and behavioral functioning of individuals with NS is variable; this may in part be associated with different methodological approaches and age of the sample. Using self-reported measures, 23% of adults with NS in one study reported having depression and taking anti-depressant medication, while 49% reported being diagnosed and treated with depression and/or anxiety (Noonan 2005; Smpokou et al. 2012). Using a symptom

checklist (SCL-90-R), a small sample of adults with NS reported having an increased amount of anxiety, depression, and "psychoneuroticism" (Verhoeven et al. 2007). However, in a study that included a healthy adult comparison group, there were no significant differences in depressive or anxious symptoms between the groups (Wingbermühle et al. 2012). When considering QoL within this age group, adults with NS report having average to above average satisfaction with different aspects of life (Verhoeven et al. 2007; Shaw et al. 2007). The main reported concern related to the inability to fit in with peers and the feeling that they were lacking an adequate social life (Shaw et al. 2007).

In children with NS, studies have reported mix findings about the prevalence of anxiety and depression. Based on parent ratings, there were no significant differences in rates of anxiety and depression when compared with typically developing children of the same age (van der Burgt et al. 1999; Wood et al. 1995; Pierpont et al. 2015). In contrast, Alfieri et al. (2014) reported that 40% of their sample experienced clinically elevated symptoms of internalizing problems, while 32% experienced behavioral problems, although there was no comparison group. In a study of observed behavioral and emotional symptoms rated by a researcher, children with NS demonstrated significantly greater symptoms of internalizing (47.5%) and externalizing (60%) behaviors (Garg et al. 2017). Using the MASC, a self-report anxiety symptom questionnaire, the prevalence of anxiety symptoms (i.e., general anxiety, separation anxiety, specific/social phobias) was 37%, with another 30% exhibiting sub-clinical anxiety in a group of children with NS (Perrino et al. 2017). These levels are 3 times greater than the prevalence of anxiety in an earlier community study of 3479 preadolescent children without NS (Nacinovich et al. 2012). When examining emotional and behavioral problems, parents have been more likely to report difficulties than teachers (Lee et al. 2005). This finding may be due to a discrepancy in the perception of the child's functioning by the different reporters, or because more parents returned their forms than teachers. When children with NS were asked to complete a self-esteem questionnaire, they reported having average self-esteem, similar to those of the standardized population (Lee et al. 2005).

Noonan Syndrome with Multiple Lentigines (Previously LEOPARD Syndrome)

There has been little to no research focused on the socio-emotional, and behavioral functioning of individuals is NSML. The only literature examining these domains had a very small sample of children with NSML (6 participants), and only one was rated as having clinically significant externalizing difficulties, while none of the children with NSML exhibited social difficulties based on the SCQ-L and the M-CHAT (Alfieri et al. 2014).

Legius Syndrome

There has been little to no research focused on the socio-emotional and behavioral functioning of individuals with Legius syndrome. A single study examining the behavioral functioning of this population including 15 children with LS and 7 unaffected sibling/family members did not report any significant differences between the groups on the CBCL (Denayer et al. 2011).

Noonan Syndrome-Like Disorder with Loose Anagen Hair

There has been no research to date examining these domains in individuals with NSLAH.

Neurofibromatosis Type 1

Research focused on social and psychological profiles in children and adolescents and adults with NF1 has been published sporadically over the past two decades, with an uptick in interest and publications over the past 7 years. Early studies suggest that children with NF1 have significantly more social problems then their unaffected siblings or typically developing peers, with almost 40% of children with NF1 exhibiting elevated social problems based on parent and teacher ratings (Dilts et al. 1996; Johnson et al. 1999; Barton and North 2004). However, these deficits may not emerge until the school-aged years, as one study showed that preschool aged children (ages 3–6 years) did not exhibit greater psychosocial difficulties than unaffected, age- and SES-matched controls (Klein-Tasman et al. 2013). However, functional communication problems were identified in this very young cohort, generating interest in the role of early communication problems on the development of social-emotional functioning.

Noll et al. (2007) reported that children with NF1 had fewer friendships, were less well-liked by peers, and were more likely to be left out of social situations. Teachers and peers perceived children with NF1 as being more socially sensitive and isolated, displaying fewer leadership behaviors, and having fewer reciprocal friendships. Additionally, greater neurological involvement (e.g., headaches, seizures, CNS tumors, ADHD, learning difficulties) was positively correlated with more social-emotional problems, suggesting that CNS involvement may play a role in identifying children at-risk for social difficulties (Noll et al. 2007).

School-aged children and adults with NF1 tend to have different self-perceptions of their social functioning than their parents, teachers, peers, or other observers. Self-report measures of social functioning in children and adults with NF1 indicated that they perceived themselves to have good social competence, while other reporters indicate greater problems in this area of functioning (Barton and North 2004; Pride et al. 2013). Individuals with NF1 may overestimate their social abilities due to weaknesses in cognitive ability (specifically social cognition) to make a comparative judgment and incorporate feedback from others for an accurate perception of their social environment (Barton and North 2004).

The high prevalence of social difficulties in children with NF1 has more recently generated interest in examining the symptom overlap of ASD in NF1. The literature on the prevalence of ASD in children with NF1 remains inconsistent, in part due to varying research methodologies used across studies. Using the Social Responsiveness Scale (SRS; Constantino and Gruber 2005), Walsh et al. (2013) reported that 40% of their sample reached clinically significant symptom levels, while 14% reached levels consistent with those observed in children diagnosed with idiopathic ASD. Elevated levels of symptomology were not explained by internalizing/externalizing behavioral disorders or NF1 disease severity (Walsh et al. 2013). In other similar studies, 27–39% of children with NF1 exhibited ASD symptoms in the mild to moderate range on the SRS (Adviento et al. 2014; Garg et al. 2013b; Morris et al. 2016). Adviento et al. (2014) and Morris et al. (2016) reported that 12.8% and 13.2% (respectively) of their samples presented with ASD symptomatology in the clinically significant range, which is comparable with the findings of Walsh et al. (2013). However, Garg et al. (2013b) reported a higher prevalence (29%) of NF1 participants scoring in this clinically significant range. There appears to be a male predominance of ASD in children with NF1 (2.68:1, male:female), with males also demonstrating greater social communication deficits than females with ASD (Garg et al. 2016). Multiple studies have now demonstrated greater social deficits in males with NF1 compared with females (Pride et al. 2013; Garg et al. 2013b; Plasschaert et al. 2014). Compared with the normative sample of the ADOS (which included children with idiopathic ASD), children with NF1 showed better eye contact, language and communication skills, and less repetitive behaviors (Garg et al. 2015).

Children with ADHD have been shown to demonstrate impaired social functioning. The hallmark symptoms of ADHD include impaired attention and impulse control that interferes with functioning. These symptoms can interfere with social interactions as children with ADHD often interrupt others, miss information secondary to inattention, and have difficulty appreciating the impact of these behaviors on others. As a result, children with ADHD can struggle to develop stable peer relationships as these behaviors may lead to peer rejection (Dumas 1998). For individuals with NF1, comorbid ADHD may be a risk factor for social difficulties as the associated behaviors can interfere with the child's ability to develop or perform socially acceptable behaviors (Barton and North 2004; Mautner et al. 2002). Children with both NF1 and comorbid ADHD have shown poor social skills and social competence and greater behavioral problems compared with children with NF1 alone or children with idiopathic ADHD.

Findings from studies investigating the prevalence of ASD symptomatology in children with NF1 have demonstrated a significant relationship between ASD and ADHD symptoms (Walsh et al. 2013; Garg et al. 2013b). Morris et al. (2016) reported that they observed a co-occurrence of ADHD and ASD symptomatology in children with NF1. However, rather than ADHD being a risk factor for ASD, they posited that this is a co-occurrence that is a function of the NF mutation causing both disorders (Morris et al. 2016). However, Garg et al. (2015) did not show a significant difference in symptoms of hyperactivity, aggressive behaviors, or anxiety compared with children with idiopathic ASD. In fact, ADHD is highly comorbid in idiopathic ASD as well, with prevalence rates of 33–37% (Berenguer-Forner et al. 2015). The relationship between attention deficits and ASD symptoms was recently further elucidated by Lewis et al. (2018), who described significant differences in time attending to faces in social scenes between children with NF1 and healthy controls. Children with NF1 showed diminished time attending to the faces, and this was associated with greater ASD symptom severity (Lewis et al. 2018).

Research has also suggested that deficits in social cognitive function (i.e., "theory of mind," interpretation of social cues, body language, facial expressions, and tone of voice) as well as expressive and receptive language impairments may contribute to social difficulties in children with NF1 (Pierpont et al. 2018; Dilts et al. 1996; Allen et al. 2016; Payne et al. 2016; Eliason 1986; North et al. 1995). Huijbregts et al. (2010) suggested that children and adolescents with NF1 have difficulty in tasks that involve top-down appraisal of social signals and bottom-up encoding of social stimuli. Studies have shown that children with NF1 show deficits compared with typically developing children in facial emotion recognition, with specific problems recognizing and identifying fear and anger facial emotions (Huijbregts et al. 2010; Lewis et al. 2017). There were also impairments in facial perception and children with NF1 spent less time viewing the face as a whole, although these difficulties were not associated with the demonstrated problems with facial affect recognition (Lewis et al. 2017). Children with NF1 have also shown to be slower and less consistent than typically developing children in their ability to recognize faces in profile views (Huijbregts et al. 2010). However, when cognitive control was entered as a factor, these differences were no longer significant, supporting the

hypothesis that cognitive deficits contribute significantly to the impaired social information processing in children with NF1 (Huijbregts et al. 2010). In a study conducted by Huijbregts and de Sonneville (2011), autistic traits from the SRS and social skills from the Social Skills Rating System (SRSS; Gresham and Elliot 1990) were significantly related to total cognition on the Amsterdam Neuropsychological Task (ANT; de Sonneville 1999). Social information processing on the ANT was significantly worse for children with NF1 than the comparison group and accounted for group differences in conduct problems (Huijbregts and de Sonneville 2011). More specifically, children with NF1 have been shown to be significantly less successful with cognitive sequencing that involved the mental states of others and understanding social scripts than unaffected controls (Payne et al. 2016).

In addition to social difficulties, children with NF1 frequently present with disruptions in emotional and behavioral functioning. Approximately, 40% of children with NF1 exhibit elevated internalizing symptoms (i.e., social withdrawal, somatic complaints, and anxiety/depressive symptoms) relative to the normative sample, and these rates are higher than the prevalence of externalizing behavior problems, which was reported to be about a quarter of the sample in one study (Johnson et al. 1999; Graf et al. 2006). This pattern has been demonstrated across the lifespan in individuals with NF1, signifying the increased risk for developing disorders of depression and/or anxiety and the importance of monitoring these symptoms in NF1 (Dilts et al. 1996; Johnson et al. 1999; Graf et al. 2006; Cohen et al. 2015; Cipolletta et al. 2017; Martin et al. 2012; Pasini et al. 2012; Rietman et al. 2017a). In fact, parent-reported elevations of internalizing problems in the preschool years appear to be associated with continued internalizing problems into school age, and these difficulties seem to intensify with time (Rietman et al. 2017a). There is some suggestion that larger cortical volumes found in children with NF1 compared with age- and sex-matched healthy controls may be associated with poorer behavioral presentations (Huijbregts et al. 2015).

Pasini et al. (2012) assessed the presence of anxiety symptoms in children with NF1 using a self-report questionnaire (Multidimensional Anxiety Scale for Children MASC; March et al. 1997), and found that children with NF1 scored significantly higher than a healthy comparison group on the Anxiety Disorder Index and the MASC total score. Within this group, there was a moderate correlation between disease severity, social anxiety, and MASC total score. Parent and teacher ratings from additional studies indicate similar emotional difficulties on the CBCL and Strengths and Difficulties Questionnaire (SDQ; Allen et al. 2016; Johnson et al. 2005). When comparing parent reports on the CBCL, children with NF1 were rated as showing more internalizing problems than typically developing children in a healthy comparison group (Allen et al. 2016). Parent and teacher ratings indicated elevated levels of internalizing problems, symptoms of anxiety and depression, and thought problems (Dilts et al. 1996; Johnson et al. 1999; Barton and North 2004; Rietman et al. 2017b). In addition, child self-reports also indicated significantly more internalizing problems and somatic complaints than the normative sample (Rietman et al. 2017b).

Adults with NF1 also experience internalizing difficulties. In a sample of 498 adults, it was found that over half of the participants scored above the threshold on the Center of Epidemiologic Studies Depression Scale (CES-D; Radloff 1977) indicating that they had a significant level of depressive symptoms and an increased risk for clinical depression (Cohen et al. 2015). The degree of depressive symptoms was strongly correlated with quality of life, with nearly one-third of the variance in overall quality of life explained by level of depressive symptoms.

Many studies report diminished quality of life (QoL) in individuals with NF1, but there are differing opinions as to contributory factors. Regularly taking pain medication correlates with significantly poorer overall QoL and an increased prevalence of depressive and anxiety symptoms (Wolters et al. 2015). Additionally, pain interference, greater disease complications, and social-emotional factors are all significant predictors of overall QoL. Social-emotional problems (caregiver-rated depressive symptoms and self-rated social stress) mediated the effects of pain interference on QoL (Wolters et al. 2015). Moderate or severe problems with anxiety and depression, visibility of NF1 symptoms (e.g., dermal neurofibromas, disfigurement), and family influences have also been shown to play a role in well-being and QoL (Cipolletta et al. 2017; Coutinho et al. 2015; Garwood et al. 2012; Krab et al. 2009; Wolkenstein et al. 2001).

While seemingly less prevalent, externalizing symptoms have been reported as problematic for individuals with NF1 as well. Recently, Rietman et al. (2017b) examined behavioral problems in children and adolescents with NF1 based on parent and teacher symptom ratings (CBCL and TRF) as well as self-report (YSR). The study found that parents ($n = 183$) reported more severe behavioral problems over a wider range of areas than teachers ($n = 173$), and teachers reported more behavioral problems than adolescents did ($n = 88$). Externalizing problems were reported as being in the borderline to clinical range by 32% of parents, 22% of teachers, and 17% of adolescent self-reports (Rietman et al. 2017b). The authors suggest that children with NF1 may experience a "positive illusory bias" when rating themselves, which is consistent with research that has shown that children with NF1 rate themselves more positively than their parents on measures including academic functioning and quality of life (Barton and North 2004; Krab et al. 2009). Additional studies find that parents and teachers report that children with NF1 display more externalizing problems, aggressive behavior, and conduct problems than typically developing children (Johnson et al. 1999;

Barton and North 2004; Allen et al. 2016; Johnson et al. 2005). Differences have been reported between reports from mothers and fathers of children with NF1. Noll et al. (2007) found that mothers described children with NF1 as exhibiting greater total behavior problems, externalizing problems, delinquent, and aggressive behaviors compared with a group of peers. There were no significant differences between these groups when the reporter was the father. A similar pattern emerged with reports of internalizing symptoms within the same study. Children with NF1 were observed by their mothers as having more internalizing symptoms, whereas there were no significant differences according to the fathers' or children's self-report (Noll et al. 2007).

Discussion

This review highlights the general lack of research on the social, emotional, and behavioral functioning of individuals with one of the RASopathies. While some syndromes have received more attention and have produced more research on this topic (e.g., NF1, CFCS), in general, we have little understanding of the prevalence, patterns, and potential genotype-phenotype associations within and across these syndromes as it relates to psychological, social, and behavioral functioning. This argues for the need for more attention within the field of RASopathies to prioritize research in these areas, develop studies to increase our understanding of these morbidities, and devise interventions to address identified problems.

In the syndromes for which there is research, there are some unifying themes that may benefit future research and clinical care. These themes do not appear to be present only in the single-gene disorders, rather there are similarities across the RASopathies. Social deficits are one of the most documented areas of difficulty and concern across the syndromes. Associated with these social impairments, research has focused on the presence of ASD symptomatology and diagnosis, and there appears to be a higher prevalence of such symptomatology in the groups studied (e.g., CFCS and NF1). Within NS in particular, there has been a possible genotype-phenotype correlation associated with the presence of greater social impairment. The second most studied area related to social-emotional functioning surrounds a general examination of internalizing and externalizing symptoms and problems across the RASopathies. While both internalizing (e.g., anxiety, depression) and externalizing (e.g., oppositionality, aggression) problems are reported in most of the syndromes, there appears to be a predominance of internalizing problems.

The presence of psychological/emotional, social, and behavioral problems can result in reduced quality of life, but can also have a significant negative impact on skills imperative to independence, such as education and employment, establishing and maintaining relationships, and developing the ability to manage daily living skills. It has been demonstrated across many disease/disorder groups as well as in the general population that the presence of untreated mental health issues has a significant impact on independent adult functioning and quality of life (Woodward and Fergusson 2001; Fergusson and Woodward 2002).

Researchers are encouraged to not simply consider these problems within a biological framework, rather to consider a comprehensive biopsychosocial model for understanding the presence of psychological and social impairments in the RASopathies. This will not only allow us to begin to understand these deficits as they relate to the Ras/MAPK pathway, but also to consider environmental, health, and other factors that may be associated with these morbidities. Such an approach also provides greater opportunity for developing the most effective interventions for these problems. Implementing interventions earlier in life has the real potential to not only improve the person's immediate quality of life, but for long-term improvements and increased levels of independence, societal contribution, and life satisfaction.

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del Castillo A: Data collection and preparation, manuscript writing
Kennedy T: Project planning, data collection and preparation
Karim AI: Data collection and preparation, manuscript writing
Semerjian C: Data collection and preparation, manuscript writing

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