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Editorial

Autism, Still A Medical Mystery?

Running Title: Autism Spectrum Disorder (ASD) and Genetic Features: Importance in Clinical Medicine!

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In 1943, the well-known child psychiatrist, Leo Kanner, announced his discovery of eleven cases of a new mental disorder [1]. He noted that «the condition differs markedly and uniquely from anything reported so far...»This condition soon became known as *autism*.

Autism spectrum disorder (ASD) is defined by impaired social interaction as well as impaired language and communication accompanied by stereotyped/heartbreaking behavioral traits and increased restricted repetitive behaviors [2]. ASD describes a range of conditions (e.g. autism, social and communication deficits, Asperger disorder, childhood disintegrative disorders, pervasive developmental disorders, and rare syndromes such as such as fragile X and Rett syndrome) [3] classified as neurodevelopmental disorders in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (*DSM) (http://www.dsm5.org/Pages/Default.aspx).

Recent epidemiology studies (http://www.autism-society.org/what-is/facts-and-statistics/) relate that: (i) about 1% of the world population has ASD; (ii) the prevalence of autism in U.S. children was estimated at 1 in 68 births in 2010, and has increased by 119.4 percent from 2000 (1 in 150) becoming the fastest-growing developmental disability and so a major public health issue with an annual cost over $200 billion; (iii) More than 3.5 million Americans live with an ASD.

In autism (MIM 209850), the problem usually emerges in early childhood (2 years old or before) and typically includes a lack of communication; This condition differs from schizophrenia in which the language problems usually occur in adolescence and adulthood and presents as disorganized speech [4]. In ASD patients, early diagnosis, appropriate behavioral therapies and rehabilitation treatments significantly affect the prognosis [5]. It is noteworthy that autism is a multifactorial neurodevelopmental disorder affecting more males than females who are affected only when they cross a higher biological threshold under a multifactorial genetic hypothesis [6]. Moreover, autism has a high heritability, although much remains unclear. In fact, this disorder can be studied as a mystifying collection of genetic variants. Emerging lines of research, integrating systematically findings of multiple levels of genomic data and studies of mouse models, are converging to show how opposing genetic pathways and clinical features can lead to this relatively common disorder. Perhaps, this lays important groundwork in understanding the biology of this complex and etiologically heterogeneous neuropathology. The recent studies highlight the period of fetal development and the processes of chromatin structure, synaptic function, and neuron-glial signaling [2]. This is to say that occurrence of autism is likely developmentally regulated *via* interaction between the genome and the environment [4].

Indeed, recent studies implicate chromatin modifiers in ASD through the identification of recurrent *de novo* loss of function mutations in affected individuals. ASD risk genes [(i.e. *CHD8* (chromodomain helicase DNA binding protein 8, 14q11.2) binding genes such as *GRIN2B* (glutamate receptor, ionotropic, N-methyl D-aspartate 2B, 12p12) [7]] are co-expressed in human mid-fetal cortex, suggesting that ASD risk genes converge in specific regulatory networks during neurodevelopment [8]. Interestingly, one of the more frequent genetic anomalies is found on chromosome 15 (i.e. duplicated or triplicated region 15q11-q13 where several genes such

as maternally expressed *UBE3A* (Ubiquitin-protein ligase E3A) linked to Angelman syndrome, *MECP2* (methyl CpG binding protein 2) linked to Rett syndrome, and the non-imprinted *GABRB3*, a gamma-aminobutyric acid (GABA(A)) receptor subunit associated with synaptic plasticity) are thought to be involved in autism [9,10]. Recent studies showed that many genes associated with language abnormalities in autism are also found in schizophrenia. Thereby, many functional genes, for example, *FOXP2* (forkhead box protein P2; 7q31), a transcription factor involved in the development of several tissues, including the brain. *COMT* (Catechol-O-methyltransferase, 22q11), *GABRB3*, and *DISC1* (Disrupted in schizophrenia 1, 1q42.1) are actually implicated in both of them [4]. Also, an emerging phenotype of autism patients with protein-disrupting *FOXP1* (3p14.1) variants includes global developmental delay, intellectual disability and mild to severe speech/language deficits [11]. Interestingly, some genomic sequences are associated with severe autism. These include the adhesive junction-associated δ-catenin protein *CTNND2*, which plays a critical role in neuronal development, has an intimate connection to chromatin biology, and for which the loss of function have been noticed in female-enriched multiplex families [6]; Sequences encoding DUF1220 protein domains (i.e. *DUF1220 subtype CON1*) exhibit an exceptional human-specific increase in copy number and have been associated with several phenotypes related to brain size, particularly in children [12].

Eventually, further studies, such clinical trials may lead to new treatments in order to enhance synaptic strength, improve memory, language and behavior in autism patients. Cost of lifelong care should be dramatically reduced with early diagnosis and intervention. Translation of genomic knowledge to clinics and clinicians, more specifically pediatricians, can be helpful to diagnose autism with more accuracy and obtain better clues about its prognosis.

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