See article by Byrne et al

Lumpers, Splitters, and Statistics: Bipolar Disorder, Schizophrenia, and Their Relationship to Seasonality

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Modern statistical methods designed to exploit the power of the genome have had to overcome a skeptical reception (particularly by clinicians in psychiatry) because of a series of hopeful genetic findings that failed to replicate. The primary goal of statistical genetic analyses is to identify genes associated with disease in order to illuminate molecular pathways and provide targets for novel therapeutics. Over the last several years, investigators around the world have contributed samples for joint analyses, dramatically increasing the statistical power and, consequently, the success rate of genetic discovery in common complex diseases, including schizophrenia and bipolar disorder.[1,2] Large samples were necessary because the associated genetic variants had small effect sizes and > 1 million single nucleic polymorphisms (SNPs) are tested in each study, requiring a high statistical bar to avoid false-positive results from multiple testing. Yet, this still leaves investigators with a large number of variants that show some evidence of association but fail to reach genome-wide significance. Recently, a number of new analytic methods have been devised to use genotypes to estimate heritability and obtain a picture of the "genetic architecture" of complex medical disorders.[3] These estimates are a function of the large number loci with positive but subthreshold evidence of association to provide a "polygenic signature." As with any modeling method, these methods may or may not turn out to be a close estimate of the "truth," even though they are often helpful in designing future experiments.

In this issue, Byrne et al[4] use polygenic risk score analysis to test genetic overlap between differing phenotypes. Polygenic risk score begins with association results from a primary genome-wide association study (GWAS), termed the *training dataset* (usually the largest available for a particular phenotype), which is "pruned" to remove redundant markers. With this information, the investigator can look in an independent dataset (the target dataset) and essentially count the number of associated alleles from the original training dataset that are present in the target dataset. Summing up these counts across all shared markers leads to the calculation of a polygenic score for each individual. A polygenic score that is higher in cases than in controls implies an association with disease after accounting for potential confounds, such as ethnic differences. Reassuringly, almost all GWAS datasets of a sufficient sample size show at least some evidence of a polygenic association when compared to an independent dataset of the same phenotype. The strength of this association usually reflects the informativeness of the training sample (usually the larger the sample, the more informative) and the actual underlying genetic relationship between the 2 samples.

An interesting application of polygenic analysis has been to explore the sharing of genetic risk factors across the major psychiatric disorders (for a review, see Wray et al[3]), especially between bipolar disorder and schizophrenia.[5] Increasingly, these approaches are being used to study genetic relationships of alternative phenotypes such as illness features or population-based traits. Byrne et al,[4] for example, focus on the relationship between the trait of seasonal variation in mood-related symptoms and the major mood and psychotic disorders. Using a twin sample from Australia and a large family-based US Amish sample, they performed a meta-analytic GWAS of the composite score from the Seasonal Pattern Assessment Questionnaire (SPAQ),[6] a widely used instrument in the study of seasonal affective disorder. Not surprisingly, the authors did not find genome-wide significant findings (schizophrenia and bipolar disorder have required initial case sample sizes > 5,000 to find genome-wide significance). Byrne et al[4] went on to test the polygenic association between 3 potentially relevant psychiatric phenotypes (bipolar disorder, major depressive disorder, and schizophrenia) and their measure of seasonality.

The authors reported 2 expected and 1 unexpected result. One of the expected results was a modest evidence for association with the bipolar polygenic score and the seasonality measure. This was expected based on prior clinical data suggesting that bipolar disorder is one of the most studied phenotypes with at least some degree of seasonal variation.[7] The second (arguably) expected result was the absence of any relationship between major depressive disorder polygenic scores and their seasonality measure—expected not because there may not be a relationship between seasonality and major depression, but because major depressive disorder has proven a challenging phenotype for genetic analysis,[8] and it is likely that the major depression training set remains underpowered to show relevant polygenic associations. The unexpected result was the strong association of the seasonality measure with the schizophrenia polygenic score, unexpected because this has been, as the authors point out, relatively unstudied at the phenotype level, although, as noted by the authors, a number of small reports have described seasonal exacerbation of psychotic symptoms.

Submitted: *November 6, 2014; accepted November 7, 2014.*

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J Clin Psychiatry 2015;76(2):e214–e215 (doi:10.4088/JCP.14com09638).

What do these results mean? Before contemplating potential connections between seasonality and psychosis, we need to ask, as Byrne and colleagues[4] do in their discussion, whether the comparisons across the different training set phenotypes were equally valid. Notably, the schizophrenia sample was larger than both the bipolar and MDD samples. In addition, the phenotype of schizophrenia may be slightly more tractable to genetic studies than that of the severe mood disorders, as suggested by the greater number of genome-wide significant findings for comparable sample sizes,[1] although formal studies testing this hypothesis have not been done. Hence, the difference between the polygenic associations with the 3 phenotypes may arise from differences in the original discovery samples. As Byrne et al[4] point out, replication in other target samples and further sensitivity-like analyses with differing training samples will be needed to allay some of these concerns.

Assuming that these results do replicate, they would suggest a reevaluation of whether seasonal patterns are seen at the phenotype level and whether they are clinically significant. Although seasonal exacerbation has not been strongly appreciated in the course of schizophrenia, this study is the type of initial impetus needed to encourage clinically oriented researchers to reassess this level of appreciation based on a careful consideration of the available data.

However, it is yet unclear what the schizophrenia polygenic score is specifically indexing: it may be a propensity toward psychosis, functional impairment, stress sensitivity, a combination of these, or something yet to be defined. Since polygenic scores are derived from associated markers throughout the genome, they may point to a broad index of psychopathology, rather than more specific or clinically useful phenotypes such as course or treatment response. Fortunately, ongoing and future studies will soon be able to shed light on this important question.

Clinicians may also ask themselves how this finding (and others from similar polygenic analyses) can affect their practice. First, can polygenic scores be used to predict the presence of clinically meaningful traits such as disease phenotype or predict clinical features such as seasonality? In theory, yes; however, this will most likely require polygenic scores derived from much larger and more focused target training sets. Even with the strong statistical association observed with the schizophrenia polygenic score and the SPAQ, the amount of variance explained by the polygenic score was small—approximately 3%. Yet, as a potential sign of things to come, the recent landmark schizophrenia GWAS article[1] on schizophrenia (including 36,989 cases and 113,075 controls) reported polygenic analyses accounting for 7%–18% of the phenotype depending on level of adjustment for case-control ascertainment and lifetime risk estimates. In a measure more familiar to clinicians, these results represent area under the curve values of 0.6–0.7, which has a predictive power below what is typically needed for clinical decisions. Hence, although there is reason to think that polygenic scores may be potentially useful in certain clinical situations (for example, in high-risk patients), this will require more predictive power from larger sample sizes. It is also important for the clinician to review the appropriateness and relevance of the measured phenotype (often a questionnaire) and its intended clinical construct. How well, for example, does the SPAQ measure clinically relevant seasonality? Despite its wide use, there is relatively little clinical validation of the use of the SPAQ to help diagnose seasonal affective disorder.[6]

By themselves, genetic studies are rarely in a position to impart clinical relevance on a particular phenotype, a limitation that reminds us of the important distinction between biological validity and clinical utility.[9] Nevertheless, the study by Byrne et al[4] is one of many emerging examples of how to use existing molecular genetic studies to revisit key nosologic and clinical questions posed well before the molecular era. No doubt there will be increasing numbers of such studies that will join the debate in defining genetically relevant nosologic boundaries. With the remarkable fall in the cost of genome sequencing, there is a pressing need for next-generation phenotyping to rapidly collect clinically informative large-scale samples. At the same time, we need better use of last-generation clinical data, such as that used by Byrne et al,[4] to design studies that reflect our patients' conditions more effectively.

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Potential conflicts of interest: None reported.
Funding/support: None reported.

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