Neuroscience and Biobehavioral Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Intellectual disability and autism spectrum disorders: Causal genes and molecular mechanisms

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ARTICLE INFO

Article history:
Received 4 October 2013
Received in revised form 30 January 2014
Accepted 12 February 2014

Keywords:
Intellectual disability
Autism spectrum disorders
Synaptic plasticity
Neurodevelopmental disorder
Molecular pathways

ABSTRACT

Intellectual disability (ID) and autism spectrum disorder (ASD) are the most common developmental disorders present in humans. Combined, they affect between 3 and 5% of the population. Additionally, they can be found together in the same individual thereby complicating treatment.

The causative factors (genes, epigenetic and environmental) are quite varied and likely interact so as to further complicate the assessment of an individual patient. Nonetheless, much valuable information has been gained by identifying candidate genes for ID or ASD. Understanding the etiology of either ID or ASD is of utmost importance for families. It allows a determination of the risk of recurrence, the possibility of other comorbidity medical problems, the molecular and cellular nature of the pathobiology and hopefully potential therapeutic approaches.

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1. Introduction

Intellectual disability (ID) and autism spectrum disorders (ASDs) are major social problems in all countries. Each, individually, have a rather high prevalence, with ID affecting 1–3% of the population and ASDs is found in 1/50 school age children (Perou et al., 2013). Both conditions are heterogeneous, thereby posing an immense challenge to the clinical geneticist in search of a diagnosis for the patient and their family in need of genetic counseling to determine recurrence risks.

Intellectual disability is a condition characterized by below average intellectual functioning (IQ < 70) in conjunction with significant limitations in adaptive functioning. Intellectual disability may occur as an isolated phenomenon or accompanied with malformations, neurological signs, impairment of the special senses, seizures and behavioral disturbances. Autism spectrum disorder comprises a group that includes autistic disorders, Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS) and Rett syndrome (American Psychiatric Association, 2000). Patients with ASDs share features of restrictive and repetitive behaviors, dysfunctional reciprocal social behavior, and impaired communication abilities (Wilkins and Matson, 2009).

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http://dx.doi.org/10.1016/j.neubiorev.2014.02.015
0149-7634/

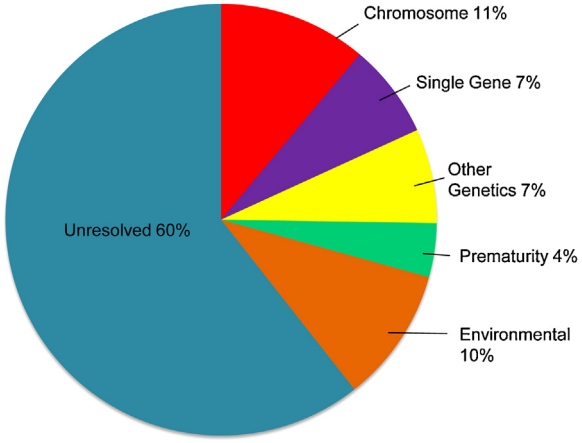

Fig. 1. Etiological causes of intellectual disability. Percentages are based on the evaluation of 15,484 individuals seen by the Greenwood Genetic Center.

Besides the heterogeneity of ID and ASDs, they are extremely likely to be related biochemically and molecularly. Both exist together in the majority of patients. Seventy percent of individuals with ASDs have some level of ID while the remaining 30% have some disability (speech, behavior) other than cognitive dysfunction (Mefford et al., 2012; Newschaffer et al., 2007; Wilkins and Matson, 2009). Conversely, at least 10% of individuals with ID have ASDs, with some ID conditions exhibiting a much higher level of co-morbidity.

The genetic causes for ID and ASDs are quite varied and similar. Single gene mutations, as well as copy number variants (CNVs), either duplications or deletions, are associated with both conditions. Additionally, hypomorphic alterations in multiple genes suggesting an oliogenic mode of inheritance have recently been noted for both conditions. Recently, large-scale whole exome sequencing (WES) studies found that no single gene was significantly associated with ASD risk. Rather a likely contribution of rare risk variants scattered across hundreds of genes was speculated (Anney et al., 2012; Liu et al., 2013). The same mutation or CNV gives rise to either ID or ASDs and variations within a large number of these genes, for example, *NRXN1*, *CNTNAP2*, *NLGN4*, *SHANK2* and *SHANK1*, have been found to be associated with ID as well as ASD (Berkel et al., 2010; Sato et al., 2012; Kim et al., 2008; Laumonnier et al., 2004; Zweier et al., 2009). These observations further substantiate the involvement of similar cellular and molecular processes and indicate the role of environment and genetic background plays in the expression of ID (Fig. 1) and probably ASD.

Many rare and inherited mutations in ASD-associated genes often display incomplete penetrance. Most pathogenic mutations in the known ASD-associated genes and in a majority of ID genes have a very low prevalence in their respective patient populations. Thus the diagnostic application and understanding of the molecular mechanisms underlying ID and ASD remain limited.

Much time and effort by multiple groups throughout the world have been devoted to identifying specific genetic causes for ID and ASDs. As a result of these efforts, at least 400 genes have been found to be associated with each of these entities (reviewed in van Bokhoven, 2011). However, it is highly probable this number only represents a minor proportion of genes involved. For examples, with respect to ID, 400 genes may account for a fourth of the genes involved based on the number of known X-linked intellectual disability genes is presently about 100, and the X chromosome accounts for about 1/20 of the human genome.

It is hypothesized that primary causative factors (monogenic causes, epigenetic and environmental factors or other as yet unidentified causative factors) do not directly result in cognitive impairment. Rather, the mutant genes or other primary causative factors directly or indirectly cause metabolic disruptions, altered neurodevelopment and interference in cell proliferation and/or migration, which then lead to the brain abnormalities that result in cognitive and behavioral disabilities. It is likely that common groups of genes, proteins and metabolites or a combination of these are affected in either a majority or subset(s) of ID patients.

Although screening of patients with ID or ASD has indeed identified viable candidate genes involved in these phenotypes, the process is laborious and, as already mentioned, quite incomplete. The number of genes is vast and the number known small. Components of common interaction networks and biological processes associated with these genes/proteins are likely critical and unique to normal cognitive and behavioral function. Therefore other approaches have been undertaken to better understand the etiologies of these conditions. One very productive approach has been that of system biology. Kou et al. (2012) used a combined network and systems biology approach to predict candidate genes for ASD and ID. Their results were quite interesting in that they were able to slow both conditions shared common pathways and had similar clusters of genes which was comforting as this was not unexpected based on the accumulating evidence alluded to before. Importantly, using these interconnected pathways, as one begins to understand ID one may then also better understand ASD and visa versa.

Cristino et al. (2013) used a similar network approach, a hypothetical 'gene network model' based on candidate genes and associated protein–protein interaction networks, to build protein modules containing about 4000 genes which might contribute to neurodevelopmental and neuropsychiatric disorders. Their data were in agreement with previous approaches in their identification of molecular pathways, functional domain and gene regulation. However, their findings also contained some novel insights. Their analysis, by including variants identified in genome wide association studies found regulatory regions for transcription factors (TF) and miRNA, located in the 5′ upstream regulatory regions and the 3′ UTR of genes. These, in turn, identified candidate genes and miRNA target sites. At the end, Christino et al. (2013) found that the TFs Q2 in a network regulated other genes in the network and the genes were enriched for miRNA sites.

2. Genes linked to ID and ASD

Functional categorization of proteins encoded by a majority of ID and ASD-associated genes and elucidation of common pathways has become crucial not only for the understanding of cellular and molecular mechanisms underlying pathophysiology of these genes but also in assessing the potential pathogenicity of new candidate genes for ID and ASD. Such a functional categorization has led to emergence of diverse cellular functions influencing neuronal structure and functions that are affected by defects in the ID and ASD genes. For example, successes in delineating the molecular basis for XLID have led to the elucidation of genetic mechanisms for specific XLID disorders and provided valuable insights into fundamental aspects of neuronal function that are involved in normal development of human cognition. These functions include but are not limited to transcription and translation regulation, protein modification, chromatin remodeling, actin cytoskeleton assembly involving neurite outgrowth, and cellular processes including RNA splicing, translation, energy metabolism, transport of small molecules, nonsense mediated decay of mRNA, and disturbances in ubiquitination. Furthermore, the identification of interacting partners of ID and ASD gene products and targets of known ID and ASD genes has led to the elucidation of specific pathways linked to ID and ASD. Many ID and ASD genes appear to convergence