

THE RAISE OF NEURODEVELOPMENTAL DISORDERS (NDS): FROM GENETICS TO EPIGENETICS

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SUMMARY

NDS are a collection of disorders that appear in the early stages of development and are variously associated with cognitive and behavioral dysfunctions. The strong heritability of these conditions (in particular autism and schizophrenia) argues in favor of a genetic origin. On the other hand, the massive increase in NDS implies a preponderant role of environmental factors and epigenetic mechanism (Panisi et al. 2021).

Key words: epigenetics - fetal programming - natural genetic engineering - CNVs

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From a neurobiological point of view, autism involves early exuberant growth of white matter and dysfunctions of neural networks that may be related to early (embryo-fetal) disturbances of neuronal differentiation and migration processes, in particular concerning the prefrontal regions and the temporal cortex, where social, emotional, communicative and linguistic functions are located. Interestingly, some genes that may have facilitated the expansion of the human brain during phylogeny are implicated in autism (Jones 2014). However, it is now well established that genetic variants associated with NDS can only explain a small part of the estimated inheritance and that hundreds of loci are involved. New exome sequencing (NGS) technology has identified many rare variants found only in children and, at least in some cases, in parental gametes (*de novo* mutations) (Garrido et al. 2021). These variants often do not refer to coding sequences and there is no obvious gene nearby. Regulatory functions are often associated with many of these altered sequences; for many others, these are only assumptions. It is also relevant that among the sequences involved emerge those encoding microRNAs (Abu-Elneel et al. 2008), which can regulate the function of many genes, participate in complex epigenetic modifications (*natural genetic engineering*) and determine changes of the same DNA sequence (CNVs) likely to be reactive to environmental exposures (*exposome*). The growing body of research into these complex molecular mechanisms has documented the preponderant role of epigenetics, which is the science that studies the mechanisms that regulate gene expression and, most importantly, genome programming in the early stages of life (*fetal programming*) (Burgio 2015).

Many rare genetic variants overlap between different disorders such as ASD and intellectual disability (ID), but also schizophrenia and bipolar disorder, which necessitates a "spectrum approach", linking previously disjointed conditions (Ameis et al. 2016). In

addition, the same *de novo* genetic variants, primarily CNVs, are involved in more than one psychiatric disorder and involve the same chromosomal loci often increasing the risk of disease in both states, deletion or duplication (Kushima et al. 2018).

Indeed, if genetics continues to gain in importance in this field, thanks to the great advances made in DNA sequencing, the field of psychiatric epigenetics has greatly improved in recent years by offering a functional context and means to better assess the non-genetic elements and environmental factors contributing to these emerging disorders (Dall'Aglio et al. 2018). Indeed, maternal malnutrition, early adversities, immune activation, atmospheric and food chain pollution can increase the risk of mental illnesses through epigenetic modifications interacting with a predisposing genetic background.

An interesting picture emerges, according to which many NDS, especially those characterized by the greatest increase and documented heredity, especially autism spectrum disorders, are said to have both genetic, epigenetic and environmental origins. In particular, certain environmental and pollutant factors such as endocrine disruptors (EDCs) can influence fetal programming, acting as (pseudo) morphogens and inducing the expression of rare genetic variants, associated with a high relative risk (Frye et al. 2012). Although these rare variants affect many different pathways, evidence is mounting on those that directly or indirectly control neurogenesis, chromatin remodeling, neuron differentiation and proliferation (Wnt signaling), and synaptogenesis (Mullins et al. 2016).

Acknowledgements: None.

Conflict of interest: None to declare.

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