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Pharmacogenomics: A Promising Approach Towards Treatment of Autism

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Abstract

Pharmacogenomics investigates variations in the human genome and the ways in which genetic diversity might influence individual response to drug treatment. Autism is a complex genetic disorder, which awaits a pharmacogenomic approach to better its treatment. This article describes recent developments of genetics and pharmacogenomics in the field of autism, and highlights the prospective of pharmacogenomics in developing novel and more effective therapies, and personalizing treatment strategies for autism.

Introduction

Autism spectrum disorders (ASDs) are among the most common neuropsychiatric disorders, with an estimated worldwide prevalence of 1%-2.6% [1-3]. The affected individuals display deficits in social communication, impaired language development, and the presence of highly restricted interests and/or stereotyped repetitive behaviours [1,2,4-6]. Although a wide variety of treatments have been used to treat individuals with ASD, no curative therapies are currently available. Treatment approaches to autism generally focus on educational and behavioural interventions. Drug therapies are mainly used to treat specific disruptive behaviours, such as anxiety, irritability, hyperactivity, inattention, obsessive-compulsive symptoms, sleep disturbances, aggression and self-injury, which are usually associated with autism and negatively affect the success of educational treatments and quality of family life [7-14].

Pharmacological treatment of ASDs is challenged by the complexities of the disorders in nature [9-11]. Obviously, the treatment is often complicated by the frequent presence of comorbid disorders, such as epilepsy, bipolar disorder, attention deficit-hyperactivity disorder, gastrointestinal and immune system disorders [12,13]. Usually, medications are used in combination to treat accompanying symptoms including anxiety, obsessions, hyperactivity, impulsivity, irritability and aggressive behaviours. The most frequently prescribed medications for patients with ASDs include antipsychotics, antidepressants, anticonvulsants, mood stabilizers, and cholinesterase inhibitors [7,8,10-13,15-17]. However, the efficacy of most of these medications among patients with ASDs has been uncertain. In fact, few placebo-controlled, double-blind studies have been performed on any of these medications. As a result, much of our current knowledge of treatment of ASDs has been from trials-and-errors regarding the selection of medications. Little attention has been paid to the atypical responses of individual patients to certain medications and the genetic background of these individuals [10,11,14,18]. Thus, a pharmacogenomic approach is definitely needed to better the treatment of ASDs.

Genetic diversity of autism

Genetic diversity, most notably through single nucleotide polymorphisms (SNPs) and copy-number variations (CNVs), together with specific environmental exposures, contributes to both disease susceptibility and drug response variability [19-21]. ASDs represent a heterogeneous group of disorders that are highly heritable, with heritability indices estimated at 85%–92% [3,22]. Advances in identifying the genetic causes of ASDs first came from the study of syndromic autism, which pinpointed the causes of disorders, such as fragile X syndrome, Rett syndrome, tuberous sclerosis, and Timothy syndrome [22-25]. However, the challenges were more from identifying the genetic causes of nonsyndromic or idiopathic autism given the lack of defining features besides the neurobehavioral phenotypes and the fact that the majority of cases were simplex. The genome-wide approaches that are capable of screening thousands of DNA mutations or structural variants at once have been applied to the studies of ASDs. Many significantly associated SNPs have been identified in these studies. Recent studies of simplex and mostly nonsyndromic ASDs, have established de novo copy number variants (CNVs) as the cause of 5%–8% of cases of simplex autism [26-28].

Generally, ASDs have been widely viewed as complex genetic disorders, with each gene having a minor effect on the overall clinical presentation [19,20]. With the development of genome-wide association (GWA) studies, more comprehensive approaches will become available and greatly accelerate genomics research in ASDs. The genome-wide study of ASDs will link more genotypes to their biological phenotypes, thus provides a foundation for the development of diagnostic screens as well as pharmacogenomic studies [29-33]. Furthermore, some of the genes associated with the identified SNPs or CNVs will offer new insight into the pathology of ASDs as well as novel therapeutic targets for treatment of ASDs [19-21,34,35].

Development of pharmacogenomics in autism

The goal of pharmacogenomics is to dissect the clinical variability between individuals with regard to drug therapy and to predict drug response and side effects based on genetic diversity [36-40]. In comparison with other neuropsychiatric disorders, such as drug addiction, schizophrenia and depression [37-39,41-43], pharmacogenomic research in ASDs is still in its initial stage [18].

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Challenges facing pharmacogenomics of ASDs are mainly from the lack of information about the biology of ASDs in addition to the well-documented clinical heterogeneity within patients of ASDs [18,34].

In recent years, there have been a few encouraging studies of pharmacogenomics in ASDs. Antipsychotic medication is commonly used in children with ASDs, with risperidone one of the most popular atypical antipsychotics prescribed. Though risperidone significantly improves behavioural problems in most situations, it is also associated with mild adverse effects [44-46]. It is known that there are considerable individual differences in response to risperidone, both regarding therapeutic and adverse effects, which actually limit the therapeutic use of the drug [46-49]. Little has been reported on the genetic factors, which may underlie this individual variability in response to risperidone therapy, particularly for autism. Correia et al. [50] explored the effects of multiple candidate genes on clinical improvement and occurrence of adverse drug reactions in patients who received single therapy with risperidone up to 1 year. Candidate genes involved in the pharmacokinetics (*CYP2D6* and *ABCB1*) and pharmacodynamics (*HTR2A*, *HTR2C*, *DRD2*, *DRD3*, *HTR6*) of the drug, and the brain-derived neurotrophic factor (*BDNF*) gene, were analysed in this study. Their results confirmed that risperidone therapy is effective in reducing some autism symptoms and cause few serious adverse effects. They further found that the *HTR2A* c.-1438G>A, *DRD3* Ser9Gly, *HTR2C* c.995G>A and *ABCB1* 1236C>T polymorphisms are predictors for clinical improvement with risperidone therapy. The *HTR2A* c.-1438G>A, *HTR2C* c.68G>C (p.C33S), *HTR6* c.7154–2542C>T and *BDNF* c.196G>A (p.V66M) polymorphisms influenced prolactin elevation. *HTR2C* c.68G>C and *CYP2D6* polymorphisms were associated with risperidone-induced increase in body mass index (BMI) or waist circumference. This study thus identified for the first time several genes implicated in risperidone efficacy and safety in autism patients. It provides hope for the personalized therapy of risperidone in autism. Another study focused on escitalopram, a selective serotonin reuptake inhibitor (SSRI), which has been found to effective in the treatment of certain symptoms of patients with ASDs, including repetitive behaviours, anxiety, irritability, aggression and self-injurious behaviours [51-53]. Since variation in the gene that codes for the primary protein target of SSRIs, the serotonin transporter, could be related to escitalopram response or final dose of treatment [52], a complex insertion/deletion/single nucleotide containing polymorphism in the promoter region of the transporter (5-HTTLPR) was chosen as the primary candidate polymorphism [54]. Owley et al. [55] determined the effect of 5-HTTPLR genotypic variation (low, intermediate, and high expression groups) on the response to escitalopram treatment of children and adolescents with ASDs. They found that groups with different haplotypes affecting expression of the serotonin transporter may differ in their response to escitalopram. Given that the study was carried out in a small sample of patients, replication in a larger independent sample is definitely needed to confirm whether serotonin transporter genotype is related to response to escitalopram in ASDs. Interestingly, the next most recent study investigated whether peripheral blood gene expression before treatment with risperidone is associated with improvements in severe behavioral disturbances following risperidone treatment in ASD patients. Lit et al. [56] compared exon expression levels in blood before risperidone treatment with pre–post risperidone change in Aberrant Behavior Checklist-Irritability (ABC-I) scores. They found that expression of exons within five genes (*GBP6*, *RABL5*, *RNF213*, *NFKBID* and *RNF40*) was correlated with change in ABC-I scores in all risperidone-treated patients. Of these five genes, *RNF40* is located at 16p11.2, a chromosome region involved in autism and schizophrenia [57,58]. They concluded that the expression of these genes before treatment is associated with subsequent clinical response. This study is the first to suggest that gene expression in blood is associated with and may predict the behavioral response to risperidone use in ASDs. The gene expression profiles identified here may reflect convergent downstream biological mechanisms across multiple genetic backgrounds that are associated with behavioral response to risperidone in ASDs.

Although the above studies have made significant progresses towards pharmacogenomics of autism, none of their results could entirely account for the heterogeneity in response to autism treatment, and all of the results have to be replicated or validated in further studies. Undoubtedly, large-scale genetic and gene expression analysis will be performed in the near future in many laboratories by using the technologies of functional genomics. The expected findings will provide novel insights into the pathophysiology of ASDs. Such detailed knowledge will ultimately have profound effects on the treatment of these disorders.

Prospective of pharmacogenomics in autism

Addressing the extensive unmet medical needs related to autism will require that novel pharmacotherapies be developed [14,59]. Numerous molecular mechanisms that could potentially be targeted have been discovered by basic research in genetics and neurobiology of autism, but clinical translation remains a challenge. Developing therapeutics targeting these mechanisms will require the approach of pharmacogenomics.

The pharmacogenomic approach takes advantage of recent advances in experimental genomics and proteomics, together with the available information of the Human Genome Project [32]. It will not only enable genome-wide screens of several millions of SNPs without the specific hypotheses or candidate gene strategy, but also functional investigations of genetic diversity and gene expression over the whole genome or proteome [32,33]. We hope that an improved understanding of complexities of ASDs by pharmacogenomic approach will continuously contribute to the optimization of current therapies and the development of novel and potentially more powerful therapeutic strategies for these disorders. Furthermore, the determination and identification of patient subpopulations in response to drug treatment will help individualize pharmacological therapy for patients of autism.

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