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Neurobehavioural vulnerability and autistic traits in RASopathies

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With the advent of the genomic era, *PTPN11* gene mutations have been identified as responsible for Noonan syndrome. This discovery did not appear to lead to systematic precise evaluation of the cognitive profile of the affected patients, at least early on, and reports of possible psychological or psychiatric concern have been sparse.[1–4] This clearly contrasts with the tremendous scientific enthusiasm afforded by the ubiquitously expressed mitogen-activated protein kinase (MAPkinase) signalling pathway and its role in a number of physiological and pathological processes, including cell proliferation. Excellent basic science and clinical research (including clinical trials) has been performed in heart development, phenotype distinctive features, fine genotype–phenotype correlations, and therapeutic trials of RAS-MAPkinase inhibitors. Many of the studies possibly overlooked the distinctly psychologic as psychiatric profiles.

Concomitantly, nosology was revisited from syndromes coined on phenotypic features to precise gene identification sharing RAS as a 'unifying' central pathway ('RASopathies'). RAS is a family of ubiquitous enzymes that are involved in cellular signal transduction. The genetic heterogeneity of RAS has been increasingly recognized, with currently 14 identified genes, leading to a total detection mutation rate of 75%.

In the present issue, Garg et al.[5] report on the features of autism spectrum disorder (ASD) and/or attention-deficit–hyperactivity disorder (ADHD) in children under 17 years of age with two RASopathies, Noonan syndrome, or cardiofaciocutaneous syndrome. It sheds a new light on neurological and psychiatric features in these children. This study has several remarkable strengths. It uses robust tools to assess ASD/ADHD profiles, which take into account comorbid cognitive problems that are known to impact the specificity of quantitative phenotypic measures. The successive inclusion of patients is also a strength, as is the homogeneous cohort of patients: 80% of patients harbor a *PTPN11* gene mutation. The main take-home message to geneticists and other clinicians involved in counselling is the incidence of 30% of ASD or ADHD features and 30% of additional related problems. The historically identified alexithymia in Noonan syndrome[1] (i.e. the inability to identify and describe one's own emotions leading to impairment in adaptive emotional behavior) therefore represents only the tip of the iceberg of neuropsychological phenotypes in RASopathies.

The present study also has a few limitations. The patient samples are small: 10 patients with cardiofaciocutaneous syndrome, a single one with Costello syndrome (logically excluded), and 40 with Noonan syndrome. This makes subgrouping based on distinctive genotype difficult while it might have led to possible links with specific pathways and postulating on the indication for finer evaluation in specific subgroups of patients. The sex bias (5:1 male to female ratio) may imply parameters that are unrelated to the RAS pathway per se. Another possible bias is previous heart surgery or any medical complications that may have resulted in brain comorbidity; this was perhaps evaluated and excluded. In sum, further confirmation of Garg et al.'s interesting findings is required before precise screening programmes for psychological and psychiatric conditions can be implemented in RASopathies.

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