# Letter regarding the article: "Striking phenotypic overlap between Nicolaides-Baraitser and CoffinSiris syndromes in monozygotic twins with ARID1B intragenic deletion"

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# Letter regarding the article: "Striking phenotypic overlap between Nicolaides-Baraitser and Coffin-Siris syndromes in monozygotic twins with ARID1B intragenic deletion"

We read the article by Pascolini et al. (2019) where they describe the overlap in facial gestalt between Coffin-Siris syndrome (CSS, OMIM 153900) and Nicolaides-Baraitser syndrome (NCBRS, OMIM 601358) in monozygotic twins with great interest. They identified an *ARID1B* deletion of exon 2–4 by array-CGH. This variant was not inherited from mother, the father could not be tested. Using Face2Gene to analyse their facial features and those of published CSS (n = 10) and NCBRS (n = 10) patients they show similarities between these patients, discuss the relevance of *ARID1B* in the NCBRS phenotype and place this in the context of previously published *ARID1B* patients. With regard to the latest developments in research in the BAFopathies field, we would like to further discuss their findings.

CSS and NCBRS are both considered BAFopathies, because the causative genes encode proteins which are members of the BAF complex. One of these genes (*SMARCA2)* is associated with NCBRS, while several other genes, including *ARID1B*, are associated with CSS. Because of this shared molecular basis, it is unsurprising that both syndromes show phenotypic overlap (Wieczorek et al., 2013). The similarities of facial gestalt between CSS and NCBRS, as illustrated both by Pascolini et al. and previously by Gripp et al. (2016) using Face2Gene, are in line with previously published observations and further confirm the clinical overlap between both syndromes. Since the clinical overlap can be explained by the shared molecular basis of both syndromes, we question whether this should be used as an argument to reclassify *ARID1B* as a gene responsible for NCBRS. Furthermore, all NCBRS patients with pathogenic variants in *ARID1B*, have been later reclassified as CSS patients (Wieczorek et al., 2013). Regardless of this perhaps semantic discussion we agree that it is appropriate to investigate *ARID1B* in *SMARCA2*-negative NCBRS-like patients, since the distinction especially in early ages can be difficult to make.

In their review of the literature Pascolini et al. reported that all *ARID1B* patients they identified have developmental or intellectual delay, autism spectrum disorder (ASD) and speech delay (49/49, 100%). This is similar to frequencies we previously reported for 60 CSS patients with pathogenic variants in *ARID1B* (Santen et al., 2014). We found developmental delay or intellectual disability in all patients, autistic traits or ASD was not systematically assessed and speech delay was present in all patients for whom data was available (45/45). Their frequencies differ somewhat from our recent report on 143 patients (i.e. intellectual disability 126/127 (99.2%), autistic traits 44/77 (57.1%), speech delay 86/131, (65.6%)) (van der Sluijs et al., 2019), which may be caused by the difference in size of the cohorts or the level of detail of clinical information.

Since almost all pathogenic variants in *ARID1B* are loss-of-function and *de novo* (van der Sluijs et al., 2019), an essential step in the interpretation of intragenic deletions is to determine whether the deleted segment is in-frame or out-frame. The deletion reported by Pascolini et al. (exon 2–4) is in-frame, and without knowing whether the variant is *de novo* we advise to be very cautious in its interpretation. Indeed, we recently encountered a patient without CSS, in whom an intragenic in-frame deletion of exon 3–4 was detected, which was inherited from an unaffected parent. To gain more confidence in the pathogenicity of the variant the methylation pattern could be assessed (Aref-Eshghi et al., 2018). However, a positive BAFopathy signature would not prove beyond doubt that this particular variant is causal, only that the patient has a BAFopathy. Given that the features of the reported patients are compatible with NCBRS, we would recommend to sequence the *SMARCA2* gene and the other BAF complex genes to exclude that other potentially pathogenic variants might be present.

To summarize, we do agree with the authors that CSS and NCBRS are BAFopathies and as such part of a clinical spectrum, and that facial analysis appears to be a useful tool in the diagnostic approach. We agree that *SMARCA2*-negative NCBRS patients should be screened for *ARID1B* and other BAF complex genes. We recommend that care should be taken when interpreting variants which do not clearly lead to haploinsufficiency especially when is it unknown if they occurred *de novo*.

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