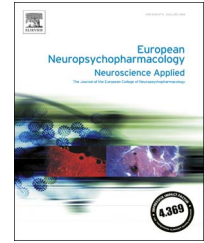




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REVIEW

Translating molecular advances in Down syndrome and Fragile X syndrome into therapies[☆]

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[☆]We dedicate this review to the memory of Annette Karmiloff-Smith who passed away at the beginning of year 2017.

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Abstract

Ongoing treatments for genetic developmental disorders of the central nervous system are mostly symptomatic and do not correct the genetic cause. Recent identification of common mechanisms between diseases has suggested that new therapeutic targets could be applied across intellectual disabilities with potential disease-modifying properties. The European Down syndrome and other genetic developmental disorders (DSG2D) network joined basic and clinical scientists to foster this research and carry out clinical trials. Here we discuss common mechanisms between several intellectual disabilities from genetic origin including Down's and Fragile X syndromes: i) how to model these complex diseases using neuronal cells and brain organoids derived from induced pluripotent stem cells; ii) how to integrate genomic, proteomic and interactome data to help defining common mechanisms and boundaries between diseases; iii) how to target common pathways for designing clinical trials and assessing their efficacy; iv) how to bring new neuro-therapies, such as noninvasive brain stimulations and cognitive training to clinical research. The basic and translational research efforts of the last years have utterly transformed our understanding of the molecular pathology of these diseases but much is left to be done to bring them to newborn babies and children to improve their quality of life.

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1. Common mechanisms causing intellectual disabilities

Down syndrome (DS) and Fragile X syndrome (FXS) are the most common genetic causes of intellectual disability (ID), for which no approved therapies are available yet. These disorders are associated with neurological complications including cognitive deficits that lead to mild to profound impairment in intellectual functioning. Current therapeutic approaches focus on behavioral therapy, educational mainstreaming and off-label medications that mitigate only a limited set of symptoms, such as hyperactivity, some cognitive deficits, seizure and anxiety. Individuals with DS, mostly males and approximately 30% of females affected by FXS, have significant intellectual deficits and social dysfunctions in adulthood, with deleterious impact on affected individuals, families and society (Lott and Dierssen, 2010; Maurin et al., 2014).

DS and FXS show striking similarities and differences. Both intellectual disabilities are genetic developmental disorders characterized by defects in structural and synaptic plasticity due to alterations in specific molecular pathways leading to cognitive impairment. Interestingly, neuroanatomical abnormalities are probably generated early during

development in the brain of patients and in mouse models for DS and FXS, and may be associated to defects in proliferation and/or differentiation of neural progenitors (Guidi et al., 2014; Castren, 2016), pointing out a critical role of Fragile X Mental retardation Protein (FMRP) and human chromosome 21 genes during neurogenesis. Children with DS (aged between 5 and 23 years) have smaller overall brain volumes with smaller cerebellum and larger subcortical grey matter volumes (Pinter et al., 2001), while children with FXS (aged between 18 and 42 months) have larger brain volumes and display enlargement in the temporal lobe white matter, cerebellar gray matter and caudate nucleus, but have a smaller amygdala (Hazlett et al., 2012). In a study analyzing boys with FXS aged 1 to 3 years, the authors found, as in the adult patients, increased caudate, fusiform gyrus, and thalamus grey matter volume (GMV) as well as reduced GMV in the superior temporal gyrus, hippocampus, insula, hypothalamus, and orbitofrontal cortex, and medial and lateral prefrontal cortices (Hoeft et al., 2010). At the cellular level, children and adults with DS show dendritic atrophy with a significant decrease in dendritic branching, length and spine density (Takashima et al., 1989). FXS patients exhibit increased density of immature dendritic spines that appear longer, denser and

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