NEW TECHNOLOGIES PROVIDE INSIGHTS INTO GENETIC BASIS OF PSYCHIATRIC DISORDERS AND EXPLAIN THEIR CO-MORBIDITY

Igor Rudan

Centre for Population Health Sciences, The University of Edinburgh Medical School, UK
Croatian Centre for Global Health, Faculty of Medicine, University of Split, Croatia

SUMMARY

The completion of Human Genome Project and the "HapMap" project was followed by translational activities from companies within the private sector. This led to the introduction of genome-wide scans based on hundreds of thousands of single nucleotide polymorphysms (SNP). These scans were based on common genetic variants in human populations. This new and powerful technology was then applied to the existing DNA-based datasets with information on psychiatric disorders. As a result, an unprecedented amount of novel scientific insights related to the underlying biology and genetics of psychiatric disorders was obtained. The dominant design of these studies, so called "genome-wide association studies" (GWAS), used statistical methods which minimized the risk of false positive reports and provided much greater power to detect genotype-phenotype associations. All findings were entirely data-driven rather than hypothesis-driven, which often made it difficult for researchers to understand or interpret the findings. Interestingly, this work in genetics is indicating how non-specific some genes are for psychiatric disorders, having associations in common for schizophrenia, bipolar disorder and autism. This suggests that the earlier stages of psychiatric disorders may be multi-valent and that early detection, coupled with a clearer understanding of the environmental factors, may allow prevention. At the present time, the rich "harvest" from GWAS still has very limited power to predict the variation in psychiatric disease status at individual level, typically explaining less than 5% of the total risk variance. The most recent studies of common genetic variation implicated the role of major histocompatibility complex in schizophrenia and other disorders. They also provided molecular evidence for a substantial polygenic component to the risk of psychiatric diseases, involving thousands of common alleles of very small effect. The studies of structural genetic variation, such as copy number variants (CNV), coupled with the efforts targeting rare genetic variation (using the emerging whole-genome "deep" sequencing technologies) will become the area of the greatest interest in the field of genetic epidemiology. This will be complemented by the studies of epigenetic phoenomena, changes of expression at a large scale and understanding gene-gene interactions in complex networks using systems biology approaches. A deeper understanding of the underlying biology of psychiatric disorders is essential to improve diagnoses and therapies of these diseases. New technologies — genome-wide association studies, imaging and the optical manipulation of neural circuits — are promising to provide novel insights and lead to new treatments.

Key words: *psychiatric diseases – genetics - human genome - genome-wide association studies - co-morbidity*

* * * * *

Introduction

The completion of Human Genome Project provided the first insight into a complete sequence of the haploid human genome. The expectations from general public, media, investors, industrial sector and researchers themselves were large, and the main hope was to revolutionize medical practice. Everyone was hoping for an era of discovery of important biological processes controlled by genes that would lead to development and creation of the new, "smarter" drugs. These novel drugs would be more targeted and effective, and have lesser side effects. There was also a hope of "personalized medicine" which would be based on predictive genetics and administration of "tailored" drugs to patients, before a disease even develops (Risch & Merikangas 1996, Collins 2010).

Instead of traditional, hypothesis-driven research, the new era of discovery in biomedical research dawned. After decades of being limited to studying environmental, social and economic factors that predisposed to human diseases, the researchers were suddenly able to measure human individual genetic make-up more precisely than any of the aforementioned risk factors. Studies were designed in which cases suffering from certain diseases were compared to healthy controls regarding their genetic make-up, without any "a priori" hypothesis. Association between genes and diseases were sought through a design called "genome-wide association study", without necessarily needing to understand anything about the function of those genes. The researchers were looking for statistically significant differences in the frequency of gene variants between diseased cases and controls at hundreds of thousands of loci in the genome (Golub 2010).

To achieve this, the whole genome needed to be "tagged" in some way, using parts of the human genome that are very different among individuals – so-called "genomic markers". The "HapMap" project (an abbreviation of "haplotype mapping") defined "blocks" of the human genome which were relatively free from the "crossing over" phenomenon. Such blocks were tagged with polymorphic genetic markers – hundreds of thousands of them across the genome. This massive project was followed by translational activities, undertaken by the companies from the private sector (e.g. *Affymetrix* Inc. and *Illumina* Inc.). This resulted in the introduction of genome-wide scans based on hundreds of thousands of single nucleotide polymorphysms (SNP). These scans were based on "common" genetic variants in human populations, in which the frequency of minor

allele is still greater than 5% in the population. The common variants were specifically chosen for scans to "tag" the "blocks" of the genome separated by "recombination hot-spots" (Wellcome 2007).

Genome-wide association studies

Hundreds of genetic variants that influence complex human diseases have been found and reported during the period between 2007 and 2010. The dominant design of these studies, so called "genome-wide association studies" (GWAS), used statistical methods which minimized the risk of false positive reports. Massive international collaborations between groups of scientists resulted in sample sizes which provided great power to detect genotype-phenotype associations. All findings were entirely data-driven rather than hypothesis-driven, which often made it difficult for researchers to understand or interpret the findings (Golub 2010, Wellcome 2007).

The recent application of this new and powerful technology to the existing datasets with information on psychiatric disorders and stored DNA resulted in an unprecedented amount of novel scientific insights related to the underlying biology and genetics of psychiatric disorders and many other complex human diseases (Burmeister et al. 2008). The application of these novel technologies to the study of genetic basis of psychiatric diseases exposed the first interesting candidate loci in the genome. Surprisingly, the findings indicated that some genes associated with psychiatric disorders seem to be non-specific, having associations in common for schizophrenia, bipolar disorder and autism. This suggests that the earlier stages of psychiatric disorders may be multi-valent and that early detection, coupled with a clearer understanding of the environmental factors, may allow prevention (Burmeister et al. 2008, Walsh et al. 2008).

The most recent studies of common genetic variation, using 3,322 European individuals with schizophrenia and 3,587 controls and two different analytic approaches, implicated the role of major histocompatibility complex in schizophrenia and other disorders. They also provided molecular evidence for a substantial polygenic component to the risk of psychiatric diseases, involving thousands of common alleles of very small effect. The same component also contributes to the risk of bipolar disorder, but not to several other non-psychiatric diseases (The International Schizophrenia Consortium 2009).

It should be stressed that genome-wide association studies rapidly become accepted as a new and powerful tool to search for novel biological insights to explain susceptibility for psychiatric diseases. However, with the possible exception of the variants in CNTNAP2 gene and its association with autism, which has been convincingly replicated by more than one group, genome-wide association studies have not brought the psychiatric research field into focus. Currently, it appears that each new large-scale association study keeps bringing new loci to attention of the research community, but very few of those identified loci are easily replicated in other cohorts. This is in contrast to other common complex diseases, such as myocardial infarction, type 2 diabetes, colorectal cancer, Crohn's disease or rheumatoid arthritis, in which all the conducted genome-wide association studies usually confirmed associations that were previously reported by other groups (Wellcome 2007, Burmeister et al. 2008, Walsh et al. 2008, The International Schizophrenia Consortium 2009, Editorial, Nature 2010).

What is the reason for this relative lack of success in finding genes with replicable associations with psychiatric diseases in comparison to other complex human diseases? There are several. Firstly, there is the issue of the precision to which we can diagnose psychiatric disorders today (Burmeister et al. 2008, Schulze 2010, Plomin et al. 2009). The power of genome-wide association studies to detect genes depends on strong links between the studied phenotype and genotypes. If the phenotype cannot be measured and quantified accurately and there is substantial misclassification of cases and controls, the power of the study diminishes very quickly. Psychiatric disorders are lot more difficult to objectively "measure" in comparison to other diseases that have reasonably straight-forward diagnostic criteria, such as e.g. colorectal cancer or Crohn's disease (Wellcome 2007, Burmeister et al. 2008, Walsh et al. 2008, The International Schizophrenia Consortium 2009, Editorial, Nature 2010).

Secondly, the current genome-wide association studies of psychiatric diseases typically involved only a few thousand cases and controls, whereas the studies of more common diseases (e.g. diabetes type 2 or myocardial infarction) managed to collect, diagnose and genotype more than 50,000 cases and controls already (Wellcome 2007, Burmeister et al. 2008, Walsh et al. 2008, The International Schizophrenia Consortium 2009, Editorial, Nature 2010). Studies of simpler phenotypes, such as e.g. human height or body mass index, have now reached more than 250,000 participants in the global effort to underpin the underlying genetic variants and understand the "genetic architecture" of complex human traits. Thus, larger sample sizes will surely bring new insights in the near future, and several quantitative test scores relevant to cognitive functioning may also prove to be more tractable "intermediate traits" (so-called "endophenotypes") for studying rather than the incredibly complex phenotype of human psychiatric diseases (Burmeister et al. 2008, Schulze 2010, Plomin et al. 2009, Mansour et al. 2009, Garriock et al. 2010).

Translation of the early results into practice and future research avenues

It is known that most psychiatric conditions are highly heritable. However, at the present time the rich "harvest" from GWAS in terms of the quantity of

discovery still has very limited power to predict the variation in psychiatric disease status at individual level. All identified variants combined together typically explain less than 5% of the total variance in disease risk between individuals. Efforts to explain the "missing heritability" of human psychiatric disorders are underway. The studies of structural genetic variation, such as copy number variants (CNV), coupled with the efforts targeting rare genetic variation (using the emerging whole-genome "deep" sequencing technologies) will become the area of the greatest interest in the field of genetic epidemiology (Tam et al. 2009, Knight et al. 2009). This will be complemented by the studies of epigenetic phoenomena, changes of expression at a large scale and understanding gene-gene interactions in complex networks using systems biology approaches (Burmeister et al. 2008, Editorial, Nature 2010, Akil et al. 2010).

Conclusion

Although psychiatric disorders are highly heritable, identifying their genetic basis has so far been challenging, with most discoveries failing to be replicated. However, improvements of classification and diagnosis of psychiatric diseases, increase in sample size, and the incorporation of intermediate quantitative traits ("endophenotypes") and multiple known environ-mental and social determinants into genetic analyses, will all help to find replicable genetic variants associated with disease risk. Further steps will include the identification of rare inherited variants and novel structural mutations (Burmeister et al. 2008, Editorial, Nature 2010, Akil et al. 2010).

A deeper understanding of the underlying biology of psychiatric disorders, such as schizophrenia, bipolar disorder or autism, is essential to improve diagnoses and therapies of these diseases. There has been little progress with treatment of these disorders over the past several decades. However, new technologies — inclu-ding not only genome-wide association studies descri-bed in this article, but also novel imaging technologies and the optical manipulation of neural circuits — are promising to provide novel insights and lead to new treatments (Editorial, Nature 2010, Akil et al. 2010).

REFERENCES

1. *Akil H, Brenner S, Kandel E, Kendler KS, King MC, Scolnick E, Watson JD, Zoghbi HY. The Future of Psychiatric Research: Genomes and Neural Circuits. Science 2010; 327:1580-1581.*

2. *Burmeister M, McInnis MG, Zöllner S. Psychiatric genetics: progress amid controversy. Nature Reviews Genetics 2008; 9:527-540.*

3. *Collins FS. Has the revolution arrived? Nature 2010; 464:674-675.*

4. *Editorial. A decade for psychiatric disorders. Nature 2010; 463: 9-10.*

5. *Golub T. Counterpoint: Data first. Nature 2010; 464: 679-680.*

6. *Risch, N. & Merikangas, K. The future of genetic studies of complex human diseases. Science 273, 1516–1517 (1996).*

7. *The International Schizophrenia Consortium: Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009; 460: 748-752.*

8. *Walsh, T. et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320, 539–543 (2008).*

9. *Schulze TG. Genetic research into bipolar disorder: the need for a research framework that integrates sophisticated molecular biology and clinically informed phenotype characterization. Psychiatr Clin North Am 2010; 33:67-82.*

10. *Plomin R, Haworth CM, Davis OS. Common disorders are quantitative traits. Nat Rev Genet 2009; 10:872-8.*

11. *Mansour HA, Talkowski ME, Wood J, Chowdari KV, McClain L, Prasad K, Montrose D, Fagiolini A, Friedman ES, Allen MH, Bowden CL, Calabrese J, El-Mallakh RS, Escamilla M, Faraone SV, Fossey MD, Gyulai L, Loftis JM, Hauser P, Ketter TA, Marangell LB, Miklowitz DJ, Nierenberg AA, Patel J, Sachs GS, Sklar P, Smoller JW, Laird N, Keshavan M, Thase ME, Axelson D, Birmaher B, Lewis D, Monk T, Frank E, Kupfer DJ, Devlin B, Nimgaonkar VL. Association study of 21 circadian genes with bipolar I disorder, schizoaffective disorder, and schizophrenia. Bipolar Disord. 2009; 11:701-10.*

12. *Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD, Reinalda MS, Slager SL, McGrath PJ, Hamilton SP. A genomewide association study of citalopram response in major depressive disorder. Biol Psychiatry. 2010; 67:133-8.*

13. *Tam GW, Redon R, Carter NP, Grant SG. The role of DNA copy number variation in schizophrenia. Biol Psychiatry. 2009; 66:1005-12.*

14. *Knight HM, Pickard BS, Maclean A, Malloy MP, Soares DC, McRae AF, Condie A, White A, Hawkins W, McGhee K, van Beck M, MacIntyre DJ, Starr JM, Deary IJ, Visscher PM, Porteous DJ, Cannon RE, St Clair D, Muir WJ, Blackwood DH. A cytogenetic abnormality and rare coding variants identify ABCA13 as a candidate gene in schizophrenia, bipolar disorder, and depression. Am J Hum Genet. 2009; 85(6):833-46.*

15. *Akil H, Brenner S, Kandel E, Kendler KS, King MC, Scolnick E, Watson JD, Zoghbi HY. The Future of Psychiatric Research: Genomes and Neural Circuits. Science 2010; 327:1580-1581.*

Correspondence:

Professor Igor Rudan, MD, DSc, PhD, MPH
Croatian Centre for Global Health, Faculty of Medicine, University of Split, Croatia
E-mail: irudan@hotmail.com