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Beyond the GWAS in schizophrenia

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The identification of the genetic factors that influence susceptibility to neuropsychiatric illness has proven challenging. Currently, several approaches are being utilized to enhance the potential of these studies. Most commonly, a 'discovery' genome wide association study (GWAS) with a focus on a single clinical diagnostic group such as schizophrenia, with subsequent replication in independent cohorts is the standard for the field. A major challenge for this approach is the necessity for increasingly large sample sizes, presumably due to modest effect sizes and genetic heterogeneity, with commensurate increased heterogeneity of study samples. A complementary approach is to seek support for genetic loci by collecting additional phenotypic data, often termed endophenotypes, which suggest that specific genetic variants have significant effects on key biological or clinical parameters that are more closely linked to gene function. For example, studies demonstrating that a putative schizophrenia risk variant in *ZNF804A* influences phenotypes assessing brain structure or function as measured by neuroimaging or neurocognitive studies (Esslinger et al, 2009; Lencz et al, 2010).

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In this issue of EMBO Molecular Medicine, Grube et al (2011) report on a variant of this approach, the so-called phenotype-based genetic association study (PGAS). These authors tested the relationship of genetic variation in the *KCNN3* gene; a gene that codes for the calcium-activated potassium channel SK3, previously implicated in cognitive function (Blank et al, 2003), but only inconsistently linked with schizophrenia, to a number of non-diagnostic phenotypes that reflect brain function. The convergent data suggest that a CAG repeat polymorphism within the gene influences cognitive ability, and thus may modify the phenotype of schizophrenia. The strength of this study is that the authors utilized a translational research approach including (i) basic data demonstrating that longer repeat length reduced SK3 channel function in transfected HEK293 cells; (ii) animal data in which transgenic mice that overexpress the murine SK3 gene demonstrated deficits in behaviours thought to reflect cognitive ability, but no effects on motor performance, motor learning or anxiety and activity levels and (iii) clinical data showing that longer repeat length was associated with better performance on specific cognitive tasks in a large cohort of patients with schizophrenia. Taken together, the resultant hypothesis is that increased repeat length within the *KCNN3* gene reduces SK3 function and results in enhanced cognitive ability (Fig 1).

Studies such as these move beyond purely statistical associations between diagnosis and genotype, as they provide convergent data on the effects of genetic polymorphism on key biological and clinical indices. Most importantly, diminished cognitive function in schizophrenia is a consistent finding, and is most closely linked to the considerable functional disability associated with illness (Shamsi et al, 2011). Moreover, attempts to enhance cognitive function with currently available treatments have had very limited success to date (Keefe et al, 2007). The consistent directionality of the results in Grube et al. provide new data with which to generate testable hypotheses for studies designed to enhance cognitive function in schizophrenia (Grube et al, 2011). Can reducing SK3 function in patients with the illness result in improved cognition? Are there specific genetic subgroups of patients identified by *KCNN3* genotype that could be targeted for treatment with potentially cognitive enhancing agents? Considerable more work is needed prior to initiating these types of studies, but the data provided here are novel and substantial first steps towards attaining these ambitious goals.

It would be especially informative to have direct evidence that blocking SK3 function will enhance cognitive function. The transgenic mouse data suggests that increased SK3 function results in diminished cognitive function, consistent with the hypothesized direction, but not the most direct test of whether reduced function improves cognition. Additional data with underexpressing or knockout mice may be useful in this

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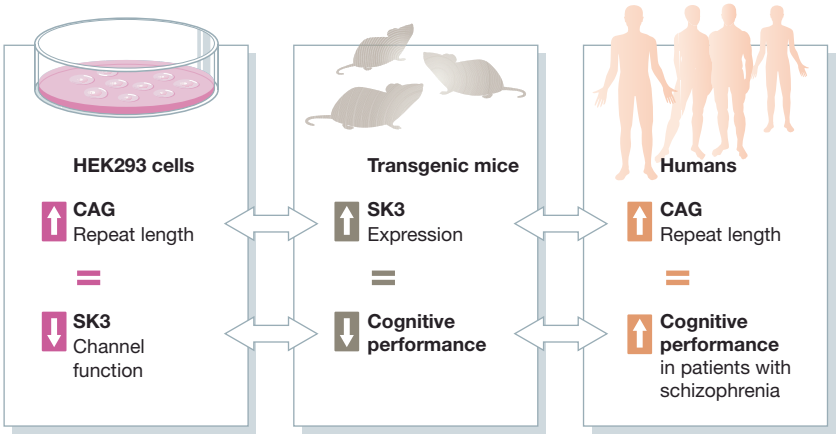

Figure 1. Translational research approach to cognitive function incorporating cellular, animal and human data.

regard. Moreover, the most direct test of an effect of the *KCNN3* genetic polymorphism on human cognitive function might be to consider a non-psychiatrically ill population for further cognitive studies. Schizophrenia patient groups commonly experience a myriad of uncontrolled factors that may influence cognitive ability including lifestyle choices, illicit drug use, treatment with medications known to impair cognitive function (e.g. anticholinergic agents used to treat the neuromotor side effects of antipsychotic drugs) and the effects of chronic illness. These potentially confounding factors are minimized in healthy control groups and therefore these data sets may yield more power. Evidence for this hypothesis is provided by genetic studies in healthy individuals that have been relatively robust for the identification of genes that influence cognition, including a recent meta-analysis of over 7000 subjects that implicated the schizophrenia candidate gene, *DTNBP1*, in general cognitive ability across multiple healthy volunteer groups (Zhang et al, 2010). With the availability of numerous cohorts of subjects comprehensively characterized for cognition across a range of test batteries, and a range of age groups, it may be feasible to test the effects of the *KCNN3* polymorphism in additional cohorts of healthy subjects (as well as additional schizophrenia cohorts). Such data could strengthen and refine the cognitive signal that Grube et al (2011) observe in their schizophrenia cohort.

Finally, it should be noted that the effect of *KCNN3* genetic variation on cognition was relatively modest. These data are consistent with other genetic studies of human cognitive function, including a meta-analysis of the catechol-*O*-methyltransferase (COMT) valine 158:108 methionine polymorphism and IQ (Barnett et al, 2008), in which the pooled effect size was 0.06, as well as the *DTNBP1* meta-analysis (Zhang et al, 2010), in which effect sizes ranged from −0.083 to −0.123, explaining approximately 0.2–0.4% of the total variance in general cognitive ability. These small effect sizes of individual single nucleotide polymorphisms (SNPs) on complex phenotypes are consistent with data from other complex phenotypes with relatively high heritability estimates. For example, a recent genome wide association study (GWAS) study identified 47 SNPs in multiple genes that were strongly associated with variation in height (Soranzo et al, 2009), a highly heritable phenotype; however, collectively these SNPs only explained approximately 5% of the total variation in adult height (Lettre, 2009). Therefore, very large samples, and/or the use of meta-analytic techniques, may be required to substantiate results of such modest effect, including *KCNN3* and cognition.

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In conclusion, the translational study of Grube et al (2011) describes a potentially powerful approach towards dissecting the heterogeneity of complex phenotypes such as neurocognitive function, and may critically inform the search for schizophrenia susceptibility loci. Data from the cellular, animal and clinical domains provide convergent support for a role of the *KCNN3* gene and the SK3 potassium channel in cognitive function, and also suggest a mechanism by which the channel may impart these effects. Further work will be needed to confirm and extend these results, but Grube et al represents a positive step in this direction (Grube et al, 2011).

The author declares that there is no conflict of interest.

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