

# Tuberous sclerosis: genes, brain, and behaviour

Major conceptual advances in the area of paediatric neurosciences have been made in the last few years, mainly due to both molecular genetics, whereby the neurological phenotypes are now tentatively correlated with specific genotypes, and functional neuroimaging, whereby the neurological signs can be mapped to specific regions or circuits in the brain.

Tuberous sclerosis (TSC), a common multisystem genetic disorder, continues to be an exciting area of research for all those interested in molecular genetic programming of brain development. TSC also provides an important model for investigating relationships between functions of genes, strategically located brain abnormalities, and mechanisms of cognition and behaviour. Gene mutations in either of the two TSC genes influence neural precursors between weeks 7 and 20 of gestation, disrupting the mTOR pathways, and resulting in abnormal cell differentiation and dysregulated control of cell size. These cells then migrate in an atypical fashion to the cortex to generate an abnormal collection of inappropriately positioned neurons. Characteristic giant cells are found in three types of brain lesions (cortical tubers, subependymal nodules, and giant-cell astrocytomas). However, in TSC there is evidence of widespread cortical disorganization and structural abnormalities throughout the brain, not just associated with tubers and nodules. Even areas that appear normal on magnetic resonance imaging may be microscopically affected.

Individuals with TSC typically present a variety of neuropsychiatric features including epilepsy, cognitive impairment, and behavioural disorders.<sup>1</sup> As the causal genes are recognized, and we are beginning to understand the functions of the proteins they encode, TSC appears to be a good model for the investigation of the relationship between the genotype and the different neurological phenotypes. Besides the overlap of many features of patients with TSC types 1 (TSC1) and 2 (TSC2), the mutation data accumulated provide evidence for specific clinical differences. Patients with sporadic TSC2 mutations had, on average, more severe disease in comparison with patients with sporadic TSC1 mutations, with an overall increased incidence of seizures including infantile spasms, more severe intellectual impairment, and a higher occurrence of autism. The various parts of TSC genes have diverse functions, and it is likely that different mutations have diverse physiological effects. This will open an avenue for child neurologists to study new correlations between the genotype and the phenotypes.

Around 45% of individuals with TSC have some degree of cognitive impairment, ranging from profound disabilities to mild learning problems. In addition, around 50% of children with TSC show behavioural problems, in the form of autism and/or attention-deficit-hyperactivity disorder (ADHD). Autism and ADHD are behaviourally defined disorders of the brain that are under-recognized, underdiagnosed, and often untreated in TSC patients. The link between brain abnorm-

alities and behavioural manifestations is currently being explored. Most of the neurobehavioural phenotypes exhibited by children with TSC are organically determined, and might also reflect direct effects of the abnormal genetic programme. Recent evidence shows that loss of TSC1 or 2 gene products triggers enlargement of somas and dendritic spines, and alters the properties of glutamatergic synapses in neurons.<sup>2</sup> Both pathological abnormalities of dendritic spines and abnormalities in glutamatergic neurotransmission can be associated with the autism phenotype. The application of functional neuroimaging with alpha-methyl-tryptophan positron emission tomography has shed new light on the mechanisms involved in autism associated with TSC, pointing towards a dysfunction of the fronto-striatal circuitry.<sup>3</sup> Frontal brain systems might be most consistently disrupted by TSC-related neuropathology, thus leading to abnormalities in attentional-executive skills and behavioural disorders. In addition, the TSC2 gene product, tuberlin, is highly expressed in frontal and temporal brain regions involved in the behavioural phenotype of the autistic disorder.

Efforts to integrate the behavioural, cognitive, structural, and functional levels of investigation hold great promise in TSC. This disease is proving to be a particularly informative model for studying contemporary issues in developmental neuroscience, and could be a prototype for understanding complex human behaviours, elucidating in a fundamental manner how the brain works. Studies of the psychiatric manifestations of neurological diseases, as well as neurobiological bases of psychiatric conditions, have produced a remarkable amount of data regarding the neural correlates of behavioural disorders. Today most child psychiatrists believe that autism and ADHD are brain disorders; child neurologists never doubted it.<sup>4</sup> Unprecedented developments in paediatric neuroscience are blurring boundaries between neurology and psychiatry. The two fields may in fact turn out to be the same in many ways; after all, we only have one brain.

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Paolo Curatolo

## References

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