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LETTER TO THE EDITOR

ARID1B mutations are the major genetic cause of corpus callosum anomalies in patients with intellectual disability

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Sir,

In their extensive review article in *Brain*, Edwards *et al.* (2014) presented physiological processes underlying the formation of the corpus callosum, as well as pathological conditions in mice and humans leading to agenesis of the corpus callosum (AgCC). They reviewed most human syndromes associated with AgCC and emphasized the great heterogeneity of known genetic causes of AgCC in

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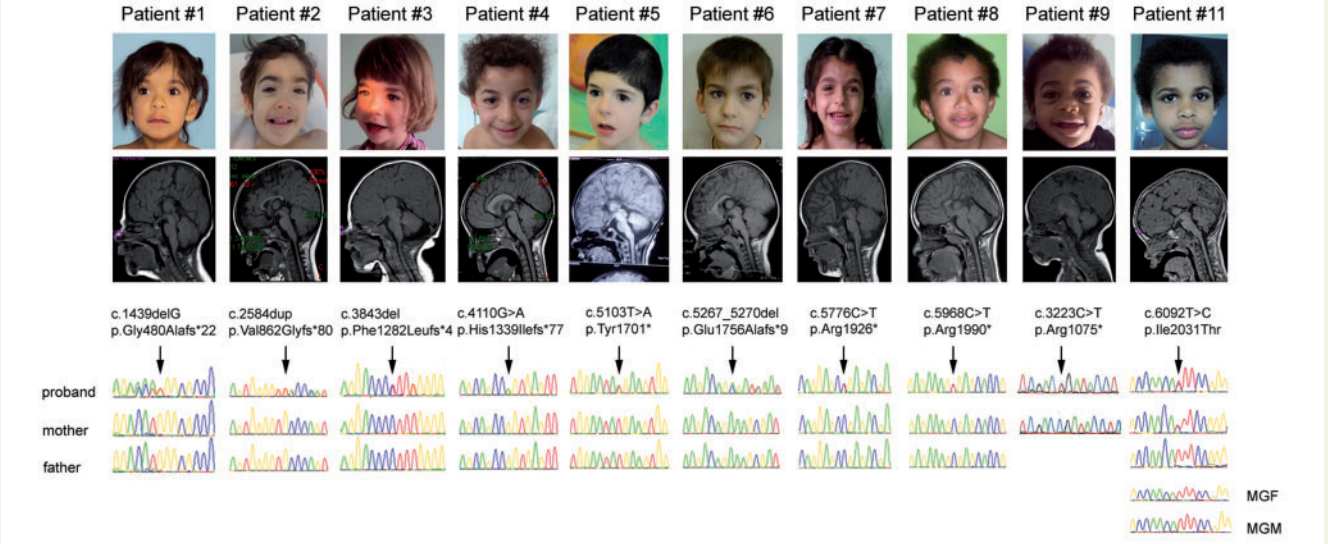

Figure 1 Clinical and molecular findings in 10 patients with *ARID1B* mutation and ACC-ID. *Top row*: Facial dysmorphy is consistent with the diagnosis of Coffin-Siris syndrome in all patients. *Middle row*: Brain MRI showed anomalies of the corpus callosum in all patients with Patient 2 having a short corpus callosum. *Bottom row*: Electrophoregrams showing *de novo* heterozygous *ARID1B* mutations in all probands and a maternally inherited mutation in Patient 11 (*de novo* in the mother). MGF = maternal grandfather; MGM = maternal grandmother. Paternal DNA of Patient 9 was not available.

humans by listing more than 70 single gene mutations and copy number variations (CNV), which altogether explain 30–45% of all cases. Most of these genetic anomalies are responsible for AgCC associated with other cerebral or extra-cerebral malformations and/or intellectual disability (ID). The association between AgCC and intellectual disability is further highlighted by the higher prevalence of AgCC in individuals with intellectual disability (2–3%) versus in the general population (0.025–0.02%) (Paul *et al.*, 2007; Sotiriadis and Makrydimas, 2012). Thereby, given the extreme genetic heterogeneity of intellectual disability (Deciphering Developmental Disorders Study, 2015) and the number of genes involved in the formation of the corpus callosum in humans, it is not surprising that genetic causes of syndromes associating AgCC and intellectual disability are so numerous. However, the prevalence of each of these genetic anomalies in individuals with this association is currently unknown.

To improve our knowledge on genetic causes of AgCC with intellectual disability, we collected prospectively clinical and molecular data from 177 individuals with anomalies of the corpus callosum (ACC, comprising patients with AgCC, or with short corpus callosum or with dysplastic corpus callosum), and intellectual disability (or developmental delay for young children; ACC-ID) between 2009 and 2015. A clinical diagnosis, further confirmed by targeted sequencing of the corresponding gene, when possible, was made for 15 patients. Among these patients, one had a diagnosis of Coffin-Siris syndrome (CSS) and a mutation in *ARID1B*, the major gene for Coffin-Siris syndrome accounting for 40% (Wieczorek *et al.*, 2013) to 68% (Santen *et al.*, 2013) of all cases. Coffin-Siris syndrome was suspected in four other patients whose DNA samples were studied on our gene panel (see below). Excluding these patients as well as patients with causal chromosomal abnormalities detected by karyotyping or SNP arrays ($n = 24$; chromosomal microarray analysis was performed in all patients, none with deletion of *ARID1B*), the cause of ACC-ID remained unknown in 138 patients (Supplementary Fig. 1). The main pitfalls possibly explaining the low diagnosis yield with the 'targeted strategy' were the extreme heterogeneity of ACC-ID, the limited knowledge on the genetic bases of the hundreds of clinical entities associated with ACC at that time and the limited availability of genetic testing.

We then undertook a molecular study of 99 index cases with unexplained ACC-ID using next generation sequencing of 423 selected genes involved in ACC in humans or mice. As expected, we found very few recurrent genes, except *ARID1B*, which proved to be prominently involved. Indeed, we found pathogenic mutations in *ARID1B* in 10 additional patients (10%).

Including the patient with a targeted molecular study, all of our 11 patients with ACC-ID and *ARID1B* mutations had typical facial features of Coffin-Siris syndrome on retrospective analysis (Fig. 1, top row). None had any extra-cerebral malformation (Table 1). Most patients ($n = 8/11$) had normal fingers and toes, three had mild anomalies of the extremities, including hypoplasia of all fingernails in one, clinodactyly of the fifth fingers in another and broad hallux with hypoplasia of the fifth toenails in a third. Facial hypertrichosis or hirsutism was found in

Table 1 Molecular and clinical data of 11 patients with ACC-ID and a diagnosis of Coffin-Siris syndrome due to *ARID1B* mutations

	Genetic anomalies		ACC	Diagnosis of ACC	Features of Coffin-Siris syndrome				
Patient #	cDNA	Protein			Typical course face	Extremities	Facial hypertrichosis or hirsutism	Extra-cerebral malformation	Other
1	c.1439delG *de novo*	Frameshift p.Gly480Alafs*22	Partial AgCC	Antenatal	Yes	Hypoplasia of fingernails	Yes	none	squint
2	c.2541_2542insG *de novo*	Frameshift p.Val862Glyfs*80	Short CC (<3rd perc.)	Post-natal	Yes	Normal	Yes	none	unilateral eyelid ptosis
3	c.3843delC *de novo*	Frameshift p.Phe1282Leufs*4	Complete AgCC	Antenatal	Yes	Normal	Yes	none	none
4	c.4110G>A *de novo*	Frameshift p.His1339Ilefs*77	Partial AgCC and thick CC	Post-natal	Yes	Broad hallux, hypoplasia of fifth toenails	No	none	scoliosis
5	c.5103T>A *de novo*	Nonsense p.Tyr1701*	Complete AgCC	Antenatal	Yes	Normal	Yes	none	growth retardation, microcephaly
6	c.5267_5270delCAAAG *de novo*	Frameshift p.Glu1756Alafs*9	Partial AgCC	Post-natal	Yes	Normal	No	none	neon. feed. diff., transmissional hypoacousia, bilateral cryptorchidism
7	c.5776C>T *de novo*	Nonsense p.Arg1926*	Complete AgCC	Antenatal	Yes	Normal	Yes	none	none
8	c.5929C>T *de novo*	Stop p.Arg1990*	Partial AgCC	Post-natal	Yes	Normal	No	none	neon. feed. diff. and hypotonia, squint
9	c.3223C>T absent in the mother	Stop p.Arg1075*	Partial AgCC	Antenatal	Yes	Normal	Yes	no	none
10	c.1468_1472delTGGGC *de novo*	Frameshift p.Trp490Glyfs*43	AgCC (TDM)	Post-natal	Yes	Normal	Yes	none	craniosynostosis
11	c.6092T>C inherited from affected mother	Missense p. Ile2018Thr	Complete AgCC	Post-natal	Yes	Clinodactyly of second fingers	Yes	none	none

CC = corpus callosum; ACC = anomalies of the corpus callosum; perc. = percentile; neon. feed. diff. = neonatal feeding difficulties.

8/11. Complete or partial AgCC had been diagnosed on brain MRI in 6/11 patients during the prenatal period and confirmed on postnatal MRI in all of them. The diagnosis of ACC was made on postnatal brain MRI only in four patients and on a CT in the eldest of the series. The ACC was a complete AgCC in four patients and a partial AgCC in five (Fig. 1, middle row). The remaining patient had a pathologically short corpus callosum (length <3rd percentile) rather than agenesis. Heterozygous *ARID1B* mutations identified in our patients were loss-of-function mutations (Fig. 1, bottom row), except one missense mutation. This mutation was inherited from an affected mother with mild intellectual disability but normal corpus callosum. The molecular study in the healthy maternal grandparents revealed that the mutation had occurred *de novo* in the patient's mother. Except for the previous case and another with unavailable father, all mutations had occurred *de novo*.

Thus, the overall prevalence of *ARID1B* mutations in our series of studied patients with unexplained ACC-ID is 10% (10/99), 7.2% (11/153) in patients with ACC-ID unexplained by chromosomal imbalance and 6.2% (11/177) taking the complete series into account. These results imply that mutations in *ARID1B* are likely the main cause of ACC-ID. *ARID1B* is one of the major genes explaining intellectual disability, with up to 0.5–1% of patients with intellectual disability carrying pathogenic *ARID1B* mutations in large-scale studies (Hoyer *et al.*, 2012; Deciphering Developmental Disorders Study, 2014). Considering 64 patients with a CSS phenotype and mutations in *ARID1B* only (i.e. excluding patients with chromosomal deletion encompassing the gene and patients with anomalies in other Coffin-Siris syndrome genes) reported in six articles (Hoyer *et al.*, 2012; Santen *et al.*, 2012, 2013; Tsurusaki *et al.*, 2012, 2014; Wieczorek *et al.*, 2013), the proportion of CSS patients with ACC is 39% (25/64). This high proportion of ACC in patients with CSS due to *ARID1B* mutations combined with the relatively high prevalence of *ARID1B de novo* mutations in individuals with intellectual disability explains the prominent position of *ARID1B* in the diagnosis of ACC-ID.

ARID1B encodes a subunit of the SWI/SNF-like BAF chromatin remodelling complex comprising other components (*ARID1A*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCE1*), in which mutations are also responsible for Coffin-Siris syndrome (with or without ACC) or for its main differential diagnosis, Nicolaides-Baraister syndrome. Though mutations in genes encoding for these proteins may be associated with ACC-ID (Kosho *et al.*, 2013; Santen *et al.*, 2013; Wieczorek *et al.*, 2013), none were found in our series, which is likely explained by their rarity.

These results have important implications for prenatal counselling when ACC (mainly AgCC) is diagnosed pre-natally. The finding of the aetiology of a prenatally diagnosed ACC and the establishment of the foetal intellectual prognosis have major impact on the parental decision to continue or terminate the pregnancy. While the finding of another visceral or brain malformation usually worsens the cognitive prognosis, parental decision-making is particularly difficult when the ACC is apparently isolated (i.e. not associated with other cerebral or extra-cerebral malformations). In the latter case, prenatal counselling is based on statistical data showing that ~70% of children born after the identification of isolated ACC have a normal intellectual development (Moutard *et al.*, 2012; Sotiriadis and Makrydimas, 2012). The Coffin-Siris syndrome phenotype is mainly identified in children with subtle morphological features of the face and extremities not detectable on prenatal echography and is not frequently associated with other (cerebral or extra-cerebral) malformations when a mutation in *ARID1B* is causative (Hoyer *et al.*, 2012; Santen *et al.*, 2013; Wieczorek *et al.*, 2013; Tsurusaki *et al.*, 2014). Likewise, the patients of our series with *ARID1B* mutations have a mild phenotype since they do not have gross malformations. Accordingly, those with an antenatal diagnosis of AgCC had isolated AgCC. These data further explain the lack of patients with mutations in other Coffin-Siris syndrome-causing genes in our series: the absence of associated malformation may have influenced the choice of parents facing the discovery of foetal ACC towards pregnancy continuation and thus increased the proportion of *ARID1B* mutations in patients with ACC-ID. Given the prevalence of *ARID1B* mutations in ACC-ID and the scarcity of additional malformations in Coffin-Siris syndrome related to *ARID1B*, our study suggests that the sequencing of *ARID1B*—and of other genes to be determined—could be performed in cases of foetal ACC along with CGH-array and morphological investigations, in order to improve the accuracy of the intellectual prognosis.

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Supplementary material

Supplementary material is available at *Brain* online.

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