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TUBULINOPATHIES IN MALFORMATIONS OF THE CEREBRAL CORTEX

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Aims To further characterise the ‘tubulinopathy’ spectrum of overlapping brain malformations (including lissencephaly, polymicrogyria and mildly simplified gyral patterning) that arise from tubulin gene variations affecting neuronal proliferation, migration and post-migrational organisation during cerebral cortex development.

Method A cohort of affected cases (n=13) with mild to unaffected cerebral cortex patterning, but with highly recognisable basal ganglia, corpus callosal and cerebellar malformations, were screened for gene-variations in a number of human brain-expressed tubulin genes.

Results We describe two unrelated individuals with mildly simplified gyration and infantile-onset epilepsy, harbouring de novo variants that affect adjacent amino acids in a novel tubulinopathy gene, TUBB2A. We also report a further four mutations in TUBA1A, TUBB2B and TUBB3 (historically associated with lissencephaly, polymicrogyria and polymicrogyria/congenital fibrosis of the extraocular muscles respectively) in individuals with normal gyration but extra-cortical abnormalities characteristic of tubulin gene involvement.

Conclusion We describe a highly stereotyped brain phenotype caused by mutations in four different genes (TUBA1A, TUBB2B, TUBB3 and a novel gene, TUBB2A), sharing high sequence homologies but with distinct spatial-temporal expression patterns. All beta-tubulins highly expressed during cerebral cortex development are now associated with brain malformations.