CORRESPONDENCE

No reason yet to change diagnostic criteria for Noonan, Costello and cardio-facio-cutaneous syndromes

The clinicogenetic relationship between Noonan syndrome (NS) and Noonan-like syndromes (Costello syndrome (CS), cardio-facio-cutaneous (CFC) syndrome) and the disruption of the RAS-ERK pathway makes for a fascinating story that has developed over the past decade, and is still developing. The discovery that the genes causing these syndromes encode proteins that converge on the same metabolic pathway facilitated understanding of the similarities that group these conditions within one family of syndromes.1 Nevertheless, their nosological classification continues to be a challenge. There is general agreement that NS is caused by mutations of PTPN11 (most cases), SOS1 or RAF1, that CFC syndrome is caused by mutations of BRAF (most cases), MEK1 or MEK2, and that CS is caused by mutations of HRAS. Cases due to KRAS mutations are of uncertain nosological classification, and there are some borderline cases for which the clinical diagnosis will be uncertain even for the best experts in the field.

The recent article by Nystrom et al5 represents another attempt at bringing some order within this complex matter. However, we think that some of the conclusions drawn by the authors are unwarranted. The main focus of this letter is on patients 3 and 8 of that study, who are unusual because, according to the authors, the former has CFC syndrome caused by a mutation in SOS1, and the latter has NS, caused by a mutation in BRAF.2 The inescapable conclusion is a further expansion of the genetic heterogeneity of both syndromes. However, it is an arguable conclusion. Although we can judge only on the basis of a very sparse clinical description in the table and small photographs in the first figure, our impression is that patient 3 is a typical case of SOS1 NS (no mental delay, no curly hair, dry skin, missing eyebrows), and patient 8 is an ordinary case of CFC syndrome due to BRAF mutation (mental delay, curly hair, other typical features). Nystrom et al5 state that their clinical diagnoses were based on criteria established by Roberts et al,6 but they had to make exceptions (arbitrarily) on at least two criteria: mental delay and curly hair. Moreover, they did not consider that Roberts et al6 published their criteria before the discovery of SOS1,5 which established the association between NS and pronounced skin involvement. Moreover, it should be pointed out that Nystrom et al5 based their diagnoses of CFC or NS solely on presence or absence of ectodermal signs that by themselves do not capture the complexity of these phenotypes, resulting occasionally in misdiagnosis.

Based on these considerations, we see no reason, at the moment, to change the generally held view that NS can be caused by mutations in three different genes (PTPN11, SOS1, RAF1), CFC syndrome by mutations in another three genes (BRAF, MEK1, MEK2), and CS by HRAS mutations, with KRAS mutations causing rather atypical cases that are difficult to classify. As Nystrom et al5 did not discuss CS in their report, it is surprising and difficult to understand why they indicate that this condition can be caused not only by HRAS mutations, but also by mutations in KRAS, BRAF and MEK1 (their third figure). There is general agreement that the diagnosis of CS should be restricted to those cases that carry a HRAS mutation,3 which implies increased risk for cancer and consequent application of a strict surveillance protocol. Again, there is no reason, at the moment, to change this stance.

REFERENCES


CORRECTIONS

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There was an error in an article published in the April 2006 issue of the journal. The authors reported possible duplication of copy number polymorphisms flanking the MEC2P region. These duplications were observed by multiplex ligation-dependent probe amplification (MLPA) in one patient and two controls (figure 2). Recent further investigations of these regions have shown that these duplications were false observations. Newly synthesised MLPA probes and better quality DNA samples showed no extra DNA copies in the region. From reanalysis of the previously obtained MLPA data, the authors conclude that the fluorescence intensity signals were outside the normal range in which the data can be correctly interpreted (100–1000) for current quality-control thresholds (>10000). The authors regret this incorrect interpretation of the data.

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