

# FRYNS-LIKE MULTIPLE CONGENITAL ANOMALIES SYNDROME WITH 1,13 Mb CHROMOSOME 16P13.11 DELETION DETECTED BY ARRAY-COMPARATIVE GENOMIC HYBRIDIZATION

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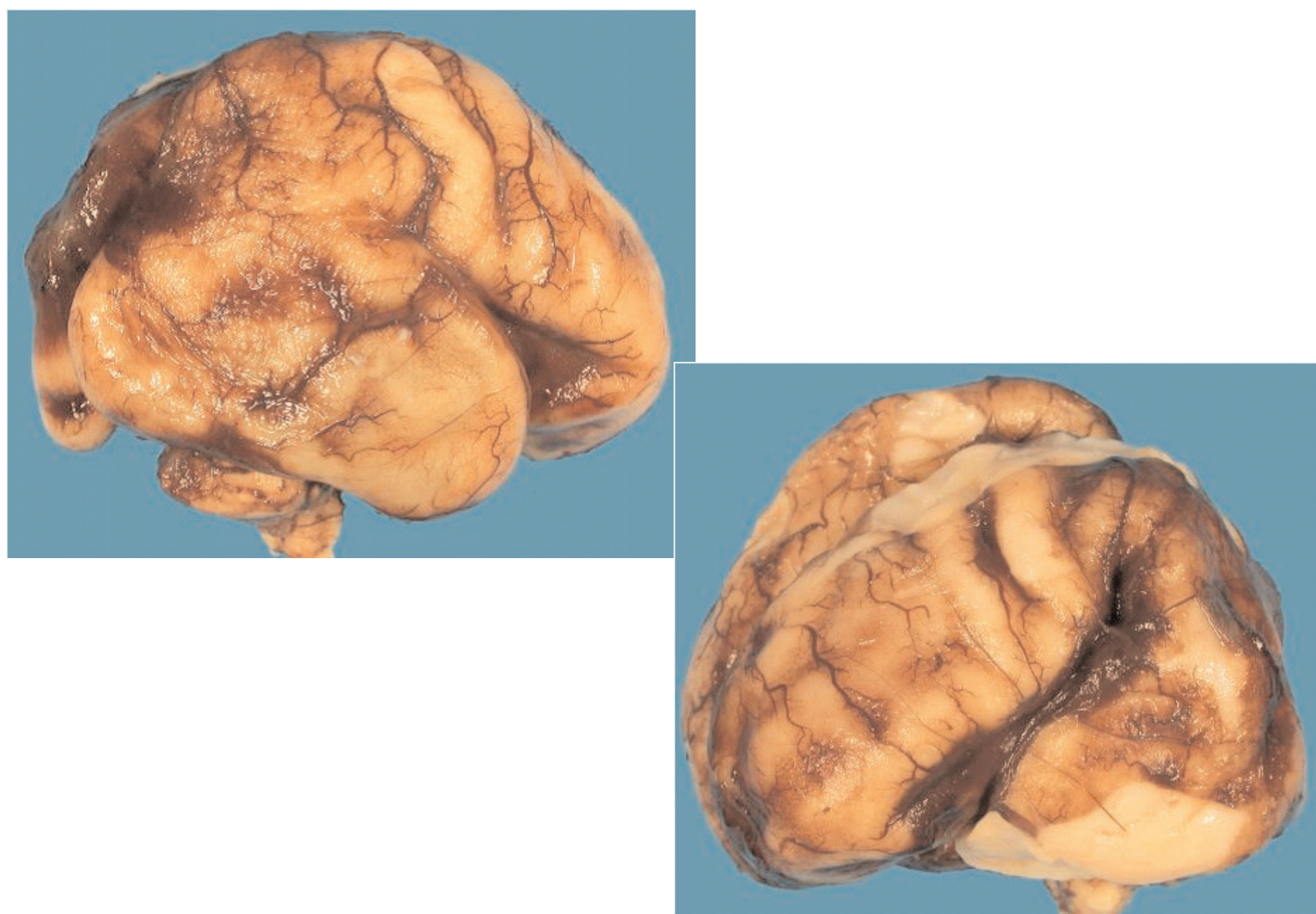
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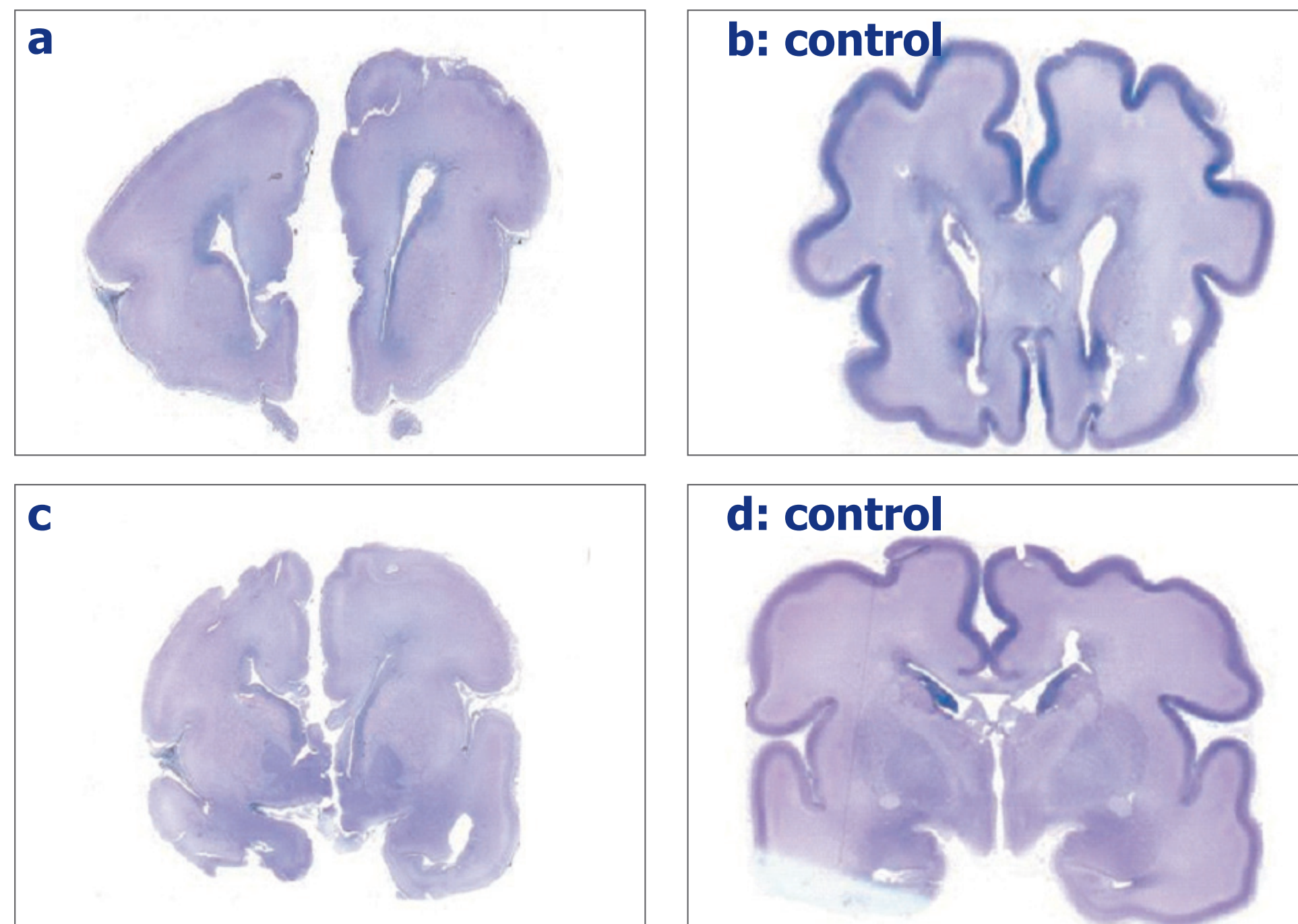
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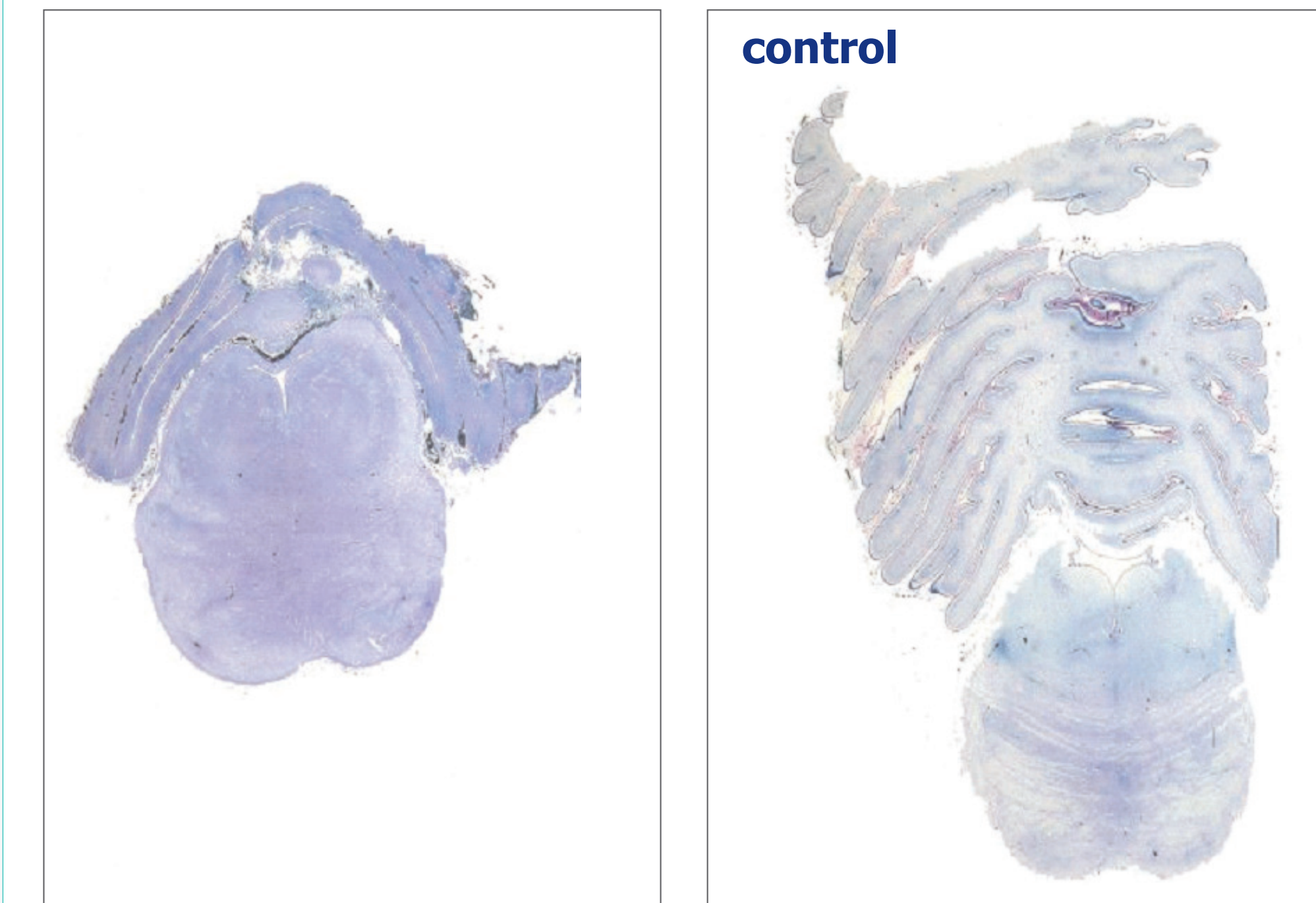
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**Fig.1:** Fetal brain at 27 weeks



**Fig.2:** Fetal brain histology: coronal sections (a, c) compared to control (b, d)



**Fig.3:** Hypoplastic cerebellum compared to control

## BACKGROUND

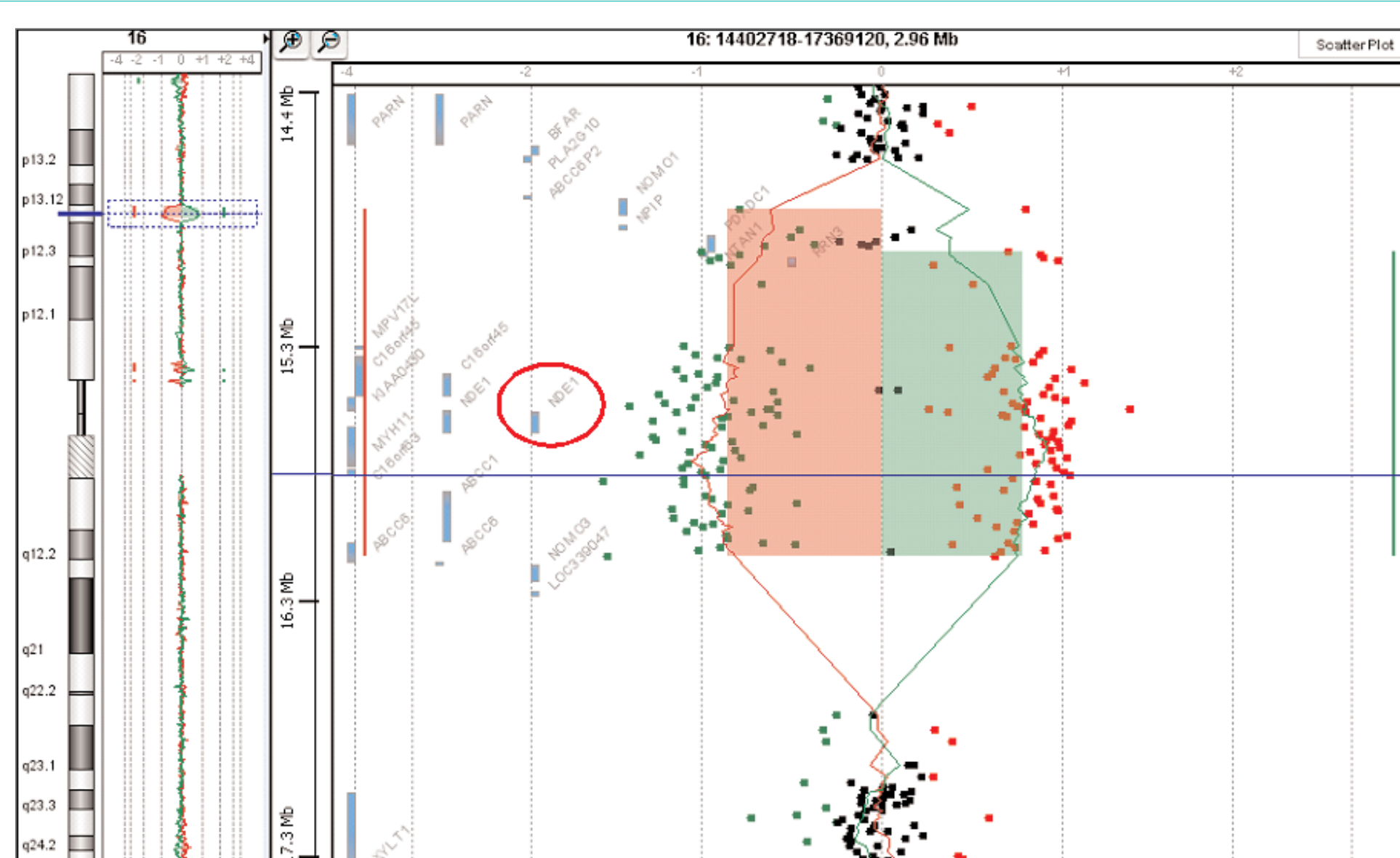
Genomic disorders are often caused by non-allelic homologous recombination between segmental duplications. Chromosome 16 is especially rich in a chromosome-specific low copy repeat, termed LCR16.

## CASE REPORT

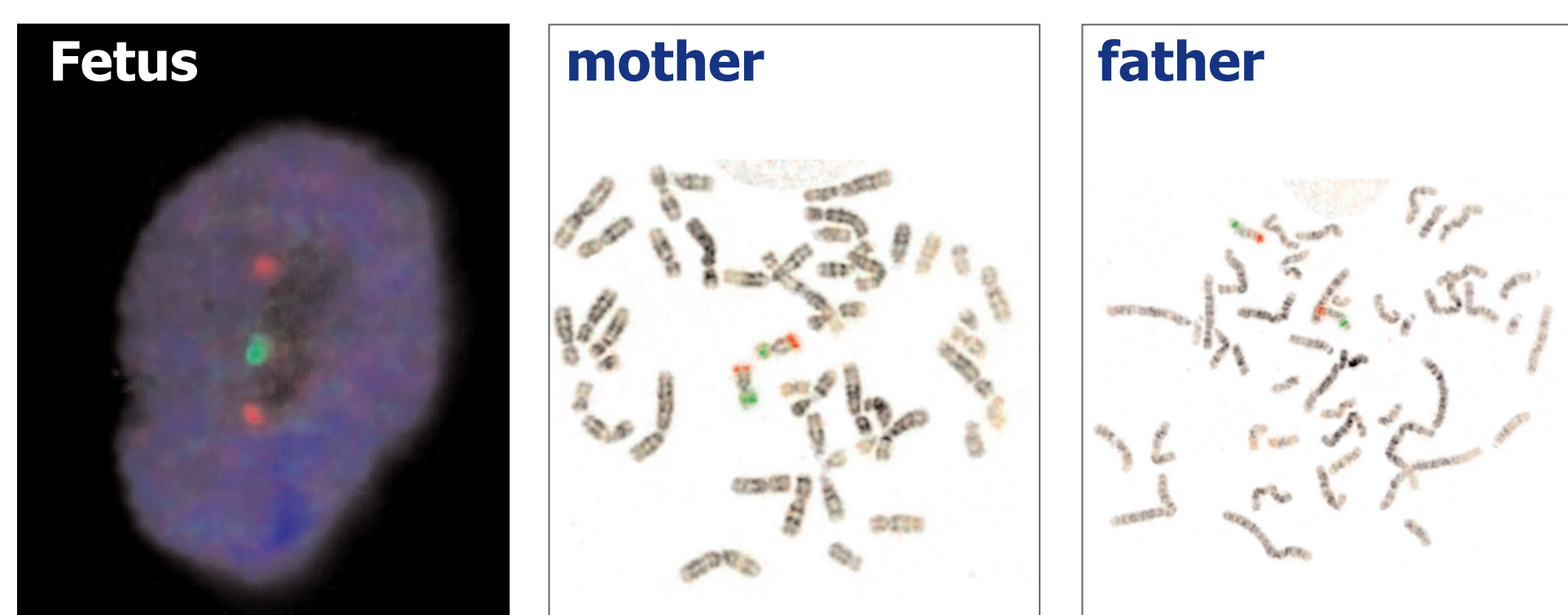
We present a 27-week fetus with Fryns Syndrome (FS)-like phenotype associating growth restriction, dysmorphic features with flat, coarse facies, depressed nasal bridge, long philtrum, retrognathia, hypoplastic ears, unilateral renal agenesis, uterine hemi-agenesis, costo-vertebral malsegmentation/fusion defects, hypoplastic terminal phalanges of fingers, pachygyria (Figure 1, 2), hypoplastic corpus callosum and cerebellum (Figure 3). He had normal karyotyping with G-banded chromosome analysis.

## METHODS

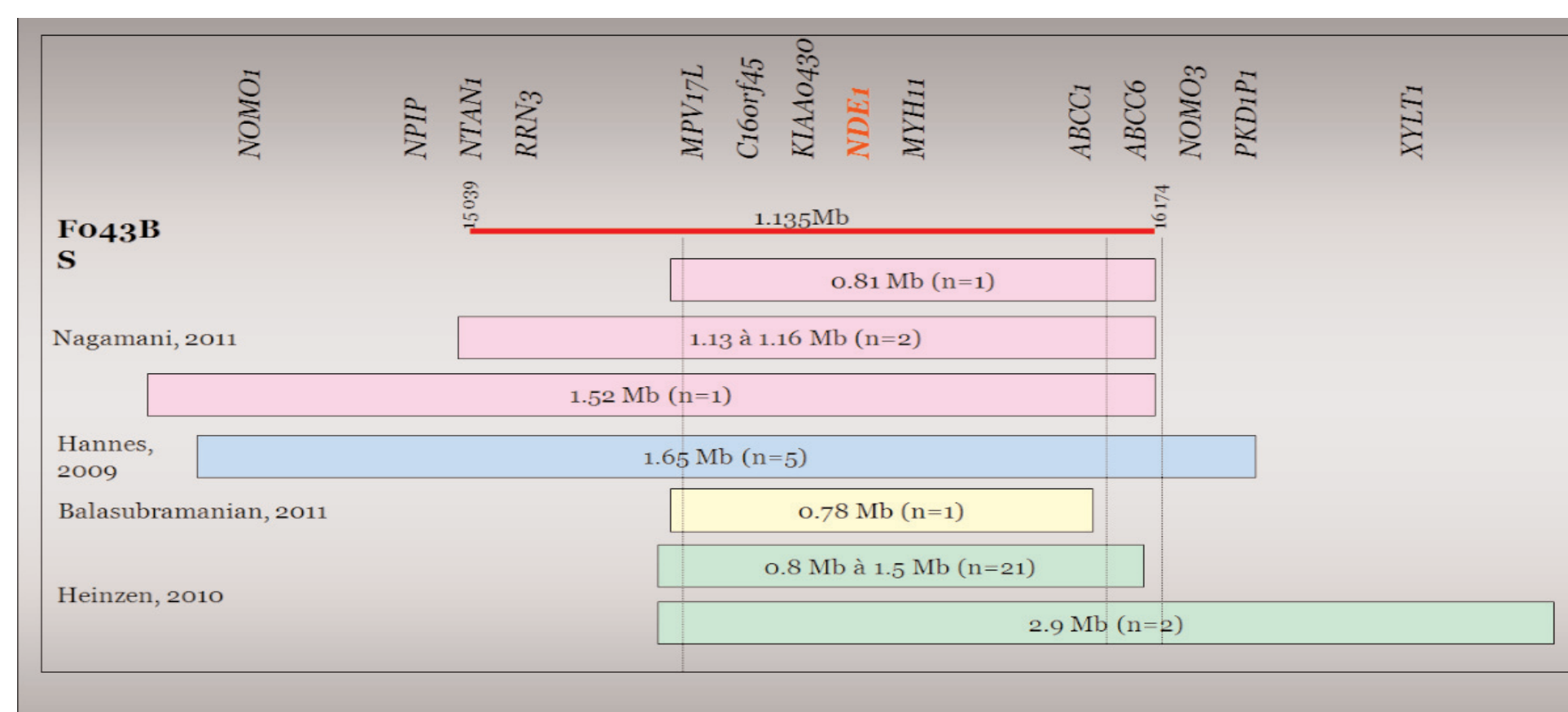
Oligonucleotide aCGH was performed with the Agilent Human Genome CGH Microarray Kit 180K, according to the manufacturer's instructions (protocol version 4.0), as previously described [Schluth-Bolard et al., 2008]. Data were analyzed with the CGH Analytics software platform (Agilent). Data were extracted with Feature Extraction 10.7.3.1 software and analyzed with WorkBench 5.0 software, with the following parameters: window 0.2 Mb, ADM2 threshold 6.0.



**Fig.4:** Array CGH profile from dye swap experiment showing the 1,13 Mb deletion in 16p13.11 including the NDE1 gene (red circle).



**Fig.5:** FISH experiment using RP11-380O18 BAC clone in green and the commercial 16qter probe in red (Cytocell).



**Fig.6:** Schematic diagram of the 16p13 chromosomal region including 16p13 microdeletion reported previously. Our patient size deletion corresponds to the red line (F043BS).

## RESULTS

Array CGH revealed a 1.13 Mb 16p13.11 deletion in the fetus between genomic positions 15,039,224-16,174,807 (hg18) (Figure 4). For confirmation of the a CGH data, we carried out FISH with the BAC clone RP11-380O18 (16p13.11) and 16qter (16qter48), control probe, from Cytocell company (Figure 5). This deletion occurred de novo, and should be presumed as a cause of this multiple congenital anomalies syndrome. This deletion includes several genes, in particular NDE1 (Figure 6). Recurrent deletions in 16p13.11 chromosomal region have been previously reported and have been associated with epilepsy, multiple congenital anomalies, and cognitive impairment. Recently, based on Nde1-null mice experiment, it was proposed that NDE1 have an essential role in human cerebral cortical neurogenesis. Moreover NDE1 deficiency causes both a severe failure of neurogenesis and a deficiency in cortical lamination. So, NDE1 haploinsufficiency could explain cerebral malformation observed in the fetus. Nevertheless other malformations described in the fetus have not been previously reported in patients with this 16p13.11 deletion.

## CONCLUSION

We conclude that phenotypes similar to FS, however without diaphragmatic hernia, can be caused by a new clinically identifiable chromosome deletion syndrome at 16p13.11 including growth retardation, genito-urinary malformations, skeletal anomalies with costo-vertebral malsegmentation defects and terminal phalangeal hypoplasia, as well as cerebral anomalies with pachygyria, hypoplastic corpus callosum and cerebellum. This case expands the clinical phenotype described in patient with 16p13.11 microdeletion. We also conclude that array CGH should be performed prior to the definite diagnosis of FS in order to provide a causal explanation and an accurate genetic counselling to the family.

## REFERENCES

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## CORRESPONDANCE TO

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