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The chromatin basis of neurodevelopmental disorders: Rethinking dysfunction along the molecular and temporal axes

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A B S T R A C T

The complexity of the human brain emerges from a long and finely tuned developmental process orchestrated by the crosstalk between genome and environment. Vis à vis other species, the human brain displays unique functional and morphological features that result from this extensive developmental process that is, unsurprisingly, highly vulnerable to both genetically and environmentally induced alterations. One of the most striking outcomes of the recent surge of sequencing-based studies on neurodevelopmental disorders (NDDs) is the emergence of chromatin regulation as one of the two domains most affected by causative mutations or Copy Number Variations besides synaptic function, whose involvement had been largely predicted for obvious reasons. These observations place chromatin dysfunction at the top of the molecular pathways hierarchy that ushers in a sizeable proportion of NDDs and that manifest themselves through synaptic dysfunction and recurrent systemic clinical manifestation. Here we undertake a conceptual investigation of chromatin dysfunction in NDDs with the aim of systematizing the available evidence in a new framework: first, we tease out the developmental vulnerabilities in human corticogenesis as a structuring entry point into the causation of NDDs; second, we provide a much needed clarification of the multiple meanings and explanatory frameworks revolving around "epigenetics", highlighting those that are most relevant for the analysis of these disorders; finally we go in-depth into paradigmatic examples of NDD-causing chromatin dysregulation, with a special focus on human experimental models and datasets.

1. Introduction

Neurodevelopmental Disorders (NDDs) constitute a broad spectrum of diseases originated during the development of the central nervous system (CNS). They are characterized by an early childhood onset leading to varying degrees of neuropsychiatric impairment, often in combination with a plethora of accompanying manifestations, whose specific configurations represent both a diagnostic and therapeutic challenge.

In this review we focus on NDD caused by genetic alterations of high, usually complete penetrance and characterized by often overlapping phenotypes. Importantly, the causative mutations target several convergent molecular axes, with genes either belonging to the same class (e.g. lysine demethylases) or operating in the same molecular pathway (e.g. Polycomb-mediated chromatin regulation). The genetic causes of a major NDD class, such as the Autism Spectrum Disorders (ASD), provide an examplary case. The Simons Foundation Austim Research Initiative (SFARI) currently lists 910 genes whose mutations lead to syndromic and non-syndromic ASDs. Following a Gene Ontology (GO) analysis of these genes (Fig. 1), a strong statistical enrichment emerges for many categories related for neuronal activity and function as well as for gene expression control. Indeed, 87 out of 910 genes are involved in molecular functions such as “demethylase activity”, “transcription coactivator activity”, “transcription factor activity”, “direct ligand regulated sequence-specific DNA binding”, and “chromatin binding”, which highlights the pivotal role of the gene expression regulation in mediating common Gene Regulatory Networks (GRNs) in vulnerable cell types, thus constituting the basis of widespread genetic dysregulation and its overlapping phenotypical manifestations.

As the distinctively human features affected in NDDs, in terms of cognition and behaviour, are arguably linked to the mechanisms engaged in cortical expansion (Rakic, 2009), we first focus on the specific susceptibilities of human cortex development. Next, we mobilize the most rigorous and productive notions of epigenetics and clarify their importance for NDD, considering the relevance of gene expression

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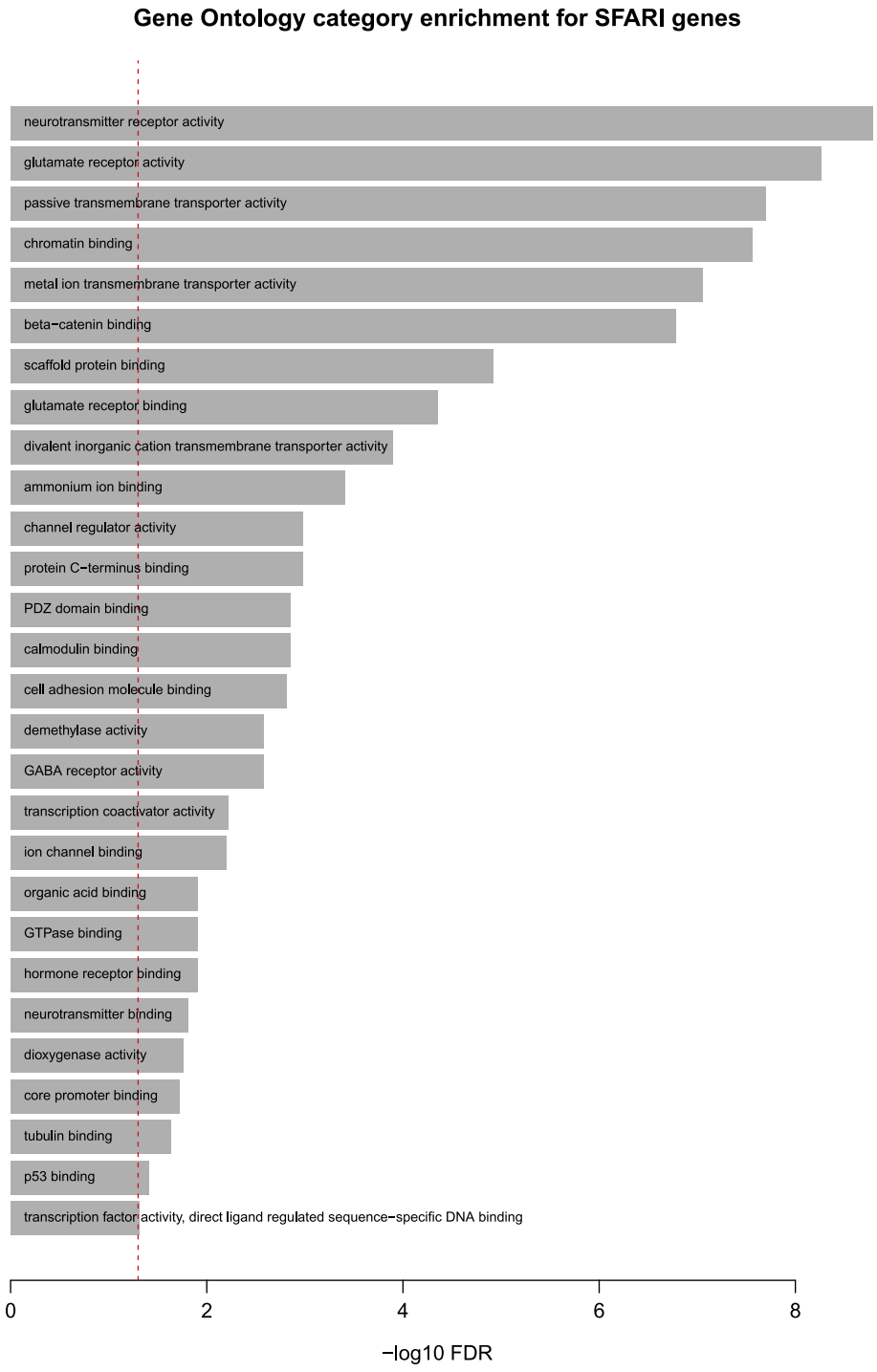

Fig. 1. Gene Ontology analysis of SFARI genes responsible for ASDs. The GO was performed using the WEB-based GEne SeT AnaLysis Toolkit (http://www.webgestalt.org/) with an Overrepresentation Enrichment Analysis. Gene ontology was used as a functional database. The gene list contains 910 user IDs in which 902 user IDs are unambiguously mapped to the unique Entrez Gene IDs and 8 user IDs are mapped to multiple Entrez Gene IDs or could not be mapped to any Entrez Gene ID. The GO Slim summary are based upon the 902 unique Entrez Gene IDs. Among the 902 unique Entrez Gene IDs, 694 IDs are annotated to the selected functional categories and also in the reference gene list, which are used for the enrichment analysis. The analysis was performed with the following parameters: Minimum number of Entrez Gene IDs in the category:1; Maximum number of Entrez Gene IDs in the category:2000; FDR Method:BH; Significance Level: FDR $<$ 0.05.

control in their pathogenesis. On the basis of this framework, we then undertake an exhaustive review of the mechanisms of gene expression regulation whose derangements have been causally linked to NDDs. Specifically, to help the reader appreciate how the interplay of epigenetic mechanisms underlies the molecular-phenotypical convergence, we review the molecular functions and physiological roles of histone methylation, acetylation, phosphorylation, DNA methylation, and nucleosome remodeling, and we underscore the importance of the dynamic balance of each of these mechanisms in the NDDs associated to them.

1.1. Vulnerable stages of human neural development

The human cortex depends on two waves of cell proliferation. First, symmetrical divisions at the ventricular and subventricular areas, 10 times more prolonged in humans than in rodents, are responsible for the expansion of the progenitor pool, resulting in the enlarged subventricular zone (SVZ) in the cortex and subgranular zone (SGZ) in the hippocampus. Later, a stage of asymmetric neurogenic divisions, 20 times longer in humans, determines the number of neurons in the different cortical layers (Florio and Huttner, 2014). Human cortical neurogenesis occurs predominantly during gestation from week 5-6 post-conception, but may continue up to 2.5 years of age (Florio and Huttner, 2014). The prolonged unfolding of neurogenic potential, along