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Failed drug discovery in psychiatry: time for human genome-guided solutions

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Our knowledge about the molecular and neural mechanisms of emotional and cognitive processes has increased exponentially in the past decades. Unfortunately, there has been no translation of this knowledge into the development of novel and improved pharmacological treatments for psychiatric disorders. We comment on some of the reasons for failed drug discovery in psychiatry, particularly on the use of ill-suited disease models and on the use of diagnostic constructs unrelated to the underlying biological mechanisms. Furthermore, we argue that the use of human genetic findings together with biologically informed phenotypes and advanced data-mining methodology will catalyze the identification of promising drug targets and, finally, will lead to improved therapeutic outcomes.

Disillusionment in psychiatric pharmacotherapy

As young residents in psychiatry in the 1990s we were initially excited by the availability of a repertoire of different psychiatric medications. Indeed, many different compounds were available for specific diseases (e.g., amitryptiline, imipramine, iproniazid for depression; haloperidol, chlorpromazine, clozapine for schizophrenia) and some drugs seemed to be efficacious across disorders. In the eyes of a psychiatry novice, this broad inventory of psychoactive drugs led to the impression that the molecular paths leading to psychiatric disorders were obvious and that drugs existed that were specifically and efficiently directed towards these paths. It did not take long to realize that this was an erroneous impression. Not only was the efficacy of these drugs limited, and the molecular pathways related to psychiatric disorders unclear, but also the broad repertoire of psychiatric medications could be slimmed down into less than a handful of key compounds, with most drugs being close relatives of one prototype. In fact, the pharmacological concepts behind these prototypes were based on serendipity and were dated back to the 1950s without a significant modification since then.

Our initial disappointment with this stagnant treatment landscape was replaced by the hope that groundbreaking developments in neuroscience and the resulting gain of knowledge about molecular and neural mechanisms of cognitive and emotional processes would lead to the identification of better treatments. Now, two decades later, this expectation remains unfulfilled [1–3]. In this article we comment on some of the issues that, in our view, contribute to the current problematic situation, and argue that human- and genome-centered research approaches [1,2,4–12] might help to overcome the depression in psychiatric drug discovery.

Failed drug discovery

Brain disorders are common and cause enormous emotional and economic burden to patients, relatives, caregivers, and to the community. A recent comprehensive assessment of the direct and indirect financial consequences of brain disorders in Europe calculated an annual cost of 1 trillion US$, pointing out that this estimate is very likely to be conservative [13]. Topping the list of cost estimates are mood and anxiety disorders. Direct healthcare expenses (i.e., medication, hospitalization, and visits to physicians) account for 37% of the total costs. Although the market for drugs directed against psychiatric diseases is large (i.e., 80.5 billion US$ sales in 2010) and still growing [3,14], major pharmaceutical companies are disengaging from research and drug-discovery programs related to psychiatry because recent decades have brought no significant progress in the identification of novel and improved drugs for psychiatric diseases. In this environment, many companies have concluded that engagement in mental health drug development might be too risky [3]. The discrepancy between the urgent need for, and large market potential of, improved therapeutic compounds and the current lack of significant development of novel and improved drugs illustrates the importance of pursuing new strategies aimed at identifying druggable targets related to psychiatric disease.

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Glossary

Cohort: a group of people with one or more common statistical characteristics (e.g., healthy adults, aged between 18 and 35 years).
Complex trait: a quantifiable property of an organism influenced by both genetic and environmental factors as well as by interactions between them.
Drug-repositioning: the use of existing drugs for new therapeutic indications. Also known as drug-repurposing.
Endophenotype/intermediate phenotype: a heritable, disease-related trait (e.g., disturbed working memory) that is observed in patients and their healthy relatives. Genes contributing to an endophenotype represent a subset of the genes contributing to the respective disease.
Episodic memory: a memory system that enables conscious recollection of past experiences (e.g., autobiographical episodes, learned material) together with their spatial and temporal contexts.
Gene-set-based analytical methods: in contrast to single-marker statistics, which focus on single variants and the corresponding main effects, gene-set-based analysis attempts to identify biologically meaningful sets of genes associated with a certain complex trait. By taking into account prior biological knowledge, gene-set-based approaches examine whether test statistics for a group of related genes have consistent deviation from chance.
Genome-wide association study (GWAS): an analysis of genetic variants (usually hundreds of thousands of variants, ideally all of the genetic variants throughout the human genome) in groups of individuals to test for statistical association of these variants with a given trait. GWAS can be performed in a case–control setting (i.e., the trait of interest is represented by a binary variable, e.g., patients with schizophrenia vs healthy controls) and/or by using a quantitative trait approach (i.e., the trait of interest is represented by a continuous variable, e.g., memory performance). In contrast to methods that specifically test one or a few genes, GWAS investigate the entire genome.
Heritability: a population-based statistical value that indicates how much of the phenotypic variance is attributable to heritable factors. Heritability values range between 0 (i.e., heritable factors explain 0% of the phenotypic variance) and 1 (i.e., heritable factors explain 100% of the phenotypic variance). Heritability is specific to the population under study and does not apply to traits not showing any variability.
High-throughput genotyping platform: array- or sequencing-based technologies enabling high-throughput analysis of genetic variants.
Long-term depression pathway: genes constituting this pathway are involved in the modulation of synaptic strength between nerve cells.
Neuroactive ligand–receptor interaction pathway: genes constituting this pathway encode neuronal receptors and their binding partners.
Odds ratio (OR): a numerical value that describes the strength of the association between two binary variables. In genetic association studies, the OR describes the strength of the association between a given genetic variant and a binary trait (e.g., disease status).
Phenotype: an observable characteristic of an organism with respect to a physiological trait (e.g., blue eye color; memory performance) or disease (e.g., depression).
Single-marker statistics: this type of genetic analysis tests for statistical association of a variant with a given trait independently of the association of other variants with that trait. In a genome-wide setting engaging the analysis of 1 million variants, this type of analysis yields 1 million independent test results.
Trait-associated single-gene locus: a gene variant that is statistically associated with the trait under study.
Variant: in genetics, a difference in DNA sequence among individuals. A common form of a genetic variant is a SNP, which occurs when a nucleotide – A, T, C, or G – differs between individuals. The human genome contains millions of SNPs.
Working memory: a limited-capacity neural network capable of actively maintaining task-relevant information during the execution of a cognitive task. Working memory deficits are characteristic of many psychiatric disorders.

Ill-suited disease models

Human psychiatric disorders are human-specific conditions, characterized by the interplay of genetic, environmental, and social factors. There is growing awareness of the limitations of some widely used animal models [15] and of the fact that many of these models poorly reflect human disease. For example, widely used murine models of depression do not model appropriately the therapeutic action of antidepressants [2]. Therefore, it is time to seriously reappraise the usefulness of animal experiments claiming to model human mental disease. The questionable comparability between animals and humans is not an issue specific to psychiatry but seems also to be inherent to other complex disorders. A recent large study comparing transcriptional responses to inflammatory insults in mice and humans revealed that, among genes changed significantly in humans, the murine orthologs poorly match their human counterparts [16].

Despite these significant caveats, ill-suited models are still being used to make go or no-go decisions to carry drug candidates forward into clinical trials [16]. The time has come, especially in psychiatry, to utilize the appropriate research tools and focus on the human situation to understand the paths leading to human-specific psychiatric disorders, and thereby to increase the success rates of drug discovery. Because of the high heritability rates (see Glossary) of psychiatric disorders, human genetics represents such an appropriate, human-centered research tool.

The promising human genome

Improving understanding, diagnosis, and therapy of human disease was a central promise of the human genome project [17]. This promise is being increasingly fulfilled, at least in some medical research fields. For example, cancer research has benefited dramatically from the discoveries of the human genome project [4], mainly because the genomic mechanisms leading to the development of many cancers are amenable to direct observation. The situation is different for disorders in which the underlying molecular events are not easily accessible, as is the case for mental disorders. Thus, it is logical to ask whether utilizing genome information will have a significant impact on the understanding of mental disease and on the development of better therapies.

Recent advances in the development of high-throughput genotyping platforms, analytical software, and collaborative efforts have led to the identification of numerous well-validated genetic risk factors for common, complex diseases (http://www.genome.gov/gwastudies). Importantly, known drug targets for such complex diseases as type 2 diabetes, hyperlipidemia, multiple sclerosis, and psoriasis have turned up in the genome-wide association studies (GWAS) [5]. Recent mega-analyses have also led to the robust identification of genetic risk factors for common psychiatric disorders [18–20] and to the notion that many of these factors are shared across diagnostic categories [21]. Thus, the use of genetic information is also likely to provide important clues about potential drug targets for psychiatric disorders.

Ill-suited phenotypes for drug discovery

Notwithstanding these recent human genetics-driven discoveries, it is important to point out that the success and relevance of human genetic research stands and falls with the choice of the appropriate phenotype. In this respect, current diagnostic constructs in psychiatry, such as those used in most GWAS, are clearly suboptimal.

Imagine a patient presenting with the following symptoms in the same 2 week period: loss of interest, feelings of guilt, weight loss, insomnia, and psychomotor agitation. This patient fulfills the diagnostic criteria for major depressive disorder (MDD) [22]. Now imagine another patient presenting with the following symptoms in the same