

## 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.<sup>1</sup> 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 Nyström *et al*<sup>2</sup> 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*.<sup>2</sup> 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). Nyström *et al*<sup>2</sup> state that their clinical diagnoses were based on criteria established by Roberts *et al*,<sup>3</sup> 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 al*<sup>3</sup> published their criteria before the discovery of *SOS1*,<sup>4</sup> which established the association between NS and pronounced skin involvement. Moreover, it should be pointed out that Nyström *et al*<sup>2</sup> 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 Nyström *et al*<sup>2</sup> 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,<sup>5</sup> 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.

G Neri,<sup>1</sup> J Allanson,<sup>2</sup> M I Kavamura<sup>3</sup>

<sup>1</sup>Istituto di Genetica Medica, Università Cattolica del S. Cuore, Roma, Italy; <sup>2</sup>Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada; <sup>3</sup>Mercidical Genetics Center, Federal University of Sao Paulo, Sao Paulo, Brazil

**Correspondence to:** Dr G Neri, Istituto di Genetica Medica, Università Cattolica, Largo F. Vito, 1 00168 Roma, Italy; gneri@rm.unicatt.it

Received 12 September 2008

Accepted 19 September 2008

*J Med Genet* 2008; **45**:832. doi:10.1136/jmg.2008.063263

## REFERENCES

1. Gelb BD, Tartaglia M. Noonan syndrome and related disorders: dysregulated RAS-mitogen activated protein kinase signal transduction. *Hum Mol Genet* 2006; **15**:R220–6.
2. Nyström A-M, Ekvall S, Berglund E, Björkvist M, Braathen G, Duchon K, Enell H, Holmberg E, Holmlund U, Olsson-Engman M, Annerén G, Bondeson M-L. Noonan and cardio-facio-cutaneous syndromes: two clinically and genetically overlapping disorders. *J Med Genet* 2008; **45**:500–6.

3. Roberts A, Allanson J, Jadico SK, Kavamura MI, Noonan J, Opitz JM, Young T, Neri G. The cardio-facio-cutaneous syndrome (CFC): a review. *J Med Genet* 2006; **43**:833–42.
4. Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, Pandit B, Oishi K, Martinelli S, Schackwitz W, Ustaszewska A, Martin J, Bristol J, Carta C, Lepri F, Neri C, Vasta I, Gibson K, Curry CJ, Siguero JP, Digilio MC, Zampino G, Dallapiccola B, Barsagi D, Gelb BD. Gain-of-function *SOS1* mutations cause a distinctive form of Noonan syndrome. *Nat Genet* 2007; **39**:75–9.
5. Kerr B, Allanson J, Delrue MA, Gripp KW, Lacombe D, Lin AE, Rauen KA. The diagnosis of Costello syndrome: nomenclature in Ras/MAPK pathway disorders. *Am J Med Genet* 2008; **146A**:1218–20.

## CORRECTIONS

doi:10.1136/jmg.2005.036178corr1

Lugtenberg D, de Brouwer APM, Kleefstra T, Oudakker AR, Frints SGM, Schrandt-Stumpel CTRM, Fryns JP, Jensen LR, Chelly J, Moraine C, Turner G, Veltman JA, Hamel BCJ, de Vries BBA, van Bokhoven H, Yntema HG. Chromosomal copy number changes in patients with non-syndromic X linked mental retardation detected by array CGH. *J Med Genet* 2006; **43**:362–70.

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 *MECP2* 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.

doi:10.1136/jmg.2008.057943corr1

There was an error in an author's name in an article published in the September issue of the journal (Khoueir R, Ibala-Rhomdane A, Méry L, Blachère T, Guérin J-F, Lornage J, Lefèvre A. Dynamic CpG methylation of the *KCNQ10T1* gene during maturation of human oocytes. *J Med Genet* 2008; **45**:583–8). The name of the first author is R Khoueir.