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Exploring the Genetic Underpinnings of Brain and Behavioral Disorders

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The pursuit of the links between genes, brain, and behavior began in the mid 20th century, led by the physicist-turned-biologist Seymour Benzer. Driven by the belief that neural traits as complex as behaviors can be traced to single genes, Benzer started his gene hunt journey in the 1960s with the fruit fly *Drosophila* (Benzer, 1971). In the ensuing half-century or so, the Benzer lab, along with other practitioners, including those in the labs of David Suzuki (Suzuki et al., 1971), Bill Kaplan (Ikeda & Kaplan, 1974), Karl Götz (Heisenberg & Götz, 1975), Bill Pak (Pak, 2010), and Bob Wyman (Wyman et al., 1984), established the field of Neurogenetics through the isolation of many single-gene mutations that disrupt a variety of neural traits, such as learning and memory, courtship, circadian rhythms, sensory-motor processing, and neural degeneration and aging. Their pioneering endeavors set the stage for the subsequent cloning and functional characterizations of these “paradigm” genes and significantly impacted the molecular neurobiology and genomic eras in the 1990s–2000s (Weiner, 1999).

It is now recognized that neural development, brain function, and behaviors are encoded at the level of genes, but most neural phenotypes are polygenic and extremely complex. We have also come to appreciate that environment has an enormous influence on the brain and behavior through activity-dependent modification of synapses and circuits and through epigenetic remodeling of DNAs and chromatins – back then this nature vs. nurture concept was still heatedly debated. It is now commonly accepted that altering genetic and epigenetic programs in neurons can severely disrupt development, function, or plasticity of the brain, leading to neurological and psychiatric disorders that are prevalent in our society. In this Special Issue of the *Journal of Neurogenetics*, we have invited experts to contribute a number of original research and review articles on several prevalent neurological and psychiatric disorders. Their articles on invertebrate and higher mammals, including humans, highlight recent advances in the genetic, epigenetic, and molecular basis of these diseases.

Huntington’s disease (HD), manifested at around midlife with chorea, cognitive decline, and neuropsychiatric conditions, is caused by a mutation in the gene *Huntingtin* (*Htt*) in a

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classical autosomal dominant fashion that leads to a preferential loss of medium spiny projection neurons (MSNs) in the striatum. Although the key pathogenic mechanism, polyglutamine (polyQ) expansion in the N-terminal of *Htt* has been recognized, it remains elusive why MSNs die preferentially in HD since *Htt* is expressed ubiquitously. Zhang and colleagues (2014)

Frontotemporal dementia (FTD) is a heterogeneous disease associated to primary degeneration of the frontal and/or temporal lobes. It is the second most common form of dementia after Alzheimer's disease (AD) but its pathological mechanisms are much less well understood compared to AD. FTD is a rapidly progressing disease often associated with changes in social and emotional behaviors with a relative preservation of memory and there is no cure. Unexpectedly, recent advances indicate that FTD is pathologically and mechanistically linked to amyotrophic lateral sclerosis (ALS). ALS, also known as Lou Gehrig's disease, is the most common form of motor neuron degenerative disease and causes muscle wasting and eventual paralysis. Gascon and Gao (2014) review recent progress in the genetics and underlying molecular mechanisms of FTD-ALS spectrum disorders, focusing on altered mRNA metabolism and in particular the microRNA pathway. The review highlights exciting opportunities for both basic and translational neuroscientists in this fast-evolving field of unique cluster of neurodegenerative diseases.

Addiction to illicit drugs is a chronic, relapsing disorder characterized by compulsive drug seeking and use in the face of grave medical and socioeconomic consequences. Like most psychiatric diseases, addiction is polygenic: variations in many different genes contribute to an individual's overall level of risk or resistance. A cornerstone hypothesis of addiction continues to focus on the neurotransmitter dopamine, as all abused drugs elevate dopamine levels in mesocorticolimbic reward circuits. The principal regulator of dopamine transmission and signaling in the brain is the dopamine transporter (DAT), which is responsible for dopamine clearance and reuptake. As such, DAT, together with other components of dopamine signaling pathways, has been a focus of addiction genetics. Two heavily abused drugs are the psychostimulants cocaine and amphetamine, which raise brain dopamine levels via different mechanisms of actions: cocaine blocks DAT whereas amphetamine reverses DAT transport. Using various genetically engineered strains of mice that express different levels of DAT, Cagniard et al. (2014) show that behavioral responses to cocaine and amphetamine could be differentially modified. This finding has the important implication that the level of DAT expression may dictate how animals respond to different psychostimulant drug types and doses, and thus an individual's susceptibility to addiction to different types of illicit drugs.

Schizophrenia (SZ) and related psychiatric disorders are heritable neurodevelopmental disorders in which mutations, polymorphisms, and copy number variations (CNV) of multiple genes have been implicated. However, only a handful of SZ susceptibility genes have been identified thus far following extensive genetic analyses, and these genes fails to explain the vast majority of SZ cases, prompting some to argue that ultimate understanding and treatments of this devastating mental illness may come from other approaches (Horváth and Mirnics, 2014). In particular, developmental disturbances of brain circuits in a neuronal type-specific manner are a common manifestation of SZ, raising the need to establish

pathological molecular signatures of various neuron types. In this Issue, Woo and colleagues (Pietersen et al., 2014a; 2014b) obtained separate microarray gene expression profiles of laser-captured pyramidal cells and parvalbumin (PV) interneurons in the superior temporal cortex from postmortem brains of SZ patients and normal subjects. Their findings uncover novel gene transcripts, signaling cascades, and non-coding regulatory microRNA pathways that appear to be specifically disrupted in excitatory and inhibitory circuits, which separately regulate distinct aspects of cortical information processing and cognitive functions. These studies represent a significant step forward over previous gene chip expression analyses of SZ post-mortem brains, which have relied on heterogenous cortical tissues, precluding effective identifications of cell type-specific gene changes. These results provide a neurobiological framework, allowing testing hypotheses about specific molecular mechanisms of pyramidal and PV interneuron dysfunctions in SZ to formulate targeted molecular interventions.

Symptoms of SZ include episodic positive (delusions, hallucinations, paranoia, and psychosis) and/or persistent negative symptoms (avolition, flattened, social withdrawal), as well as cognitive impairments. These symptoms typically begin during puberty or young adulthood. A key for effective intervention or possible prevention of SZ is early diagnosis before its onset. Current diagnosis is based on patient behaviors and sometimes a prodrome. Genetic screening is not helpful for the vast majority of cases and identification of reliable biomarkers from accessible tissues (such as blood) is highly desirable. An emerging concept is that environment and genetic risk factors act through similar epigenetic mechanisms to alter the DNA methylation profiles and/or histone codes of some SZ susceptibility genes in the brain and in peripheral lymphocytes of SZ subjects. In their article, Guidotti and colleagues (2014) review converging evidence that supports this brain/lymphocyte homology hypothesis and discuss potential epigenetic mechanisms and candidate SZ genes that may undergo parallel regulations in brain and blood. Despite skepticisms and hesitations, identification of peripheral epigenetic biomarkers may have profound implications in prognosis, early intervention, and clinical decisions regarding prophylactic treatment leading to prevention of the prodromal syndrome, the onset of the first episode, or an impending future relapse.

The primary treatment for SZ is antipsychotic medications, which can reduce the positive symptoms of psychosis. The most effective antipsychotic drug (APD) is clozapine, classified as an atypical APD that targets dopamine and serotonin receptors, as well as other neurotransmitter systems and unidentified intracellular mechanisms (Gray and Roth, 2007). Consequently, clozapine produces serious unwanted and often toxic side effects, such as agranulocytosis, metabolic syndrome, and developmental impairments if used early in life. Understanding the molecular mechanisms underlying the therapeutic and side effects of clozapine and other APDs can facilitate improvement in SZ medications. Using a genome-wide RNAi screen for suppressors of clozapine-induced larval arrest in *C. elegans* – the first genetic suppressor screen for APD targets in an animal – Buttner and colleagues (Saur et al., 2013) had previously identified 40 putative clozapine targets. These include a nicotinic acetylcholine receptor subunit homolog, which they had already shown to be a novel APD target in the worm (Saur et al., 2013), and a transient receptor potential (TRP) M channel

(encoded by the *gtl-2* gene), which they characterize in this issue (Wang et al., 2014). The combined genetic, developmental, and behavioral analysis suggests that GTL-2 is important for clozapine's effects in *C. elegans* larval development and implicates for the first time a TRP channel in APD action.

The recent development of the induced pluripotent stem cell (iPSC) technology represents a revolutionary milestone in neurodegenerative and psychiatric research. In particular, it is now feasible to generate iPSC lines from patients and differentiate them to various neuronal and glial fates in the CNS, providing an unprecedented opportunity to study disease mechanisms and test therapeutic strategies in patient-derived relevant cell types. This was previously impossible due to the lack of accessibility to live patient brains. In their article, Srikanth and Young-Pearse (2014) provide a comprehensive, thorough, and critical review of the progress in the field since its launch, and describe both the advantages and pitfalls of modeling different brain diseases using this technology. The review covers all patient-derived iPSC lines created to date for different neurological and psychiatric diseases, the cell fates examined for each, and the cell and molecular phenotypes observed. The authors spell out important factors that must be taken into consideration when performing iPSC research, such as genetic variability among lines, epigenetic memory variation at disease loci, and X-inactivation status. In addition, limitations of using iPSCs to model neurodevelopmental and neurodegenerative diseases, two clusters of disorders that differ in onset, cell fate restriction, and pathological hallmarks, are discussed along with potential solutions. This insightful contribution provides an invaluable, all-inclusive resource for the iPSC community employing this approach to study causes and treatments of neurological and psychiatric diseases.

Some fifty years have gone by since Benzer and his associates launched the field of Neurogenetics. During this span, many causative disease loci have been hunted down in humans, virtually every gene has been genetically disrupted or modified in the mouse, and whole genomes of many species, including humans, have been sequenced at a single nucleotide resolution. Powerful genetic tools such as genome-wide association studies (GWAS) and CNV analysis have been developed that allow geneticists to untangle complex genetic interactions that may contribute to disease susceptibility. We have undoubtedly moved forward, yet the more we learn, it seems, the less we know. Nevertheless, this is an exciting era filled with unprecedented technology breakthroughs (e.g. optogenetics, genome editing, nanomedicine, etc) and opportunities for neuroscientists (e.g. the BRAIN initiative in the US, and its equivalents in the EU and Asian countries). Now that the field of Neurogenetics has matured and its concepts and approaches have permeated every branch of basic and clinical research endeavors, our resolve to crack the "genetic and operational codes" of the brain and to cure many of its pathologies is more promising than ever.

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