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Disease signatures for schizophrenia and bipolar disorder using patient-derived induced pluripotent stem cells

Bradley Watmuff[*,+,#], **Shaunna S. Berkovitch**[*,#], **Joanne H. Huang**[*,#], **Jonathan Iaconelli**[*,#], **Steven Toffel**[*,+,#], and **Rakesh Karmacharya**[*,+,#,^,1]

[*]Center for Experimental Drugs and Diagnostics, Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Harvard Medical School and Massachusetts General Hospital, Boston, MA 02114

[+]Harvard Stem Cell Institute, Harvard University, Cambridge, MA 02138

[#]Center for the Science of Therapeutics, Broad Institute of Harvard and MIT, Cambridge, MA 02142

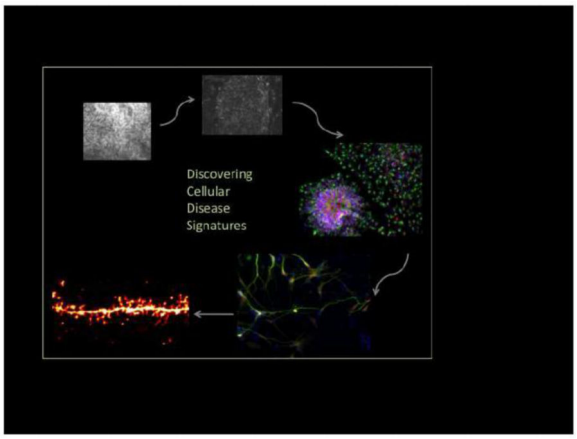
[^]Schizophrenia and Bipolar Disorder Program, McLean Hospital, Belmont, MA 02478

Abstract

Schizophrenia and bipolar disorder are complex psychiatric disorders that present unique challenges in the study of disease biology. There are no objective biological phenotypes for these disorders, which are characterized by complex genetics and prominent roles for gene-environment interactions. The study of the neurobiology underlying these severe psychiatric disorders has been hindered by the lack of access to the tissue of interest – neurons from patients. The advent of reprogramming methods that enable generation of induced pluripotent stem cells (iPSCs) from patient fibroblasts and peripheral blood mononuclear cells has opened possibilities for new approaches to study relevant disease biology using iPSC-derived neurons. While early studies with patient iPSCs have led to promising and intriguing leads, significant hurdles remain in our attempts to capture the complexity of these disorders *in vitro*. We present here an overview of studies to date of schizophrenia and bipolar disorder using iPSC-derived neuronal cells and discuss potential future directions that can result in the identification of robust and valid cellular phenotypes that in turn can lay the groundwork for meaningful clinical advances.

Graphical abstract

[1]To whom correspondence should be addressed: Center for Human Genetic Research, Harvard Medical School and Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114. Tel.: 617-726-5119; Fax: 617-726-0830; karmacharya@mgh.harvard.edu.



Keywords

schizophrenia; bipolar disorder; stem cells; iPSC; microglia; gene-environment; neuronal differentiation

Introduction

Schizophrenia (SCZ) is a chronic and debilitating psychiatric disorder that is characterized by hallucinations, paranoid delusions, disordered thought processes, and cognitive deficits (Lewis and Lieberman, 2000). Bipolar disorder (BPD), also known as manic-depressive illness, is characterized by debilitating episodes of mania and depression that are often accompanied by psychotic symptoms (Keck et al., 2003, Goodwin and Ghaemi, 2003). SCZ and BPD both afflict ~1% of the population (Kessler et al., 2005, Merikangas et al., 2007). These illnesses manifest themselves in late adolescence or early adulthood, and follow a chronic course requiring treatment for the rest of a patient's life (Fenton and McGlashan, 1991a, Fenton and McGlashan, 1991b, Salvatore et al., 2007). Patients with SCZ and BPD have a very high risk of suicide compared to the general population (Palmer et al., 2005, Pompili et al., 2013). The diagnosis and treatment of SCZ and BPD are based on clinical symptomatology and there are no biomarkers to aid in diagnosis, in guiding treatment decisions, or in monitoring treatment response (Pillai and Buckley, 2012, Frey et al., 2013).

SCZ and BPD are highly heritable but their genetic architecture is very complex (Kendler and Diehl, 1993, McGuffin et al., 2003). These disorders have monozygotic concordance rates of ~50% and dizygotic concordance rates of ~10% (Davis et al., 1995, Kieseppä et al., 2004, Kety et al., 1971). Despite the strong genetic component to these severe psychiatric disorders, genetic studies are only beginning to identify risk variants (Consortium, 2014, Group, 2011). Recent genome wide association studies have also found recurrent microdeletions and copy number variants that are associated with SCZ and BPD (Georgieva et al., 2014). Genetic studies point to some shared genetic susceptibility to SCZ and BPD (Lichtenstein et al., 2009, Consortium, 2013).

There is a marked dearth of medications that target the underlying disease biology in SCZ and BPD (Insel and Scolnick, 2006). Current antipsychotics were derived from the

serendipitous discovery of chlorpromazine in the 1950s when scientists were trying to develop drugs with sedative and anti-histaminergic properties to use during surgeries (López-Muñoz et al., 2005, Ban, 2007). Similarly, lithium, the most efficacious treatment for BPD, was discovered in 1949 (CADE, 1949). The last major clinical advance in the treatment of SCZ was the development of clozapine in 1970s (Rodová et al., 1973) which had better efficacy compared to other antipsychotic medications (Baldessarini and Frankenburg, 1991). Current treatment of SCZ is based on the hypothesis that psychosis results from increased level of dopaminergic activity in the brain (Seeman, 2013). Antipsychotic medications are believed to work by acutely blocking the binding of dopamine to the D2 receptor (Kapur and Mamo, 2003, Seeman, 2006). However, there is significant variability in efficacy in different patients and there is often a lag time in therapeutic response that creates significant challenges in properly and effectively treating these patients (Pouget and Müller, 2014, Case et al., 2011, Takeuchi et al., 2012).

The development of novel therapeutics for SCZ and BPD has been hindered by the lack of our understanding of the neurobiology underlying these disorders. Most biological studies to date of small molecules with potential roles in the treatment of psychiatric disorders have been carried out in animal models (Nestler and Hyman, 2010). Studies in rodents have yielded a wealth of knowledge on basic biology and pathophysiology, including in our understanding of neurobiology. Animal models have been routinely used to identify new therapeutic leads for various human diseases, including for psychiatric disorders (Woodcock and Woosley, 2008). While these studies have led to a better understanding of the biology, there has been a lack of compounds that have translated successfully from animal models to humans (Pound et al., 2004, Hackam and Redelmeier, 2006, Medicine, 2013). Recent studies have found that genomic responses in humans to specific pathophysiological processes often have poor correlation with such responses in rodent models (Seok et al., 2013). In addition, studies in induced human neurons and in cortical neurons from knockout mice showed species-specific differences in the effects of NRXN1 mutations on synaptic biology (Pak et al., 2015). These considerations have led to a note of caution about focusing exclusively on animal studies for preclinical studies and spurred efforts to study the biology relevant to neuropsychiatric diseases in human neuronal cells (van der Worp et al., 2010, Rice, 2012, Haggarty and Perlis, 2014).

Until recently, a significant hurdle to the development of novel therapeutics has been the inability to study live human neurons in the laboratory. Cellular reprogramming methods now enable generation of human iPSCs from patient fibroblasts, which can be differentiated to neurons (Okita and Yamanaka, 2011, Takahashi et al., 2007, Takahashi and Yamanaka, 2006, Brennand et al., 2014a, Brennand et al., 2014c, Brennand et al., 2011, Yu et al., 2014, Pedrosa et al., 2011, Yoon et al., 2014, Wen et al., 2014, Vaccarino et al., 2011, Chen et al., 2014). Given the complexity of brain development and diversity of neuronal subtypes, generation and identification of specific neuronal subtypes may seem daunting. However, there have been recent methodological advances in human iPSC differentiation along specific neuronal lineages (Shi et al., 2012a, Shi et al., 2012c, Yu et al., 2014, Mariani et al., 2012). These advances enable the study of disease-related features in specific neuronal subtypes derived from patient iPSCs. We review here the current status of the field in studying patient iPSC-derived neurons in SCZ and BPD, with a discussion focused on

approaches that incorporate environmental factors and clinical information in order to discover disease signatures that can lead to novel therapeutics.

Stem cell models in schizophrenia

There have been a number of promising studies of iPSC-derived neurons in SCZ (Brennand et al., 2014c). In the initial study of iPSC-derived neurons in patients diagnosed with SCZ, an experimental approach that involved transmission of modified rabies virus in differentiated neuronal cultures was used to show that neurons from SCZ patients had decreased neural connectivity, decreased neurites and decreased levels of the synaptic protein PSD95, even though they showed normal physiological properties by whole-cell patch recordings and calcium imaging (Brennand et al., 2011). Gene expression patterns of the SCZ neurons revealed altered expression of genes involved in Wnt signaling, cAMP signaling and glutamate receptors (Brennand et al., 2011). Another study with neural progenitor cells (NPCs) that focused on gene expression and proteomics found abnormalities in cytoskeletal remodeling and oxidative stress in NPCs from SCZ patients (Brennand et al., 2014a).

A number of studies have also been done with SCZ patients that carry specific disease-related genetic abnormalities. iPSCs from a SCZ patient with 22q11.2 del (velocardiofacial syndrome) showed deficits in the down regulation of pluripotency-related genes during neuronal differentiation (Pedrosa et al., 2011). Further studies with iPSC-derived neurons from SCZ 22q11.2 del patients showed altered miRNA expression profiles that recapitulated previously described patterns in postmortem brains and peripheral cells (Zhao et al., 2015). 15q11.2 CNVs have been reported as risk factors for SCZ (Stefansson et al., 2008, Consortium, 2008) and iPSCs from subjects with 15q11.2 del have also been studied. These studies showed that the NPCs derived from these iPSCs had abnormalities in adherens junctions and apical polarity (Yoon et al., 2014). Disrupted in Schizophrenia 1 (DISC1) is another gene associated with SCZ, as well as with other psychiatric disorders (Chubb et al., 2008, Mackie et al., 2007). iPSCs from family members carrying a frame-shift DISC1 mutation were differentiated along the forebrain lineage and were found to have synaptic deficits and dysregulation of many synaptic genes (Wen et al., 2014). Isogenic iPSC lines generated by gene editing showed that mutant DISC1 depleted wild-type DISC1 protein and led to abnormalities in synaptic vesicle release (Wen et al., 2014). While these studies focuses on NPCs and cortical neurons, another study examined iPSC-derived hippocampal neurons from SCZ patients, and showed that hippocampal NPCs had reduced neuronal activity and resulted in deficits in generation of DG granule neurons (Yu et al., 2014).

Stem cell models in bipolar disorder

In the first study of iPSC-derived neurons in BPD, NPCs and neurons from three patients and three subjects were studied (Chen et al., 2014). This study found that while the iPSC transcriptomes were not different between BPD and controls, there were significant differences in the neuronal transcriptomes, with increased expression of ion channels and membrane-bound receptors in BPD neurons. Neurons from control iPSCs were found to express genes involved in dorsal telencephalic fate specification while BPD neurons

expressed transcripts for ventral fate specification. This study also found that the calcium transients and wave amplitudes in BPD neurons were significantly decreased by exposure to lithium compared to control neurons (Chen et al., 2014). Another study of NPCs from two BPD patients and their unaffected parents found significant differences in neurogenesis and in expression of genes involved in the WNT signaling and ion channel subunits (Madison et al., 2015). In addition, overexpression of miR-34a, which targets multiples genes implicated in BPD, was shown to result in abnormalities in neuronal differentiation and morphology as well as in the expression of synaptic proteins (Bavamian et al., 2015).

A recent study examined hippocampal dentate gyrus (DG) granule cell-like neurons differentiated from BPD patients and controls(Mertens et al., 2015). Gene expression studies of the patient-derived neurons suggested mitochondrial abnormalities in young neurons from BPD subjects while functional studies revealed hyperexcitability in these BPD neurons. Moreover, they compared the hyperexcitability phenotypes in neurons from patients who were lithium responders and non-responders and found that lithium selectively decreased the hyperexcitable phenotype only in neurons from the responders, and not in neurons from the non-responders (Mertens et al., 2015).

Searching for disease phenotypes – the relevance of cell type

Brain imaging studies of patients consistently show that patients with SCZ and BPD have enlarged ventricles, indicating loss of cortical volume (Steen et al., 2006, Arnone et al., 2009). Patients with SCZ and BPD both show gray matter loss in the cortex, though in different areas of the brain (Sheline, 2003). BPD patients treated with lithium show greater gray matter density compared to untreated patients (Bearden et al., 2007). In addition to findings in the cortex, abnormalities have also been reported in hippocampal volumes in SCZ and BPD (Heckers and Konradi, 2010), specifically in dentate gyrus (DG) and cornu ammonis 3 (CA3) (Mathew et al., 2014, Tamminga et al., 2012, Tamminga et al., 2010). In studies of patients with BPD, treatment with lithium was associated with larger hippocampal subfield volumes (Giakoumatos et al., 2015, Yucel et al., 2007, Yucel et al., 2008).

Postmortem studies in SCZ and BPD do not show any gross pathological abnormalities in the brain. In SCZ, postmortem studies show decreased neural stem cell proliferation in the dentate gyrus (Reif et al., 2006) and indicate deficits in GABAergic neurons (Lewis et al., 2005, Benes and Berretta, 2001). Postmortem SCZ and BPD brains show well replicated but subtle differences in the brain – pyramidal neurons in cortical layer III, but not in other cortical layers, show decreased dendritic spine density and fewer synapses (Glantz and Lewis, 2000, Glausier and Lewis, 2013, Rosoklija et al., 2000, Konopaske et al., 2014). In BPD, postmortem brains also show decreased glial cells in the subgenual prefrontal cortex (Ongür et al., 1998). In postmortem studies of hippocampal tissue, CA3 neurons from SCZ subjects showed increased levels of PSD95 and GluN2B–containing NMDA receptors, as well as a higher number of thorny excrescences and increased dendritic spine density in CA3 neurons, suggesting increased excitatory signaling in CA3 neurons in SCZ (Li et al., 2015).

Studies to date in SCZ and BPD have included investigations in iPSCs, NPCs, differentiated cortical cultures, and hippocampal DG granule-cell like neurons. The postmortem studies

can guide decisions on neuronal subtypes that are most likely to reveal disease-related differences. Recent advances in neuronal differentiation of human iPSCs enable the generation of many of the neuronal subtypes of interest in the study of SCZ and BPD, including cortical neurons with dual-SMAD inhibition (Figure 1) (Shi et al., 2012c, Shi et al., 2012a, Mariani et al., 2012) and with Neurogenin-2 overexpression (Zhang et al., 2013), hippocampal dentate gyrus (DG) granule neurons (Figure 2) (Mertens et al., 2015, Yu et al., 2014) and cortical interneurons (Nicholas et al., 2013, Maroof et al., 2013). Human iPSC-derived neurons have been shown to exhibit appropriate functional properties in Ca^{2+} imaging experiments and in patch clamp studies (Kim et al., 2011, Prè et al., 2014, Paşca et al., 2011, Shcheglovitov et al., 2013). Ca^{2+} imaging of the iPSC-derived cortical neurons display spontaneous oscillations and bursts of Ca^{2+} fluorescence at baseline and respond robustly and reliably to a depolarizing stimulus with KCl (Figure 3). Studies in SCZ and BPD that have used specific neuronal subtypes derived from iPSCs have focused on cortical and hippocampal neurons (Wen et al., 2014, Mertens et al., 2015, Yu et al., 2014). Investigations focused on disease biology often aim to study pure populations of specific neuronal subtypes. However, it can also be argued that studying different neuronal subtypes in a more heterogeneous neuronal culture may better reflect the natural physiological surroundings of such neurons *in vivo*. The optimal nature of the cell populations to be studied will depend on the type of experiments planned, i.e. while homogeneous cell populations may be suitable for gene-expression studies and assay development for high-throughput screens, heterogeneous cultures with glial cells may be more suitable for detailed studies of neuronal morphological features.

In addition to neuronal differentiation of human iPSCs, there have also been methodological advances in direct induction of somatic cells into neurons, using forced expression of the neurogenic transcription factors Brn2, Ascl1 and Myt1l (Pang et al., 2011) as well as with the microRNAs miR-9/9* and miR-124 (Yoo et al., 2011). While direct reprogramming of human fibroblasts have resulted in the generation of excitatory neurons (Pang et al., 2011, Yoo et al., 2011, Qiang et al., 2011) dopaminergic neurons (Pfisterer et al., 2011, Caiazzo et al., 2011) striatal medium spiny neurons (Victor et al., 2014) and spinal motor neurons (Son et al., 2011), differentiation protocols for human iPSCs lend themselves to the generation of a diverse array of neuronal subtypes from different niches in the human brain, including specific cortical and hippocampal populations that are of special interest in the disease biology of schizophrenia and bipolar disorder (Brennand et al., 2015).

The studies to date in SCZ and BPD iPSC-derived neurons have been carried out in adherent monolayer cultures and focused on abnormalities at the cellular level. This approach assumes that the effects of the underlying complex genetic vulnerabilities converge at the cellular level (Figure 4). Recent developments in the generation of three-dimensional culture systems and organoids present the opportunity to study disease biology in more complex environments and to possibly study the biology at the circuit level. Cerebral organoids can generate three-dimensional neuronal structures that mimic the organizational aspects of the human cortex (Mariani et al., 2012, Lancaster and Knoblich, 2014, Lancaster et al., 2013). Methods have also been developed to generate iPSC-derived human cortical spheroids that recapitulate aspects of human cortical development and organizations (Paşca et al., 2015). Another approach to the generation of three-dimensional networks of stem cell derived

neurons has included the use of a matrigel-based support matrix that allow NPCs to differentiate into complex networks *in vitro* (Choi et al., 2014, Kim et al., 2015). While these three-dimensional approaches have been used to study the disease biology of Alzheimer's disease and microcephaly, they have yet to be used in the study of SCZ and BPD. Given significant evidence for circuit-level dysfunction in SCZ and BPD (Baker et al., 2014), three-dimensional approaches may lend themselves to models where rudimentary circuits can be formed and interrogated for dysfunctions at the circuit level. Alternatively, microelectrode arrays can also be utilized in conjunction with adherent monolayer cultures to study network function/dysfunction *in vitro* in neurons from patients and controls (Obien et al., 2014).

Uncovering disease phenotypes – the role for perturbations

Complex psychiatric disorders that have strong gene-environment interactions are difficult to model *in vitro*. Environmental factors impinge on the underlying genetic vulnerability of SCZ and BPD, which results from small contributions from many different genes, for manifestation of the disease. The fact that monozygotic twin concordance in SCZ and BPD is ~ 50%, and not 100% (Davis et al., 1995, Kieseppä et al., 2004, Kety et al., 1971), suggests that additional environmental factors are involved in SCZ pathogenesis (Brown, 2011). While multiple environmental factors have been implicated in SCZ and BPD (van Os et al., 2008, Brown, 2011), there is no easy way to translate such environmental factors into specific cellular perturbations. Cellular stress has been used to uncover underlying disease-related vulnerabilities in cellular systems. In a study mitochondrial electron transport gene expression in lymphocytes from BPD cases and healthy controls, there were no differences when cells were cultured under normal conditions. However, when lymphocytes were cultured in low-glucose conditions, the BPD lymphocytes had a markedly aberrant response compared to cells from healthy controls (Naydenov et al., 2007). Cellular perturbation can be to undertaken in a larger scale in an unbiased way using a range of small molecules that interfere uniquely with different signaling pathways (Seashore-Ludlow et al., 2015). Cellular pathways involved in disease biology can potentially be identified systematically by perturbing specific pathways and identifying perturbations that lead to differential responses in patient cells but not in control cells (Basu et al., 2013).

Co-culture models

Immunological mechanisms have also been implicated in the pathophysiology of SCZ and BPD (Khandaker et al., 2015, Khandaker and Dantzer, 2015, Barbosa et al., 2014). A major neurodevelopmental process that takes place in the adolescent brain is that of synaptic pruning, a process by which superfluous excitatory synaptic connections are eliminated (Petanjek et al., 2011, Rakic et al., 1986, Zecevic et al., 1989, Huttenlocher and Dabholkar, 1997, Giedd et al., 1999). Synaptic pruning during this critical period is hypothesized to be aberrant in SCZ, the same time frame when most patients have their first psychotic break (Feinberg, 1982, Lieberman, 2006, Selemon and Zecevic, 2015). The excessive elimination of synaptic connections during the pruning process in SCZ is believed to result in greater loss of cortical gray matter volume during adolescence and result in decreased dendritic spines in the pyramidal neurons in specific cortical layers (Lewis and Sweet, 2009, Garey et

al., 1998, Glantz and Lewis, 2000, Konopaske et al., 2014, Rosoklija et al., 2000, Rapoport et al., 1999, McGlashan and Hoffman, 2000, Selemon and Zecevic, 2015). Microglia, the resident macrophages in the brain, play a central role in synaptic pruning (Kettenmann et al., 2013, Bilimoria and Stevens, 2015). Postmortem studies in SCZ show microglial activation and infiltration in the cortex (Fillman et al., 2013, Radewicz et al., 2000, Steiner et al., 2008, Steiner et al., 2006). In addition, *in vivo* positron emission tomography (PET) studies in patients show strong evidence for increased microglial activity in the brain in SCZ (van Berckel et al., 2008, Bloomfield et al., 2015, Doorduin et al., 2009). Recent developments in directed differentiation methods now enable the generation of microglial cells from human monocytes (Ohgidani et al., 2015, Ohgidani et al., 2014). This method provides new approaches for co-culturing human iPSC-derived cortical neurons with microglial cells derived from monocytes isolated from the same patient.

Harnessing clinical information – modeling medication response *in vitro*

The heterogeneity of clinical presentations and genetic makeup often create a hurdle in research efforts, especially when large number of samples cannot be studied (Dacquino et al., 2015). A clinical feature that can be used to validate cellular phenotypes is the pattern of treatment response in patients. An example of such an approach was recently described in the study of iPSC-derived hippocampal DG granule cell-like neurons in BPD. The study found that young neurons in this hippocampal lineage showed a hyperexcitable phenotype, with increased numbers of spontaneous and evoked action potentials (Mertens et al., 2015). They further studied these neurons in two groups of BPD patients – patients that had good therapeutic response to lithium, and patients that did not respond well. When such young neurons were studied in the presence of lithium, only neurons from the lithium responders showed decreased hyperexcitability in the presence of lithium, while neurons from lithium non-responders showed no such change (Mertens et al., 2015). This is an intriguing example of supporting the validity of cellular phenotypes by correlating effects of small molecules *in vitro* with patterns of medication response in patients.

Conclusion

SCZ and BPD are complex psychiatric disorders that have their symptomatic onset in late adolescence or early adulthood. The disorders become manifest in brains that have been developing over two decades, with concomitant interactions with various environmental factors that impinge on their underlying genetic backgrounds. We are attempting to use iPSC-derived neurons from patients, often in two-dimensional neuronal cultures differentiated over a few weeks, to capture the crux of the disease biology that develop in the most complex organ of the human body over many years. While this prospect seems daunting, there have been many important advances in the last few years that provide a compelling rationale to pursue this quest for cellular disease signatures. New approaches that incorporate environmental perturbations as well as co-cultures with other relevant cell types are potential avenues that can aid in modeling the complexity in these disorders. In addition to a providing us with a better understanding of the cellular-molecular features of SCZ and BPD, identification of robust, reliable and valid cellular disease signatures will

enable us to develop assays that can be used in high-throughput screens to discover promising small-molecule leads for therapeutic development.

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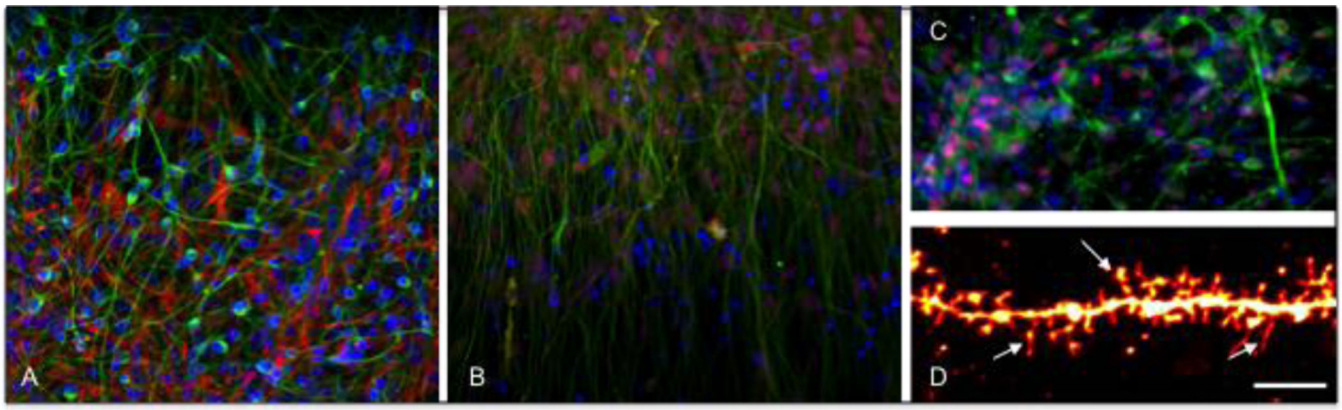

Figure 1.

Human iPSC-derived human cortical neurons. A. Differentiated cultures with neurons and glial cell: β-III tubulin (green), GFAP (red), DAPI (blue) B. Upper-layer cortical neurons : β-III tubulin (green), layer II-IV marker Brn2 (red), DAPI (blue). C. Deep-layer cortical neurons : β-III tubulin (green), layer VI marker Tbr1 (red), DAPI (blue) D. High-magnification image of a dendrite stained with DiI, arrows pointing to dendritic spines. Scale bar: 10 μm.

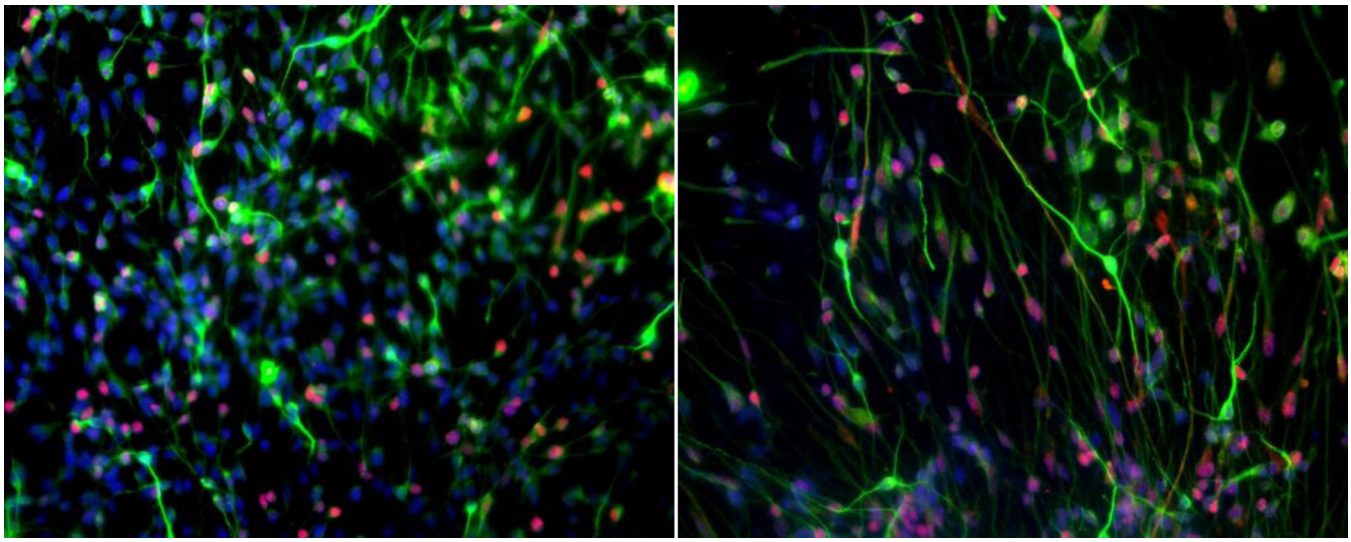

Figure 2.
Human iPSC-derived human hippocampal neurons. : MAP2 (green), PROX1 (red), DAPI (blue).

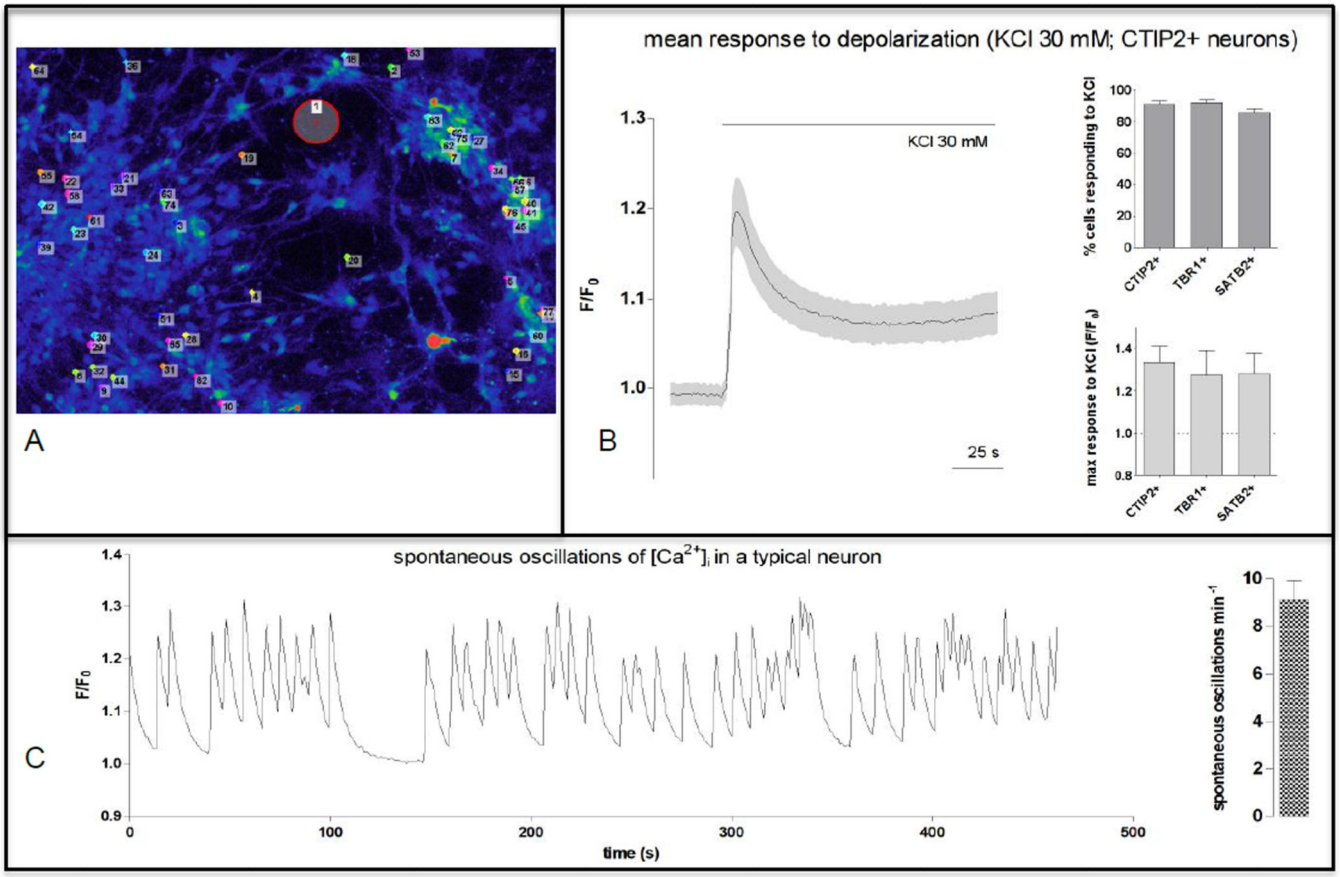

Figure 3.

Ca^{2+} imaging of human iPSC-derived cortical neurons shows characteristics of functional neurons. A. Neurons incubated with Ca^{2+} indicator Fluo-4 AM, for measurement of intra-neuronal Ca^{2+} flux. Immunocytochemistry performed to enable identification of responses belonging to neurons that express cortical markers SATB2, TBR1, and CTIP2. B. >90% of neurons responded to depolarizing stimulus (KCl 30mM). C. Neurons displayed spontaneous oscillations and bursts of Ca^{2+} fluorescence at rest.

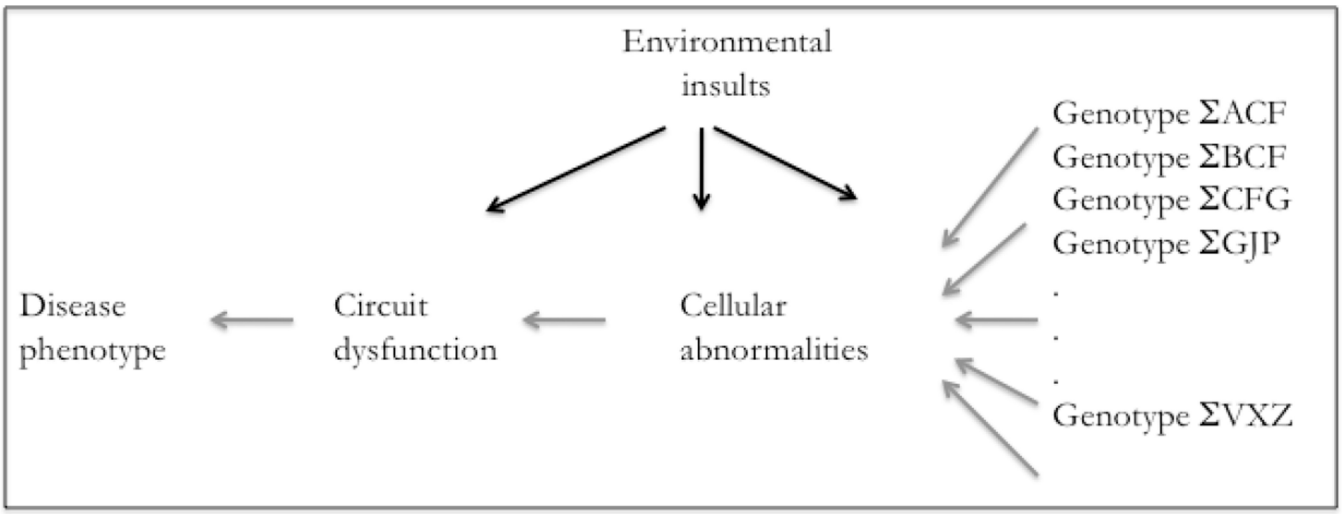

Figure 4.
Schematic model for interactions of genetic predisposition with environmental factors that result in cellular and circuit abnormalities leading to disease phenotype.