Main topic

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Out of the lab and into the clinic: steps to a pragmatic new era in psychiatric genetics

https://doi.org/10.1515/medgen-2020-2013

Despite its high frequency and many decades of research, the biological basis of psychiatric disease remains poorly understood. This has implications in terms of treatment, with many currently available therapies showing limited efficacy or, in the case of drug therapy, adverse side effects. For many years, researchers have hoped that breakthroughs in the biological understanding of psychiatric diseases could be achieved through the use of genetic approaches. Even early descriptions of psychiatric disorder cases reported a familial occurrence [1]. Formal genetic studies have demonstrated that this familial occurrence is mainly attributable to genetic factors. Since the mid-1980s, attempts have been made to identify the implicated genes. These attempts have been facilitated by the advent of molecular genetic methods. Initially, this proved to be a frustrating endeavor, with the generation of a large number of non-replicable findings. From our current perspective, these studies were limited by: 1) insufficient power (overestimation of the expected effect sizes of common genetic variants); 2) insufficient coverage of genes or genomic regions (investigation of a few variants in individual candidate genes); and/or 3) the indiscriminate application of methods that had shown high success in the analysis of monogenic diseases (linkage studies with subsequent positional cloning), but which failed to take into account the complex nature of the genetic contribution to psychiatric disease. In the meantime, however, the situation has undergone a fundamental change. For many psychiatric disorders, unequivocal disease-relevant sites or regions in the human genome have now been identified.

The aim of this special issue is to provide insights into the current status of research into the genetic basis of psychiatric disease. We have focused on common disorders, which collectively impact a wide range of the human lifespan. The articles emphasize that the diagnostic categories used in psychiatry have no clear correspondence with etiological entities. In fact, from a scientific point of view, psychiatric diseases should be viewed more as dimensional disorders with partially overlapping etiologies, as suggested, for example, in the Research Domain Criteria (RDoC) project, which was initiated by the US National Institute of Mental Health [2]. Notwithstanding, the articles in this special issue refer to the currently established nosological entities, since: 1) these are still applied in the majority of scientific studies; and 2) they will continue to play an important role as symptom-based concepts for clinical practice in the foreseeable future. For the field of child and adolescent psychiatry, this special issue presents the current status of research into the autism spectrum disorders [3] and anorexia nervosa [4]. For the area of adult psychiatry, affective [5] and schizophrenic [6] disorders are discussed.

The identification of disease-relevant genetic variants/regions is a crucial step towards understanding the molecular causes of psychiatric disease. However, additional studies are required to generate a detailed, mechanistic understanding of the respective biological relationships [7]. Scientists in the field now have access to a large repertoire of research methods. In addition to the ever important bioinformatic analyses, which can draw upon rapidly growing databases of diverse types of biological information, innovative experimental approaches are now available, including the investigation of biological effects of human mutations in other species (e. g., CRISPR/Cas induced mutations in mouse models), and the generation of genetically stratified human brain cells and organoids via induced pluripotent stem cells. One insurmountable difficulty in the biological research of psychiatric disease is that the affected organ – the brain – cannot be examined directly in the living patient. However, external imaging methods, which are now generating increasingly precise insights into the structure and functioning of the brain, can be applied. This approach and its multiple applications are described in the article by Mühleisen et al. [8]. To achieve a full understanding of the biology of psychiatric disease, the effects of external, non-genetic influences must also be taken into account. At the biological

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level, these influences convey their effects, among others, via intracellular epigenetic mechanisms. The article by Keverne and Binder [9] summarizes the current status of epigenetic findings for psychiatric disease.

How does progress in understanding the genetic basis of psychiatric disease impact clinical practice? For several years, psychiatric drug development has been stagnant, with several large pharmaceutical companies having withdrawn from this area of indication. The genetically-based characterization of biological metabolic pathways may generate a renewed momentum [10]. The fact that genetic studies identify genes that code for established drug targets (e. g., dopamine D2 receptor in schizophrenic disorders), or for close interaction partners, serves as a proof of principle. Available genetic findings suggest various promising biological fields of intervention for the schizophrenia and bipolar affective disorder spectra [5, 6, 11, 12].

While the development of new drugs is a lengthy and extremely time-consuming process, the translation of genetic findings into diagnostics can – in principle – be achieved much more rapidly. For example, a genome-wide investigation for copy number variants (CNVs) is now a component of the routine diagnostic evaluation of patients with intellectual disability or an autism spectrum disorder [3]. The article by Degenhardt [6] proposes that CNV testing could also be applied to patients with schizophrenia spectrum disorders, and discusses the research questions that would need to be addressed before this could become a routine diagnostic procedure.

What is the potential role in clinical practice of polygenic risk scores (PRS), which are calculated from the summary of the contribution of common genetic variants? In their article, Andlauer & Nöthen [13] summarize the scientific aspects of the PRS concept, and its possible applications in both research and clinical practice. For the latter, adding PRS information to CNV diagnostics in order to generate more precise information on penetrance and associated phenotypic spectrum might be a promising first example of its introduction within the clinical setting. Other exciting prospects for the use of PRS exist. However, additional studies will be necessary before clinical application can be considered.

We are proud that the first issue of the journal *medizinischegenetik* under its new publishing house, De Gruyter, Berlin, focuses on psychiatric disease. In the immediate aftermath of World War 2, psychiatric genetics failed to gain a foothold within the German human genetics community, as a consequence of the sinister abuses of the Nazi era. In response to the training and inspiration of his academic mentor Prof. Friedrich Vogel (1925–2006), it

Prof. Peter Propping

was Prof. Peter Propping (1942–2016) who became the central figure in terms of re-establishing German psychiatric genetic research [14]. For this reason, we dedicate this special issue to this exceptional scientist, teacher, colleague, and friend.

The journal *medizinischegenetik* is a cornerstone of the German-speaking medical genetic/human genetic community. However, this is the first issue of *medizinischegenetik* to publish all articles in English. This is an acknowledgement of the international nature of the medical genetics community, and is intended to open up *medizinischegenetik* to a wider international readership.

Finally, much appreciation is due to the authors for their dedicated contribution to this special issue. They have made a very convincing case for the success of the genetic approach to psychiatric disease, both in terms of understanding causality and facilitating initial steps towards applications within clinical practice.

We hope the readers will enjoy this special issue!

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