doi:10.1093/brain/aww171 BRAIN 2016: 139; 1–3 | e65

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

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

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Sir,

We read with interest the Letter to the Editor by Mignot *et al.* (2016), which reports that mutations in the chromatin-remodelling gene *ARID1B* are a major genetic cause of isolated agenesis of the corpus callosum in patients with intellectual disability. Agenesis of the corpus callosum (ACC) is among the most common brain malformations (Guillem *et al.*, 2003; Wang *et al.*, 2004; Glass *et al.*, 2008), and can be associated with no or variable levels of intellectual disability (Paul *et al.*, 2007). The term 'isolated ACC' is used to distinguish ACC that is not associated with additional cerebral or extra-cerebral malformations, from syndromic ACC. This distinction is prognostically useful, because whilst individuals with isolated ACC are still likely to have learning difficulties, intellectual disability (ID) is more common in syndromic ACC (Moutard *et al.*, 2012; Sotiriadis and Makrydimas, 2012). The genetics underlying ACC associated with intellectual disability (ACC-ID), however, remain poorly understood. Moreover, as this and previous studies have demonstrated (Bedeschi *et al.*, 2006; Schell-Apacik *et al.*, 2008), karyotyping and targeted sequencing do not identify a genetic cause in the majority of cases of ACC.

Mignot and colleagues used next generation sequencing of 423 genes that had previously been associated with ACC in humans or mice in a cohort of 99 index cases with unexplained ACC associated with intellectual disability or developmental delay (ACC-ID). They report that pathogenic mutations in *ARID1B*, the most common cause of Coffin-Siris syndrome (Santen *et al.*, 2012), were identified in 10 of these patients (10%). On retrospective reflection, all 10 individuals had typical course facial features of Coffin-Siris syndrome; eight individuals had two or more Coffin-Siris syndrome core features (course face, hypoplasia of the fifth digit, and facial hypertrichosis/hirsutism) (Fleck *et al.*, 2001; Schrier *et al.*, 2012), and of these individuals, two had extremity abnormalities. The prevalence of *ARID1B* mutations in ACC-ID (6.2% in the present study) and in previously described intellectual disability cohorts (0.9% in Hoyer *et al.*, 2012) is consistent with significant phenotypic overlap among Coffin-Siris syndrome, intellectual disability and ACC-ID. This underscores the importance of considering mild variants of known syndromes in ACC-ID, many of which do not exist as a single clinical entity, but rather as a spectrum of intellectual disability with brain and other malformations. It is possible that milder variants of ACC syndromes are under-diagnosed, or misdiagnosed as isolated ACC, as they do not meet all the criteria for inclusion in a known syndrome and are thus difficult to distinguish clinically. As a means to improve diagnostic efficiency, Mignot and colleagues have demonstrated the potential value of utilizing a gene panel

Advance Access publication July 29, 2016

based on current understanding of ACC genes to delineate the genetic causes of ACC-ID. Such approaches will likely lead to improved precision of diagnosis, and therefore have important implications for prognostication, especially in the area of intellectual disability.

Based on this finding, Mignot and colleagues argue that *ARID1B* mutations are the most common genetic cause of intellectual disability associated with ACC. They note, however, that the high discovery rate of *ARID1B* mutations in their cohort may result from a systematic bias in patient selection and inclusion, rather than true prevalence in ACC-ID. This is an issue that is inherent in ACC studies, since the patterns of patient inclusion and exclusion are likely to differ between sites and there is no international standard for diagnosis of ACC disorders. In addition, the success of a candidate gene approach is determined by gene selection, which is limited by our current understanding of genetic causes of ACC. Unbiased genetic studies in large, well-defined patient cohorts would be invaluable in identifying new causes of ACC-ID and to determine whether the high prevalence of *ARID1B* mutations in the present study could reflect inherent difficulties in diagnosing mild syndromic forms of ACC. However, by analogy, individuals with syndromic ACC have only a slightly higher risk of having a *de novo* chromosomal deletion when compared to patients with isolated ACC, suggesting that even the genetics of these isolated cases often arise from *de novo* highly penetrant genetic events (Sajan *et al.*, 2013).

Lessons can be learned from the study of intellectual disability, which affects 1–3% of humans (Maulik *et al.*, 2011) and, like ACC, is genetically heterogeneous (Piton *et al.*, 2013; Hu *et al.*, 2016). To date, more than 100 genes found on the X chromosome have been implicated in intellectual disability, many of which are included in diagnostic gene panels (Piton *et al.*, 2013). Recent concerted efforts towards large-scale whole exome sequencing in multiple intellectual disability cohorts continue to identify new intellectual disability genes. For example a recent large-scale study found mutations in *DDX3X* as one of the major causes of intellectual disability in females, accounting for between 1–3% of cases. Of note, 13/37 (35%) of patients with *DDX3X* mutations were also reported to have corpus callosum hypoplasia (Snijders Blok *et al.*, 2015).

At present, the relationship of intellectual disability to specific disorders of cerebral connectivity is poorly understood. An urgent need has thus arisen to correlate clinical genetic susceptibility and brain dysmorphology (by MRI and ultrasound) with the cognitive and neuropsychological outcomes of the child. To address this, an international consortium of researchers and clinicians has been established to pool and collect data on large cohorts of individuals with (any) cerebral malformation but, more specifically, with those of the corpus callosum or cerebral connectivity. The consortium is called the 'International Research Consortium for the Corpus Callosum and Cerebral Connectivity (IRC)'. Additional studies with current genetic tools will continue to unravel many of the genetic causes and subtypes of ACC, and will inform the ongoing development of targeted gene sequencing. This will translate into improved efficiency of diagnosis in ACC, which is still a primary issue in the field, and will lead to improved accuracy of foetal prognosis early in pregnancy.

Funding

The authors gratefully acknowledge the following funding sources: National Health and Medical Research Council Australia grant GNT1100443 (L.J.R. and E.H.S.) and a Principal Research Fellowship to L.J.R. National Institutes of Health USA grants NINDS 2R01 NS35129 (A.J.B.) and NINDS 5R01 NS058721 (E.H.S. and L.J.R.). T.J.E. is supported by a University of Queensland Research Scholarship and a Queensland Brain Institute Top-Up Scholarship.

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