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Nuclear Factor One X Mice model for Malan syndrome: the less the better

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Malan syndrome (OMIM 614753) is distinguished by a characteristic facial phenotype, growth disturbance, intellectual disability, and behavioral issues. It is caused by heterozygous sequence variants or deletions of the gene *NFIX*, located on chromosome 19p13.2. The syndrome is allelic to Marshall-Smith-syndrome (OMIM 602535), which is characterized by unusual face, distinctive dysostosis, postnatal failure to thrive with ultimate short stature, respiratory insufficiency, and moderate to severe developmental delay [1]. Although clinical assessments have determined the underlying symptoms of Malan syndrome, the fundamental mechanisms contributing to them remains undefined. In particular enlarged head circumference and intellectual disability seems to be a constant feature as recently reported in a review of a consistent new patients' series [1]. However, the cause of macrocephaly in these patients remains unclear.

Megalencephaly defines an increased growth of cerebral structures related to dysfunctional anomalies during the various steps of brain development in the neuronal proliferation and/or migration phases or as a consequence of postnatal abnormal events that cause excessive cerebral growth. In contrast, in macrocephaly, the increased head circumference is linked to various events that can result in an increase of orbito-frontal head circumference for age, including anomalies of bone skull structures, subdural fluid collections, hydrocephalus, intracranial masses, and arteriovenous malformations. Sometimes, megalencephaly and macrocephaly may coexist in the same individual especially in syndromic patients, so it is possible that the macrocephaly phenotype featured in Malan syndrome patients is due to megalencephaly [2].

In this issue of *EBioMedicine*, Oishi and colleagues [3] used *Nfix* heterozygous mice as a model to investigate some typical aspects of Malan syndrome. By using in-depth neuroimaging and histological analyses using adult *Nfix* +/− mice they revealed that *Nfix* heterozygosity in mice results in an overall increase in the number of neurons and glia within the adult neocortex. Combining the MRI volumetric and immunohistochemical analyses they showed that *Nfix* heterozygosity culminates in elevated neural and glial cell number within the adult neocortex leading to an expansion of cortical thickness and culminating in increased neocortical volume. Although no prove, it may be reasonable that the increase in cell number is likely due to prolonged self-renewal of neural stem cells in the embryonic mouse forebrain, resulting in the overproduction of neurons and astrocytes as reported by Harris and colleagues [4] who evidenced a significant delay in Neuronal IPC production in mice lacking the transcription factor nuclear factor I/X (Nfix) and prolongation of the neurogenic window, resulting in an increased number of neurons in the postnatal forebrain.

Malan patients typically show a peculiar neurobehavioral phenotype characterized by moderate to severe intellectual disability, autistic spectrum disorder traits, high anxiety levels, sensitivity to noise, and auto/etero aggressive behavior [1,5–7]. Through DTMRI tractography studies, the authors evidenced aberrant microstructural organization of the major forebrain commissure. This last finding addressed them to perform a more in-depth analysis of brain connectivity using the in silico NBS toolbox and compare each connection of the structural connectome to identify individual nodes that were significantly altered in the *Nfix* +/− brain compared to wildtypes. Their results were surprising: they identified significantly abnormal connections within structures clearly associated with memory consolidation, emotional processing, such as anxiety, fear and aggression, and stress-response [8,9], They eventually demonstrated Deficits in learning and memory function in *Nfix*+/− mice likely underlined by reduced hippocampal neurogenesis [10], which is known to be critical for learning and memory function. Overall this work on both brain structural and functional mouse model stresses the urgency of detailed cognitive and behavioral studies in Malan syndrome patients to better define abnormal developmental processes leading to Malan syndrome and to eventually better provide future cognitive therapies on Malan patients for correction of deficits in cortically-controlled behavior. It also provides new hints on possible role of *NFIX* in self-renewal of NSCs and, in general, on hypothetical cell overproduction and increase stem cells reservoir at the basis of this overgrowth syndrome.

Conflict of interest

The authors declare no conflicts of interest.

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