Dysgyria, brainstem asymmetry and midline anomalies: featuring fetal brain findings associated to a dominant TUBB3 mutation

**OBJECTIVES**
The term dysgyria refers to an abnormal gyral pattern in which the cortical surface is normally layered but the sulci course at unusual angles and depths. The association with hypoplastic CC, vermis and brainstem asymmetry was identified in patients with tubulinopathies. The aim of this study was to describe the prenatal neuroimaging findings of patients with a novel TUBB3 mutation.

**METHODS**
Four patients presenting a familial dominant TUBB3 mutation – two fetuses, a 3.5 years-old sibling and their mother. The index case was referred to neurosonographic scan at 32w for asymmetric ventriculomegaly. The pregnancy was terminated at 34w without genetic investigation. A second fetus presenting similar findings was studied and compared to the first-born child and the mother. Whole exome sequencing determined the final diagnosis - a novel mutation in the TUBB3 gene in the mother and children (pThr312Met, g.90001794c>t). Characteristic neuroimaging features were identified and compared.

**RESULTS**
Pontine and vermian hypoplasia and brain asymmetry with abnormal sulcation pattern were described in US and MRI of the first fetus. PM study identified a pattern compatible with dysgyria. By 26 weeks of the 3rd pregnancy, the first child who was previously considered healthy, presented yet with developmental delay and cerebellar commitment. The second fetus presented with recurrent findings of supratentorial asymmetry, dysgyria, irregular frontal interhemispheric fissure, small corpus callosum and vermis, asymmetric brainstem and unilateral ventriculomegaly with abnormal frontal horn at US and MRI. With regard to the clinical presentation of the mother (normal intelligence and very subtle cerebellar findings) and the first child (mild developmental delay), the couple was counselled and decided to continue the pregnancy. Follow up at 1.5 years reveals normal neurological development.

**CONCLUSIONS**
The association of abnormal gyral pattern that does not attend the imaging requirements for known entities as polymicrogyria and pachgyria, with callosal and vermian hypoplasia and brain asymmetry are very suggestive of tubulinopathies and must be suspected even in fetal life. Whole exome sequencing may identify the main mutations and aid for proper counselling and management of these challenging cases.