BRAIN RESEARCH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

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Review

Using hiPSCs to model neuropsychiatric copy number variations (CNVs) has potential to reveal underlying disease mechanisms

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ARTICLE INFO

Article history:
Accepted 3 November 2015

Keywords:
Schizophrenia
CNV
Mouse models
Hipsc models

ABSTRACT

Schizophrenia is a neuropsychological disorder with a strong heritable component; genetic risk for schizophrenia is conferred by both common variants of relatively small effect and rare variants with high penetrance. Genetically engineered mouse models can recapitulate rare variants, displaying some behavioral defects associated with schizophrenia; however, these mouse models cannot recapitulate the full genetic architecture underlying the disorder. Patient-derived human induced pluripotent stem cells (hiPSCs) present an alternative approach for studying rare variants, in the context of all other risk alleles. Genome editing technologies, such as CRISPR-Cas9, enable the generation of isogenic hiPSC lines with which to examine the functional contribution of single variants within any genetic background. Studies of these rare variants using hiPSCs have the potential to identify commonly disrupted pathways in schizophrenia and allow for the identification of new therapeutic targets.

This article is part of a Special Issue entitled SI:StemsCellsinPsychiatry.

Contents

Abbreviations: hiPSC, human induced pluripotent stem cell; CNV, Copy number variation; SNP, Single nucleotide polymorphism; PPI, Paired pulse inhibition

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http://dx.doi.org/10.1016/j.brainres.2015.11.009
0006-8993/

Please cite this article as: Flaherty, E.K., Brennand, K.J., Using hiPSCs to model neuropsychiatric copy number variations (CNVs) has potential to reveal underlying disease mechanisms. Brain Research (2015), http://dx.doi.org/10.1016/j.brainres.2015.11.009

1. Introduction

Schizophrenia is a debilitating yet relatively common psychiatric disorder, affecting approximately 1% of the world population (Health, 2013). It is uniquely characterized by positive symptoms including delusions, hallucinations and disorganized thinking. Negative symptoms, including depression and anhedonia, and cognitive symptoms such as working memory impairments are also important features in the disorder. The type and severity of symptoms presents heterogeneously within the patient population (Weinberger, 1987). Currently available antipsychotics are fairly effective at treating the positive symptoms, but have little effect on the negative or cognitive symptoms. One-third of patients do not experience any symptom amelioration after antipsychotic treatment and less than 20% of patients will return to adequate social functioning after their first psychotic episode (Robinson et al., 2004). The inability to treat a large percent of patients results in an increased risk of suicide and homelessness among schizophrenia patients. Typically, the onset of schizophrenia occurs in early adulthood, creating a high societal burden relative to many other neurological disorders with onsets much later in life. Although schizophrenia is diagnosed in early adulthood, abnormal neurodevelopmental processes can begin much earlier and it is now thought of as a neurodevelopmental disorder.

Epidemiological studies of affected families as well as twin studies have established schizophrenia to be a highly heritable disorder with heritability estimates between 50% and 80% (Sullivan et al., 2003). Although highly heritable, there is no one gene responsible for schizophrenia. Instead, it has been suggested that there are both many common variants with small effect sizes as well as more penetrant and difficult to detect rare variants that can contribute to the disorder. The debate underlying the genetics of schizophrenia has surrounded these two hypotheses; the common variant common disease and the rare variant common disease models (Malhotra and Sebat, 2012). It is now becoming clear that both types of genetic variation contribute to the development of schizophrenia (reviewed Chen et al. (2015)), and perhaps contribute additively to symptom severity and prognosis. For example, childhood-onset schizophrenia (COS), which is a rare and severe form of the disorder, coincides with both significantly more rare CNVs (Ahn et al., 2014b) and polygenic risk burden (Ahn et al., 2014a).

This review will focus on the role of rare variants in schizophrenia, beginning with what we have learned from human genetic studies and animal models. We suggest that patient-derived human induced pluripotent stem cells (hiPSCs) provide an advantageous model with which to investigate the casual role of rare variants on the underlying cellular and molecular phenotypes of schizophrenia. Identification of common biological pathways may provide insight into the mechanisms underlying schizophrenia, allowing for development of new therapeutics. Along with studies of basic disease mechanisms, hiPSC models can support drug discovery and development through high throughput drug screening, stratification of patient populations, and improved assessment of drug toxicity.

2. Contribution of copy number variants to schizophrenia genetics

Rare copy number variations (CNVs) were the first type of genetic defect associated with psychiatric illness. CNVs are often very large (>100 kb) and typically occur at hotspots in the genome (Conrad et al., 2011). CNVs can arise from non-allelic homologous recombination, non-homologous end joining, fork stalling/template switching, and L1-mediated retro-transposition, which all result in large duplications or deletions within a chromosomal region (Malhotra and Sebat, 2012). Due to their size, CNVs were easy to detect using original microarray technologies; now, the application of more current genotyping platforms and new algorithms for CNV discovery has enabled identification of new *de novo* CNVs as well as very rare variants (Neale and Sklar, 2015). CNVs greater than 10 kb occur at rate of 0.01–0.02 per generation, which is very rare compared to the estimated 30–100 single nucleotide polymorphisms per generation (Malhotra and Sebat, 2012; Mills et al., 2011). Despite their rarity, the relative contributions of CNVs to genomic variation is substantial, at least in part because CNVs can affect multiple genes and potentially disrupt many functions at one site (reviewed Hiroi et al. (2013) and Rodriguez-Revenga et al. (2007)).

To investigate the role of rare CNVs in schizophrenia, two main genetic approaches have been undertaken. The first approach compares the CNV burden in cases of schizophrenia to controls while the second examines the impact of *de novo* CNVs. The focus on rare CNVs in schizophrenia begin with cytogenetic studies, which demonstrated an enrichment of detectable chromosome abnormalities in autism and schizophrenia patients (Malhotra and Sebat, 2012). Over the last 10 years there have been many, increasingly larger, studies performed which all reveal an increase in the number of CNVs in schizophrenia cases compared to a healthy control population (International and Consortium, 2008; Rees et al., 2014b; Stefansson et al., 2008; Walsh et al., 2008). With tens of thousands of patients and controls now genotyped, 2.5% of patients with schizophrenia and 0.9% of controls carry one of the 11 significantly associated schizophrenia CNVs (Rees et al., 2014b).

There have also been numerous studies looking for *de novo* CNVs by sequencing both parents and the affected child, or proband. These trio studies demonstrate that rare *de novo*

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