

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

Andreas Papassotiropoulos^{1,2,3,4} and Dominique J.-F. de Quervain^{2,4,5}

¹ University of Basel, Department of Psychology, Division of Molecular Neuroscience, Basel, Switzerland

² University of Basel, Psychiatric University Clinics, Basel, Switzerland

³ University of Basel, Department Biozentrum, Life Sciences Training Facility, Basel, Switzerland

⁴ University of Basel, Transfaculty Research Platform, Basel, Switzerland

⁵ University of Basel, Department of Psychology, Division of Cognitive Neuroscience, Basel, Switzerland

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., amitriptyline, 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.

Corresponding authors: Papassotiropoulos, A. (andreas.papas@unibas.ch); de Quervain, D.J.-F. (dominique.dequervain@unibas.ch).

1364-6613/

© 2015 Elsevier Ltd. All rights reserved. <http://dx.doi.org/10.1016/j.tics.2015.02.002>

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

2 week period: depressed mood, fatigue, weight gain, hypersomnia, and psychomotor retardation. This patient also fulfills the diagnostic criteria for MDD, despite a different clinical picture. This example instantly highlights one of the central problems in psychiatry: the absence of biologically operationalized diagnostic criteria. Psychiatric diagnoses are still treated as constructs based on clinical phenomenology and represent a consensus list of different symptoms, mostly unrelated to the underlying biology. Such diagnostic lists, although useful in clinical terms, compromise the search for biological underpinnings of disease and jeopardize the development of targeted and causal therapies.

Exclusive dependency on phenomenology and a list of symptoms may lead to arbitrary classifications. For example, although the current DSM version offers 11 combinations of criteria to arrive at diagnostic threshold for autism spectrum disorder, the previous DSM version offered a total of 2027 different combinations [23]. There is no biological rationale for the justification of either number of combinations, but the influence of this arbitrary classification on research and the development of targeted treatments is obvious.

Appropriate phenotypes for drug discovery

As long as psychiatric classification results in an insufficient description of the neurobiological heterogeneity of human psychopathology, the search for targeted – and hopefully more effective – therapies of disorders related to pathological cognitive or emotional states will be seriously compromised. Mental disorders are not always dichotomous categories. At least in the case of common and heterogeneous disorders, such as depression, schizophrenia, and autism, the evidence suggests that mental disease represents the extremes of a normal distribution of symptoms on multiple dimensions – for example, cognitive, emotional, and behavioral dimensions [24–31] (but see also [32,33]). Fortunately, this fact has received increased attention. The idea of deconstructing psychiatric categories into measurable and biologically informed dimensions has its roots in the endophenotype/intermediate-phenotype concept [8,34], which supports the notion that genetic associations will be stronger at the level of biological substrates of a given psychiatric illness than at the level of the respective diagnostic category [8]. Recent work, mostly related to the schizophrenia spectrum and to functional brain imaging as the relevant intermediate phenotype, has provided important empirical evidence in support of this rationale [35–38].

Along the lines of the intermediate phenotype concept, the recently launched Research Domain Criteria (RDoC) initiative aims at establishing a new classification framework for research on mental disorders by capitalizing on the current developments in neuroscientific methodology [39]. However, caution needs to be exercised when deconstructing psychiatric categories and diagnoses into biologically informed dimensions. As pointed out recently, even clear and important behavioral dimensions observed in patients may be difficult to assess in healthy individuals [33]. Specifically, it might prove erroneous to assume that the mechanisms that give rise to a given dimension

Box 1. Key criteria for biologically informed domains in psychiatry

Relevance criterion: the domains represent physiological traits that are known to be disturbed in neuropsychiatric diseases. Examples: working memory, episodic memory, attention, verbal fluency, cognitive control.

Neural correlate criterion: the domains have specific and testable neural correlates (e.g., as shown in human brain imaging studies). This allows for further corroboration at the neural systems level.

Genetic criterion: the domains are heritable. This enables the utilization of human genetic information to identify molecules related to the domain under study.

in a non-diseased population are the same mechanisms associated with this dimension in patients. For example, auditory hallucinations can be present in healthy individuals; however, it is unclear whether the same mechanisms are in place in psychiatric patients experiencing acoustic hallucinations during a psychotic episode [32]. Consequently, a study on the genetic underpinnings of acoustic hallucinations performed in the general population might identify biological mechanisms that are not linked to psychosis and which are therefore ill-suited for further consideration as potential drug targets.

Despite these caveats, we believe that a deconstruction of psychiatric categories and diagnoses into biologically informed domains will be key for improving drug discovery in psychiatry, provided that such domains fulfill the criteria listed in [Box 1](#).

Appropriate data mining for drug discovery

GWAS employing single-marker statistics have been successful in identifying trait-associated single-gene loci [40]. It is, however, widely accepted that single-marker-based analyses have limited power to identify the genetic basis of a given trait. For example, many loci will fail to reach the stringent genome-wide significance threshold despite the fact that they may be genuinely associated with the trait. Statistical approaches for the analysis of gene expression have recently made gene-set-based analytical methods available. These methods aim to identify biologically meaningful sets of genes associated with a particular trait rather than focusing on a single GWAS gene locus [41]. 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 [41,42]. As shown recently in studies on working memory [43], autism [44], bipolar disorder [19,45], attention deficit hyperactivity disorder (ADHD) [46], and schizophrenia [47], such approaches can identify convergent molecular pathways relevant to neuropsychiatry. Importantly, the identification of groups of functionally related genes is likely to facilitate drug discovery because the most significant single loci from a GWAS might not be the best candidates for therapeutic intervention [7,48]. This pathway approach has been already integrated into corporate drug-discovery pipelines because the more genes for any given pathway are identified, the greater the confidence that this pathway should be prioritized over others [10].

Facilitating drug discovery through human genetics

With the launch of multinational collaborative efforts and the initiation of large-scale GWAS, the robustness and reliability of genetic association findings on complex traits and disorders have finally reached the level of confidence required for further consideration of the trait-associated genes as starting points for drug discovery. This increase in confidence also applies to the psychiatric genetics field, which has also benefited from the formation of large consortia [18]. However, phenotype definition in these large studies still relies on diagnostic constructs which, as described above, are not driven by biological information.

In the past few years, pharmaceutical companies have made large investments with the expectation that some of the GWAS findings will ultimately lead to novel therapeutic agents. It remains to be seen how successful the translation of such findings to novel drugs will be. Allowing enough time for this judgment will be crucial because the GWAS field is rather new and the road from target identification to regulatory approval of a new drug takes more than a decade. Nevertheless, it is fair to ask whether there is any support for the potential of this genetic approach to facilitate drug discovery. Evidence comes from a recent study which assessed the utility of GWAS in identifying alternative indications of existing drugs [11]. By implementing a systematic and comprehensive analysis pipeline, the study demonstrated that GWAS genes are significantly more likely to be theoretically druggable or biopharmable targets than expected only by chance. Importantly, the study showed that GWAS data may lead to immediate translational opportunities for drug discovery and development through successful drug-repositioning [11]. It is therefore logical to assume that GWAS have the potential of translating into novel treatment targets for psychiatric conditions. Indeed, strategies for applying human genetics to drug discovery in neuroscience are being developed [10].

We recently conducted a study focusing on a physiological cognitive domain fulfilling the criteria described in Box 1, and we addressed the question of whether the use of human genetic information would lead to the identification of compounds modulating human cognition [12]. In a first step we performed a multinational collaborative study that included assessment of aversive memory – a trait central to post-traumatic stress disorder – and a genetic analysis in healthy individuals. Gene-set-based analysis identified two pathways, the neuroactive ligand–receptor interaction and the long-term depression pathway, that were enriched with genes associated with aversive memory. A total of 20 genes constituting these pathways were replicated in two independent cohorts and represent potential drug target genes. To provide a rapid proof-of-concept for human genetics-guided identification of memory-modulating drugs, we selected from these 20 candidate targets only gene products with already existing therapeutic compounds. Diphenhydramine, which targets the histamine 1 receptor (encoded by *HRH1*) that is a member of the neuroactive ligand–receptor interaction pathway, was given highest priority for a subsequent pharmacological intervention trial. Diphenhydramine led to significant

reduction of aversive memory in healthy participants. Further studies are needed to assess whether this finding translates into the therapy of a clinical condition, such as post-traumatic stress disorder. This study demonstrated that genome information can be used as a starting point for the identification of memory-modulating compounds. In addition to diphenhydramine and other already well-known drugs, it provided several novel drug targets that may serve drug development purposes.

Notwithstanding the potential of the human genetics approach for drug discovery in psychiatry, it is important to realize that this approach also comes with challenges and limitations. For example, despite the reliable identification of disease-associated genomic loci, the connection between GWAS locus and biology of the respective disorder is not always readily clear and straightforward [9]. In this context, the assignment of a given locus to a gene and the identification of causal genes are important and nontrivial tasks. Even when a gene is identified as causal, the direction of the effect of this gene on disease processes is rarely known [10]. Further, the genomic architecture of psychiatric disorders is complex. Human genetics alone cannot entirely capture and describe this complexity, and should be therefore considered as only one of multiple possible sources of information within a framework of methods aimed at identifying causal biological mechanisms of disease and pharmacological remedies for targeting these mechanisms. Another issue worth mentioning is the fact that most GWAS to date are performed in populations of European ancestry. Thus, it is not clear whether a drug identified through such GWAS will be efficacious in populations with distinct genetic backgrounds.

Of note, the vast majority of the GWAS-derived risk variants show low effect sizes (e.g., the odds ratios of the recent large GWAS of schizophrenia cluster around 1.1). One may think of this observation as another potential limitation. However, it is not possible to extrapolate from the odds ratio of a gene to biological effect size [49] or to the therapeutic potency of a drug discovered through genetic association [9,10]. For example, the effect size of common variants of the genes encoding HMG-CoA-reductase (*HMGCR*) and peroxisome proliferator-activated receptor- γ (*PPARG*) on blood lipid levels and risk for type 2 diabetes is small, but these genes point to potent drugs for the treatment of hyperlipidemia and type 2 diabetes, respectively [50–52].

Concluding remarks

Drug discovery in psychiatry has been jeopardized by the use of ill-suited disease models and diagnostic constructs unrelated to underlying biological mechanisms. We anticipate that the exponential increase in knowledge about the genetic basis of complex human traits, including neuropsychiatric disorders, will be a game-changer. Together with appropriate, biologically informed phenotypes, and appropriate data-mining methodology, such knowledge is an ideal starting point for the identification of novel drug targets. Although it remains to be seen whether such approaches will ultimately improve therapeutic outcomes, they bear considerable potential for understanding the neurobiology of human psychopathology.

References

- 1 Insel, T.R. (2012) Next-generation treatments for mental disorders. *Sci. Transl. Med.* 4, 155ps119
- 2 Hyman, S.E. (2012) Revolution stalled. *Sci. Transl. Med.* 4, 155cm111
- 3 Abbott, A. (2011) Novartis to shut brain research facility. *Nature* 480, 161–162
- 4 Lander, E.S. (2011) Initial impact of the sequencing of the human genome. *Nature* 470, 187–197
- 5 Collins, F.S. (2011) Reengineering translational science: the time is right. *Sci. Transl. Med.* 3, 90cm17
- 6 Healy, D.G. et al. (2004) Population genetics for target identification. *Drug Discov. Today Technol.* 1, 69–74
- 7 Muglia, P. (2011) From genes to therapeutic targets for psychiatric disorders – what to expect? *Curr. Opin. Pharmacol.* 11, 563–571
- 8 Rasetti, R. and Weinberger, D.R. (2011) Intermediate phenotypes in psychiatric disorders. *Curr. Opin. Genet. Dev.* 21, 340–348
- 9 Plenge, R.M. et al. (2013) Validating therapeutic targets through human genetics. *Nat. Rev. Drug Discov.* 12, 581–594
- 10 Schubert, C.R. et al. (2014) Translating human genetics into novel treatment targets for schizophrenia. *Neuron* 84, 537–541
- 11 Sansseau, P. et al. (2012) Use of genome-wide association studies for drug repositioning. *Nat. Biotechnol.* 30, 317–320
- 12 Pappasotiropoulos, A. et al. (2013) Human genome-guided identification of memory-modulating drugs. *Proc. Natl. Acad. Sci. U.S.A.* 110, E4369–E4374
- 13 Gustavsson, A. et al. (2011) Cost of disorders of the brain in Europe 2010. *Eur. Neuropsychopharmacol.* 21, 718–779
- 14 Smith, K. (2011) Trillion-dollar brain drain. *Nature* 478, 15
- 15 Editorial (2013) Of men, not mice. *Nat. Med.* 19, 379
- 16 Seok, J. et al. (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. U.S.A.* 110, 3507–3512
- 17 Editorial (2011) Best is yet to come. *Nature* 470, 140
- 18 Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427
- 19 Sklar, P. et al. (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* 43, 977–983
- 20 Wang, K. et al. (2009) Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* 459, 528–533
- 21 Cross-Disorder Group of the Psychiatric Genomics Consortium and Genetic Risk and Outcome of Psychosis Consortium (2013) Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 381, 1371–1379
- 22 American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, American Psychiatric Association
- 23 McPartland, J.C. et al. (2012) Sensitivity and specificity of proposed DSM-5 diagnostic criteria for autism spectrum disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 51, 368–383
- 24 Kendler, K.S. and Gardner, C.O., Jr (1998) Boundaries of major depression: an evaluation of DSM-IV criteria. *Am. J. Psychiatry* 155, 172–177
- 25 Zammit, S. et al. (2013) Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *Am. J. Psychiatry* 170, 742–750
- 26 Whittington, J.E. and Huppert, F.A. (1996) Changes in the prevalence of psychiatric disorder in a community are related to changes in the mean level of psychiatric symptoms. *Psychol. Med.* 26, 1253–1260
- 27 van Os, J. (2013) The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. *Am. J. Psychiatry* 170, 695–698
- 28 Lundstrom, S. et al. (2012) Autism spectrum disorders and autistic like traits: similar etiology in the extreme end and the normal variation. *Arch. Gen. Psychiatry* 69, 46–52
- 29 Anderson, J. et al. (1993) Normality, deviance and minor psychiatric morbidity in the community. A population-based approach to General Health Questionnaire data in the Health and Lifestyle Survey. *Psychol. Med.* 23, 475–485
- 30 Touloupoulou, T. et al. (2007) Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Arch. Gen. Psychiatry* 64, 1348–1355
- 31 Quee, P.J. et al. (2014) Cognitive subtypes in non-affected siblings of schizophrenia patients: characteristics and profile congruency with affected family members. *Psychol. Med.* 44, 395–405
- 32 David, A.S. (2010) Why we need more debate on whether psychotic symptoms lie on a continuum with normality. *Psychol. Med.* 40, 1935–1942
- 33 Weinberger, D.R. and Goldberg, T.E. (2014) RDoCs redux. *World Psychiatry* 13, 36–38
- 34 Gottesman, I.I. and Gould, T.D. (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160, 636–645
- 35 Egan, M.F. et al. (2004) Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. *Proc. Natl. Acad. Sci. U.S.A.* 101, 12604–12609
- 36 Callicott, J.H. et al. (2005) Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proc. Natl. Acad. Sci. U.S.A.* 102, 8627–8632
- 37 Esslinger, C. et al. (2009) Neural mechanisms of a genome-wide supported psychosis variant. *Science* 324, 605
- 38 Bigos, K.L. et al. (2010) Genetic variation in CACNA1C affects brain circuitries related to mental illness. *Arch. Gen. Psychiatry* 67, 939–945
- 39 Insel, T. et al. (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167, 748–751
- 40 Manolio, T.A. (2010) Genomewide association studies and assessment of the risk of disease. *N. Engl. J. Med.* 363, 166–176
- 41 Wang, K. et al. (2010) Analysing biological pathways in genome-wide association studies. *Nat. Rev. Genet.* 11, 843–854
- 42 Mooney, M.A. et al. (2014) Functional and genomic context in pathway analysis of GWAS data. *Trends Genet.* 30, 390–400
- 43 Heck, A. et al. (2014) Converging genetic and functional brain imaging evidence links neuronal excitability to working memory, psychiatric disease, and brain activity. *Neuron* 81, 1203–1213
- 44 Voineagu, I. et al. (2011) Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 474, 380–384
- 45 Holmans, P. et al. (2009) Gene ontology analysis of GWA study data sets provides insights into the biology of bipolar disorder. *Am. J. Hum. Genet.* 85, 13–24
- 46 Stergiakouli, E. et al. (2012) Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. *Am. J. Psychiatry* 169, 186–194
- 47 O'Dushlaine, C. et al. (2011) Molecular pathways involved in neuronal cell adhesion and membrane scaffolding contribute to schizophrenia and bipolar disorder susceptibility. *Mol. Psychiatry* 16, 286–292
- 48 Gaudet, M.M. et al. (2010) Common genetic variants and modification of penetrance of BRCA2-associated breast cancer. *PLoS Genet.* 6, e1001183
- 49 Okada, Y. et al. (2014) Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 506, 376–381
- 50 Kathiresan, S. et al. (2008) Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat. Genet.* 40, 189–197
- 51 Burkhardt, R. et al. (2008) Common SNPs in *HMGCR* in micronesians and whites associated with LDL-cholesterol levels affect alternative splicing of exon13. *Arterioscler. Thromb. Vasc. Biol.* 28, 2078–2084
- 52 Altshuler, D. et al. (2000) The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat. Genet.* 26, 76–80