Variability in neuropsychological functioning in patients with downstream RAS pathway mutations

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Introduction

Gene mutations within the Ras-mitogen-activated protein kinase (RAS-MAPK) signaling cascade have been associated with multiple genetic syndromes with varying degrees of neurocognitive impairment. Current research has focused on how specific molecular alterations in RAS pathway genes may predict the presence and severity of neurocognitive sequelae. Results from cohort studies suggest greater frequency of neurocognitive and adaptive impairment with more downstream mutations (i.e., Cesarini et al., 2009; Pierpont et al., 2010), with a high degree of variability noted across individuals with the mutations in the same gene (e.g., Pierpont et al., 2016).

Objectives

The aim of the current study was to examine the neurocognitive profiles of individuals with downstream RAS pathway mutations with respect to intellectual abilities and adaptive functioning.

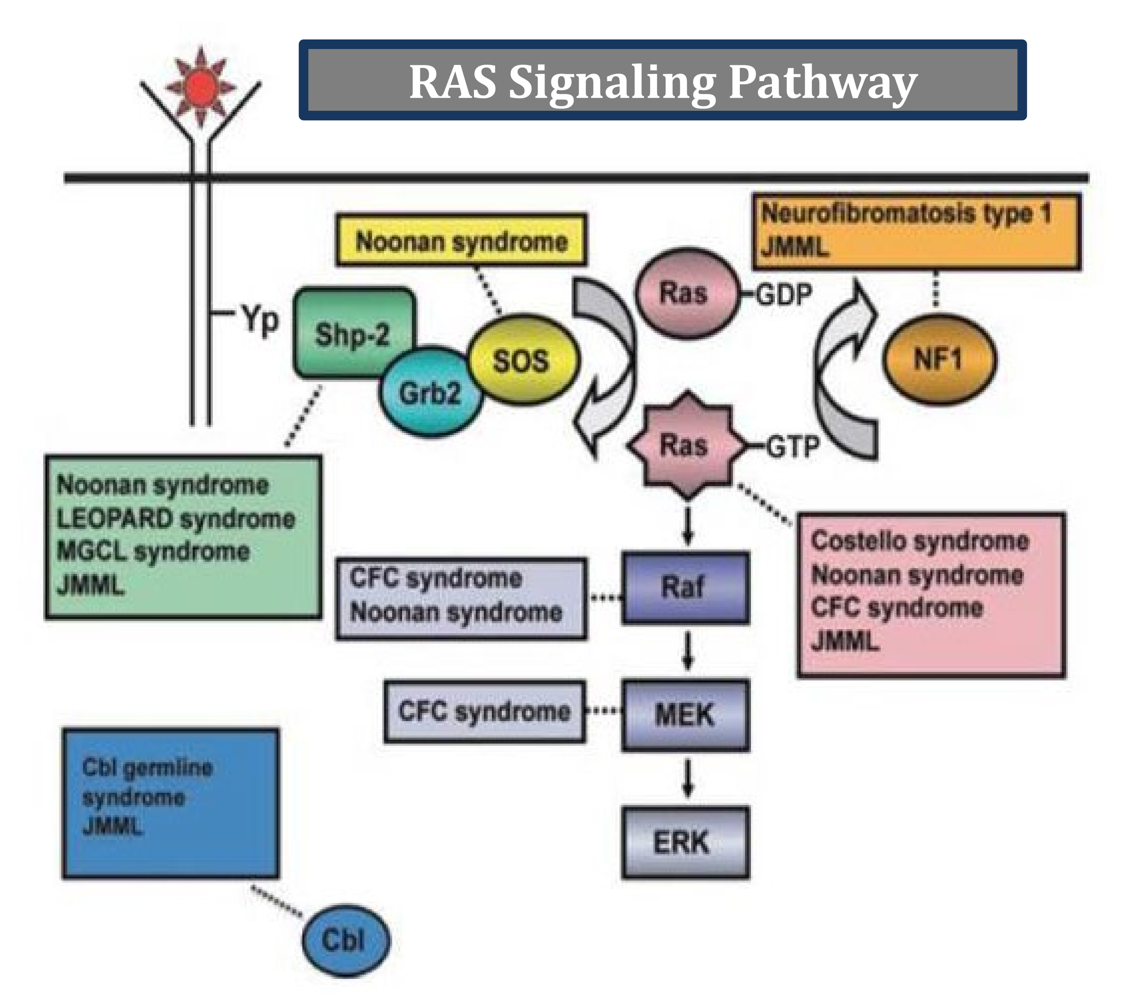

Figure 1. Individuals with RASopathies (a) neurofibromatosis type 1; (b) Noonan syndrome (PTPN11 mutation); (c) Costello syndrome (p.G12S HRAS mutation); (d) cardio-facio-cutaneous syndrome (MEK2 mutation) (Rauen, 2013).

PARTICIPANTS

	KRAS (n=6)	MAP2K2/MEK2 (n=3)	BRAF (n=4)
Patient Demographics	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age at assessment	10.69 (4.83)	14.51 (10.44)	10.86 (6.06)
Gender	2 M, 4 F	3 M	2 M, 2 F
# Diagnosed with heart disease	3	2	1
# Diagnosed with seizures	--	--	2

MEASURES

Differential Ability Scales – Second Edition	**DAS-II**
Kaufman Brief Intelligence Test, Second Edition	**KBIT-2**
Peabody Picture Vocabulary Test, Fourth Edition	**PPVT-IV**
Vineland Adaptive Behavior Scales, Third Edition	**Vineland-3**

Methods

- Participants were administered neurocognitive evaluations, including measures of nonverbal intellectual ability, receptive vocabulary, and adaptive functioning.
- Nonverbal reasoning (DAS-II & KBIT-2) and receptive vocabulary (PPVT-IV) scores were compared alongside overall parent-rated adaptive skills (Vineland-3).

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Table 1. Participant performance on measures of nonverbal intelligence, receptive vocabulary, and caregiver rated adaptive functioning.

Participant	Gene Mutation	Nonverbal IQ	Verbal IQ PPVT	Overall Adaptive
RAS001	KRAS	81	85	71
RAS004	KRAS	38	20	65
RAS009	KRAS	105	92	85
RAS011	KRAS	43	64	76
RAS012	KRAS	32	20	34
RAS013	KRAS	50	66	72
RAS002	MAP2K2/MEK2	52	66	56
RAS005	MAP2K2/MEK2	53	76	72
RAS006	MAP2K2/MEK2	84	80	102
RAS003	BRAF	52	36	43
RAS007	BRAF	49	52	69
RAS008	BRAF	40	48	67
RAS010	BRAF	32	20	49

Note: All scores are based on standard scores (M = 100, SD = 15). Ranges were classified as average (Score ≥ 85), below average (Score ≥ 70 – 84), and impaired (Score ≤ 69).

Results

- Intellectual disability was classified as impaired performance (Standard Score ≤ 69) in both intellectual functioning and adaptive functioning domains. More than half of the sample (54%) met criteria for intellectual disability, with significant neurocognitive variability among the remaining participants.
- Parent-rated adaptive functioning was generally higher in those patients whose verbal skills were relatively strong compared to nonverbal abilities.
- Further exploration of adaptive functioning skills indicated relative strengths in social skills for the majority of the current sample.

Table 2. Participant performance across caregiver rating domains of adaptive functioning.

Participant	Gene Mutation	Communication	Daily Living	Socialization
RAS001	KRAS	68	63	60
RAS004	KRAS	53	68	68
RAS009	KRAS	88	83	96
RAS011	KRAS	77	79	76
RAS012	KRAS	20	38	32
RAS013	KRAS	72	76	71
RAS002	MAP2K2/MEK2	54	60	41
RAS005	MAP2K2/MEK2	71	70	78
RAS006	MAP2K2/MEK2	96	102	107
RAS003	BRAF	38	45	32
RAS007	BRAF	71	60	79
RAS008	BRAF	65	60	77
RAS010	BRAF	30	50	50

Note: All scores are based on standard scores (M = 100, SD = 15). Ranges were classified as average (Score ≥ 85), below average (Score ≥ 70 – 84), and impaired (Score ≤ 69).

Conclusion

- While there was a high degree of variability across participants, patterns of cognitive and adaptive functioning emerged based on the specific gene mutation.
- *BRAF* mutation was associated with a greater degree of neurocognitive impairment.
- Study findings may assist with guiding treatment planning and family-based interventions.