



# Copy Number Variations Found in Patients with a Corpus Callosum Abnormality and Intellectual Disability

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**Objective** To evaluate the role that chromosomal micro-rearrangements play in patients with both corpus callosum abnormality and intellectual disability, we analyzed copy number variations (CNVs) in patients with corpus callosum abnormality/intellectual disability

**Study design** We screened 149 patients with corpus callosum abnormality/intellectual disability using Illumina SNP arrays.

**Results** In 20 patients (13%), we have identified at least 1 CNV that likely contributes to corpus callosum abnormality/intellectual disability phenotype. We confirmed that the most common rearrangement in corpus callosum abnormality/intellectual disability is inverted duplication with terminal deletion of the 8p chromosome (3.2%). In addition to the identification of known recurrent CNVs, such as deletions 6qter, 18q21 (including *TCF4*), 1q43q44, 17p13.3, 14q12, 3q13, 3p26, and 3q26 (including *SOX2*), our analysis allowed us to refine the 2 known critical regions associated with 8q21.1 deletion and 19p13.1 duplication relevant for corpus callosum abnormality; report a novel 10p12 deletion including *ZEB1* recently implicated in corpus callosum abnormality with corneal dystrophy; and) report a novel pathogenic 7q36 duplication encompassing *SHH*. In addition, 66 variants of unknown significance were identified in 57 patients encompassed candidate genes.

**Conclusions** Our results confirm the relevance of using microarray analysis as first line test in patients with corpus callosum abnormality/intellectual disability. (*J Pediatr* 2017;185:160-6).

The corpus callosum is the main commissure in the human brain connecting homotopic and heterotopic regions of the cerebral hemispheres.<sup>1</sup> Corpus callosum abnormality is among the most common brain malformations, affecting 1 out of 4000 newborns<sup>2</sup> and 2%-3% of individuals with intellectual disability.<sup>3,4</sup> Three major classes of corpus callosum abnormality are distinguished: complete agenesis, partial agenesis, and dysgenesis.<sup>5</sup> The corpus callosum abnormality may be associated with additional cerebral or extracerebral malformations or may be an isolated finding.<sup>6</sup> Intellectual disability ranging from mild to severe, epilepsy, and behavioral difficulties<sup>7,8</sup> are commonly associated with corpus callosum abnormality.

Genetic causes have been ascribed to 30-45% of corpus callosum abnormality, including chromosomal rearrangements (10%-20%) and mendelian conditions (30%).<sup>5,9</sup> These causes are characterized by their extreme heterogeneity with more than 300 different causative genes identified to date.<sup>9</sup> Over the past years, chromosomal analyses using microarray studies have identified numerous disease-causing copy number variations (CNVs) in multiple disorders, including

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CNVs	Copy number variations
DGV	Database of genomic variants
NF1	Neurofibromatosis type 1
<i>SHH</i>	Sonic hedgehog
VOUS	Variants of unknown significance

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syndromes with corpus callosum abnormality. O'Driscoll et al<sup>10</sup> provided a first genetic map, including several genomic loci involved in corpus callosum development. These loci may contain genes in which variations cause or predispose to corpus callosum abnormality.

The purpose of this study was to investigate chromosomal rearrangements in a well- characterized French cohort of 149 patients with corpus callosum abnormality and intellectual disability using SNP microarrays. We report here known and new likely pathogenic CNVs with candidate genes.

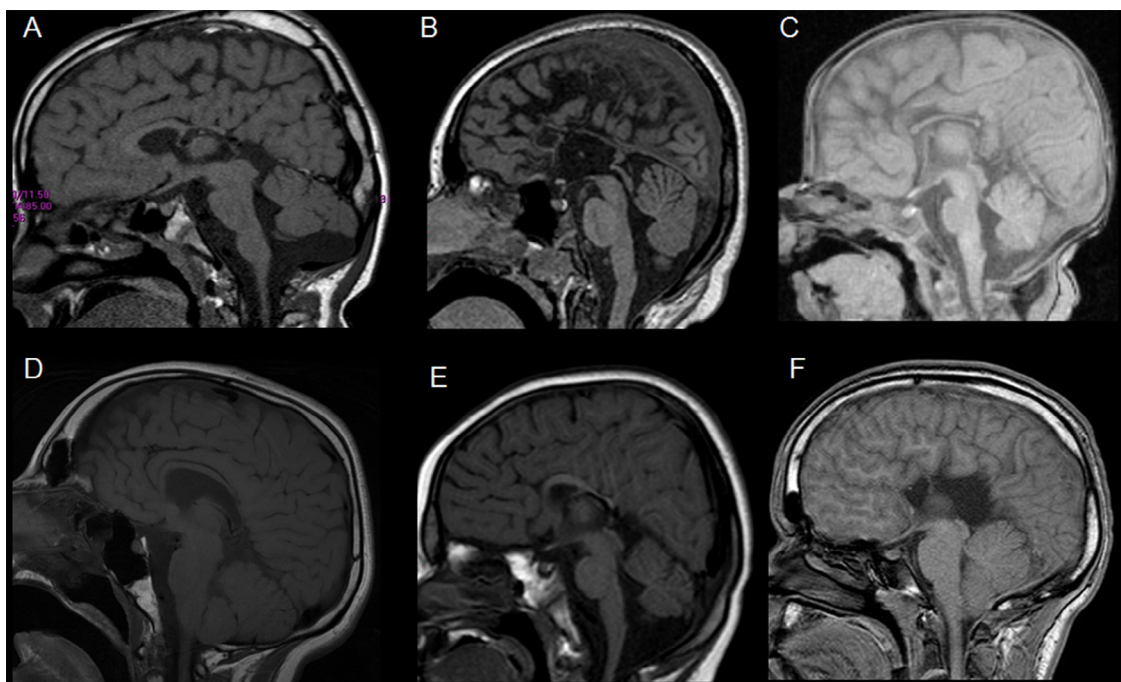
## Methods

Between 2009 and 2014, we ascertained prospectively 159 patients (from 3 to 41 years old), recruited in the French national study on corpus callosum abnormality/intellectual disability (Agénésie du Corps Calleux avec Retard Mental cohort). All parents signed an appropriate consent form for genetic analysis, in accordance with national ethic rules and recommendations of the National Heart, Lung and Blood Institute Working Group.<sup>11</sup> This project was submitted to the appropriate ethics committee (Comité de Protection des Personnes Ile-de-France).

All patients had corpus callosum abnormality (partial or complete agenesis or dysgenesis of the corpus callosum) on brain magnetic resonance imaging (Figure) and intellectual

disability or developmental delay for youngest patients. All brain magnetic resonance imaging were gathered in the coordinating center and ascertained collectively by a team comprising a radiologist, a neuropediatrician, and a geneticist to classify the corpus callosum abnormality into 3 categories: partial corpus callosum agenesis, complete corpus callosum agenesis, or dysgenesis of the corpus callosum. Complete corpus callosum agenesis was defined as the absence of corpus callosum, including the absence of any anatomic remnant, and partial corpus callosum agenesis as the absence of at least 1, but not all, regions of the corpus callosum. Dysgenesis of the corpus callosum was used to designate a complete corpus callosum (all anatomic regions are present) with an abnormal shape.<sup>5</sup> Corpus callosum abnormality was considered as associated (associated corpus callosum abnormality) when another brain malformation and/or another extracerebral rare malformation was discovered. When no other malformation was detected, corpus callosum abnormality was considered as isolated (isolated corpus callosum abnormality).

Corpus callosum abnormality was diagnosed either during the prenatal period ( $n = 71$ , 44.5%) or postnatally when the patients were referred for neuroimaging for neurodevelopmental delay or intellectual disability ( $n = 88$ , 55.5%). In all patients with a prenatal diagnosis, corpus callosum abnormality was confirmed by postnatal neuroimaging performed after 2 years of age. All patients had a clinical evaluation by a geneticist and a pediatric neurologist at the time of inclusion. The



**Figure.** Brain magnetic resonance imaging of patients with corpus callosum abnormality/intellectual disability. **A**, Partial corpus callosum agenesis in a patient carrying a 3q29 deletion. **B**, Complete corpus callosum agenesis in a patient carrying 14q12 deletion. **C**, Partial corpus callosum agenesis in a patient with invdupdel8p. **D**, Partial corpus callosum agenesis in a patient with 3p26 deletion. **E**, Dysgenesis of the corpus callosum in a patient carrying 18q21 deletion. **F**, Complete corpus callosum agenesis in a patient carrying 7q36 duplication.

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