Future of individualized psychiatric treatment

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‘...a more immediate solution to improve patient care is to maximize current treatment effectiveness by using genetic information ... to enhance individual responsiveness to antipsychotic medication.’

Antipsychotic medications are the preferred treatment for schizophrenia. Given that there are differences in individual responses to different antipsychotic medications, a significant challenge to enhancing treatment is to move beyond trial-and-error approaches to more individualized care that maximizes treatment success. The era of the human genome provides new hope for patients through the application of pharmacogenomics [1,2], the use of sequence variation in schizophrenia risk genes that may more accurately predict response to treatment.

We recently published an exploratory pharmacogenomics study reporting that variants of the gene encoding regulator of G-protein signaling 4 (*RGS4*) predict antipsychotic treatment response in schizophrenia [3]. *RGS4* had been identified by ourselves and others as a candidate risk gene for schizophrenia [4,5]. We genotyped eight *RGS4* gene SNPs in individuals with schizophrenia from the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE), which included DNA that was available from 198 individuals of inferred African ancestry and 397 individuals of inferred European ancestry. Ethnic stratification was performed, as the allele frequencies of the *RGS4* genetic variants differed between the two groups. Two *RGS4* SNPs, rs951439 and rs2842030, were associated with differential antipsychotic treatment response in individuals of inferred African ancestry. Individuals of African descent and *RGS4* rs951439 genotype CC responded significantly better to perphenazine treatment compared with ziprasidone treatment. These individuals continued on perphenazine treatment three-times longer (391 vs 124 days) and had a 21% improvement during perphenazine treatment on the Positive and Negative Symptoms Scale (PANSS) total score compared with a 5% worsening of symptoms

on ziprasidone. Similarly, individuals of African descent and *RGS4* rs2842030 genotype TT responded significantly better to perphenazine treatment (24% improvement in PANSS symptoms) than treatment by quetiapine, risperidone or ziprasidone (5% worsening of PANSS symptoms). Among individuals of European descent, risperidone treatment was more effective in those with rs951439 genotype TT compared with those with genotype CC. Similarly, individuals of European descent and rs2842030 genotype GG responded better to risperidone treatment than those of genotype TT [3]. An independent study of Chinese individuals with schizophrenia found that *RGS4* SNP rs2661319, which lies between rs951439 and rs2842030 on chromosome 1, predicts differential response to risperidone [6]. Thus, two independent reports provide evidence that *RGS4* variants can be used to predict the effectiveness of antipsychotic treatment response in three different ethnic groups.

RGS4 has been of particular interest biologically, as the protein regulates the activity of the same G-protein-coupled receptors (GPCRs) that are targeted by antipsychotic drugs, including those receptors activated by dopamine, acetylcholine and serotonin. *RGS4* is part of a large family of regulators of G-protein signaling, all of which act by shortening the duration of neurotransmitter signaling through GPCRs. We recently tested a hypothesis regarding the specificity of *RGS4* in predicting antipsychotic treatment response by genotyping 59 SNPs spanning the *RGS2*, *RGS5*, *RGS8* and *RGS16* genes in the CATIE sample. Each of these GPCR-regulating genes lies near the *RGS4* gene on chromosome 1 and is expressed in brain regions implicated in schizophrenia. The results of the genetic studies indicate that only *RGS4* variants correlate with antipsychotic treatment response [7]. The biological basis of the specificity of *RGS4* is being investigated currently.

‘As *RGS4* may be critical to both etiology and predicting treatment effectiveness in schizophrenia, one priority should be to determine the function of the genetically associated variants.’

The two reports of *RGS4* genotype predicting antipsychotic treatment response add to a substantial body of evidence implicating *RGS4* in schizophrenia. The initial focus on *RGS4* came from our laboratory's gene microarray and *in situ* hybridization studies, which demonstrated decreased expression levels of *RGS4* transcript across cortical regions [8]. Decreased levels of *RGS4* protein were subsequently demonstrated in the frontal cortex [9]. Genetic association of *RGS4* variants with schizophrenia diagnosis was originally described in three small, independent family-based samples [10]. Like all risk genes for schizophrenia to date, there is both replication and nonreplication of genetic association that may be due to a number of factors, including disease heterogeneity [5]. However, a recent meta-analysis of more than 13,000 samples demonstrated support for genetic association of *RGS4* with schizophrenia in the context of etiological heterogeneity [11]. There are also biological indicators that *RGS4* is an important risk factor in schizophrenia. *RGS4* genotype is associated with reduced volume of the dorsolateral prefrontal cortex in first-episode patients with schizophrenia and in healthy controls [12], and with functional activity and connectivity during working memory tasks [13]. Finally, recent independent studies, in European ancestry and Chinese samples, also indicated association of *RGS4* genotypes with baseline schizophrenia symptom severity as measured by the PANSS total score [3,14].

'A new focus on the differences across ethnic groups can lead to better treatment access for those individuals typically underserved by the medical community, and implementation of more successful treatment strategies for all who use antipsychotic medications for the treatment of schizophrenia.'

As *RGS4* may be critical to both etiology and predicting treatment effectiveness in schizophrenia, one priority should be to determine the function of the genetically associated variants. Two reports have begun to address the function of *RGS4* variants. Chowdari *et al.* [15] used transcription assays to identify a 311-bp enhancer region and two larger (~2-kb) regions containing strong transcriptional repressor elements. Ding *et al.* [16] identified five splice variants of *RGS4* that use three different transcription start sites. Each of the splice variants is expressed in the human cerebral cortex, and higher levels of each transcript are

observed in the prefrontal cortex compared with the visual cortex [16]. Future experiments should focus on determining whether the genetic variants associated with schizophrenia and antipsychotic treatment response specifically influence *RGS4* transcript isoform expression.

RGS4 is one of a small group of promising schizophrenia susceptibility genes [4,5]. Ongoing genome-wide association studies will likely identify additional genes involved in the etiology of schizophrenia [17,18]. It is likely that these genome-wide association studies will not immediately lead to new drug discovery for the treatment of schizophrenia, as identification of potential risk genes is just the first of many steps required to understand the neurobiological consequences of dysfunction of the candidate gene in schizophrenia. Furthermore, one conclusion drawn from the CATIE study is that second-generation antipsychotic drugs are not a dramatic improvement over the first-generation antipsychotics that have been available for over 50 years [19]. The treatment field need not wait passively for new drug discoveries. We suggest that a more immediate solution to improve patient care is to maximize current treatment effectiveness by using genetic information, perhaps by using a combination of variants of multiple risk genes, to enhance individual responsiveness to antipsychotic medication. Companies developing technologies for genetic diagnosis of mental illness [20] might also consider focusing their efforts to develop the type of individualized medicine strategy described here.

We make one additional recommendation. All clinical trials of antipsychotic medications should include in the study design the collection of DNA from blood samples. The benefit:cost ratio for this design is extremely high. With reference to our study, not all individuals in the original CATIE study had their DNA collected, which resulted in a smaller than optimal sample size and thus a more challenging design of our exploratory analysis. However, the collection of DNA samples from another seemingly underpowered sample of only 120 patients has provided new insight into the ability of genetic variants to predict the efficacy of the antipsychotic medication risperidone. The results of these genetic analyses indicate that risperidone treatment efficacy is predicted by genetic variants in dopamine receptors [21,22], serotonin receptors [23] and, most recently, *RGS4* [6]. A more comprehensive genetic analysis of risperidone treatment success may indicate other important genetic indicators or combinations of genetic predictors.

Finally, all clinical trials should, like CATIE, include substantial representation of hitherto under-represented ethnic groups. ‘Population stratification’ is generally considered to be undesirable in genetic association studies, as the requirement to stratify typically reduces the power to detect significant genetic differences. However, our exploratory study illustrates that, given sufficient power in each stratum, population stratification should be encouraged. As noted above, we found that the allele frequencies of the *RGS4* SNPs differed markedly between individuals of European descent and individuals of African descent. In the absence of a known functional variant, we have to assume that the same alleles mark different inheritance patterns of a functional variant in *RGS4* in the two strata. A new focus on these differences across ethnic groups can lead to better treatment access for

those individuals typically underserved by the medical community, and implementation of more successful treatment strategies for all who use antipsychotic medications for the treatment of schizophrenia.

Financial & competing interests disclosure

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Bibliography

- Reynolds GP: The impact of pharmacogenetics on the development and use of antipsychotic drugs. *Drug Discov. Today* 12, 953–959 (2007).
- Arranz MJ, de Leon J: Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol. Psychiatry* 12, 707–747 (2007).
- Campbell DB, Ebert PJ, Skelly T *et al.*: Ethnic stratification of the association of *RGS4* variants with antipsychotic treatment response in schizophrenia. *Biol. Psychiatry* 63, 32–41 (2008).
- Levitt P, Ebert P, Mirnics K, Nimgaonkar VL, Lewis DA: Making the case for a candidate vulnerability gene in schizophrenia: convergent evidence for regulator of G-protein signaling 4 (*RGS4*). *Biol. Psychiatry* 60, 534–537 (2006).
- Sullivan PF: The genetics of schizophrenia. *PLoS Med.* 2, E212 (2005).
- Lane HY, Liu YC, Huang CL *et al.*: *RGS4* polymorphisms predict clinical manifestations and responses to risperidone treatment in patients with schizophrenia. *J. Clin. Psychopharmacol.* 28, 64–68 (2008).
- Campbell DB, Lange LA, Skelly T, Lieberman J, Levitt P, Sullivan PF: Association of *RGS2* and *RGS5* variants with schizophrenia symptom severity. *Schizophr. Res.* (2008) (Epub ahead of print).
- Mirnics K, Middleton FA, Stanwood GD, Lewis DA, Levitt P: Disease-specific changes in regulator of G-protein signaling 4 (*RGS4*) expression in schizophrenia. *Mol. Psychiatry* 6, 293–301 (2001).
- Erdely HA, Tamminga CA, Roberts RC, Vogel MW: Regional alterations in *RGS4* protein in schizophrenia. *Synapse* 59, 472–479 (2006).
- Chowdari KV, Mirnics K, Semwal P *et al.*: Association and linkage analyses of *RGS4* polymorphisms in schizophrenia. *Hum. Mol. Genet.* 11, 1373–1380 (2002).
- Talkowski ME, Seltman H, Bassett AS *et al.*: Evaluation of a susceptibility gene for schizophrenia: genotype based meta-analysis of *RGS4* polymorphisms from thirteen independent samples. *Biol. Psychiatry* 60(2), 152–162 (2006).
- Prasad KM, Chowdari KV, Nimgaonkar VL, Talkowski ME, Lewis DA, Keshavan MS: Genetic polymorphisms of the *RGS4* and dorsolateral prefrontal cortex morphometry among first episode schizophrenia patients. *Mol. Psychiatry* 10, 213–219 (2005).
- Buckholtz JW, Meyer-Lindenberg A, Honea RA *et al.*: Allelic variation in *RGS4* impacts functional and structural connectivity in the human brain. *J. Neurosci.* 27, 1584–1593 (2007).
- So HC, Chen RY, Chen EY, Cheung EF, Li T, Sham PC: An association study of *RGS4* polymorphisms with clinical phenotypes of schizophrenia in a Chinese population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 147, 77–85 (2008).
- Chowdari KV, Bamne M, Wood J *et al.*: Linkage disequilibrium patterns and functional analysis of *RGS4* polymorphisms in relation to schizophrenia. *Schizophr. Bull.* 34, 118–126 (2008).
- Ding L, Mychaleckyj JC, Hegde AN: Full length cloning and expression analysis of splice variants of regulator of G-protein signaling *RGS4* in human and murine brain. *Gene* 401, 46–60 (2007).
- Sullivan PF: Schizophrenia genetics: the search for a hard lead. *Curr. Opin. Psychiatry* 21, 157–160 (2008).
- Sullivan PF, Lin D, Tzeng JY *et al.*: Genomewide association for schizophrenia in the study CATIE: results of stage 1. *Mol. Psychiatry* (2008) (Epub ahead of print).
- Lewis S, Lieberman J: CATIE and CULASS: can we handle the truth? *Br. J. Psychiatry* 192, 161–163 (2008).
- Couzin J: Science and commerce. Gene tests for psychiatric risk polarize researchers. *Science* 319, 274–277 (2008).
- Lane HY, Lee CC, Chang YC, Lu CT, Huang CH, Chang WH: Effects of dopamine D2 receptor Ser311Cys polymorphism and clinical factors on risperidone efficacy for positive and negative symptoms and social function. *Int. J. Neuropsychopharmacol.* 7, 461–470 (2004).
- Lane HY, Hsu SK, Liu YC, Chang YC, Huang CH, Chang WH: Dopamine D3 receptor Ser9Gly polymorphism and risperidone response. *J. Clin. Psychopharmacol.* 25, 6–11 (2005).
- Lane HY, Chang YC, Chiu CC, Chen ML, Hsieh MH, Chang WH: Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. *Am. J. Psychiatry* 159, 1593–1595 (2002).