

Coming of Age of Genetic Investigations in Late-Life Mental Health

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Genetic epidemiologic studies have documented the heritability of clinically psychiatric disorders over and over again. Molecular genetic studies have been challenging and success has been slow. Nevertheless, the last decade has seen hundreds of positive genetic findings for complex human diseases. The reason for this turn-around is not only to be found in the dramatic progress in methodology and technology, but as important has been the development of the necessary infrastructure that has enabled large-scale collaborations on an unprecedented scale.¹ Bio- and data-repositories spearheaded by the National Institute of Mental Health (NIMH), for example, the NIMH Repository and Genomics Resource (NRGR), the NIMH Phenotypic and Genetic Database (NPGD), and the National Center for Biotechnology Information Database of Genotypes and Phenotypes (dbGaP), made tens of thousands of samples and millions of genotypes available to researchers all over the globe. Replication of results is standard and without such replication, getting published has become challenging. Researchers are sharing data and biomaterials so that their use is maximized. Psychiatric genetics is finally blooming.

Although the field of genetics of psychiatric disorders has thus bourgeoned over the past decade, the field of geriatric psychiatry has been slower to take part in these developments. Studies in late-life mental health have been dominated by candidate genetic approaches typically considered in the context of a specific psychiatric disorder, or focused on a specific genetic marker due to its potential involvement in the

pathophysiology of the disorder. With the exception of Alzheimer disease, large-scale genome-wide association studies (GWAS) in geriatric psychiatry are very few and these have been limited by relatively small sample sizes. The infrastructure for sharing of biosamples and data is still in its early development, and candidate gene approaches are still dominating the field.

In this issue of *The American Journal of Geriatric Psychiatry*, however, we highlight six articles that present a step forward in the development of approaches in genetic research in late-life psychiatry. These articles also provide an opportunity to look forward and apply the lessons we have learned in psychiatric genetics to mental health disorders in late life. The six studies capture a variety of approaches to characterizing the genetic basis of geriatric psychiatric disorders, including broader agnostic approaches, imaging genetics, and genetic markers of treatment response. Each of these studies highlights the challenges and opportunities facing investigators aiming to identify the genetic basis of psychiatric disorders in late life.

The turf of the relationship of the candidate genetic marker APOE-e4 to cognitive decline and dementia is very well trodden, but the focus on the impact of age, documented here by Valerio et al.,² is extremely important and highlights the importance of age as a critical moderator of genetic effects in older adults. Comparing subjects who were cognitively intact or demented, the authors found that the association of APOE-e4 with dementia attenuated with advanced

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age. The results are highly suggestive of a survivor effect model for successful aging. Such a result is consistent with findings of other studies. Not all age effects in genetics of late-life psychiatric disorders reflect a survivor effect, however. Age can profoundly impact the expression of a gene and physiological changes with age can result in a very different impact of a genetic marker than occurs earlier in the lifespan. One example of this is from consideration of the serotonin transporter polymorphism (5HTTLPR), whereby the interaction of the short allele and stress on depression was not consistently observed in older adults, with the largest effect sizes observed in younger subjects. Yet, counter to intuition, it may simply not be a question of those carrying the short allele exhibiting worse performance with age. In one of our own recent investigations of 5HTTLPR and resilience in older adults, we found an attenuation with age of the impact of the gene with reduced resilience in the long allele carriers with stable performance across age in the short allele carriers.³ Rather than increased resilience with age accounting for the lack of association of the s-allele with lower resilience in older adults, it may be that age-related depletions in serotonergic neurotransmitter efficiency reduce any difference between the impact of the l- and the s-alleles.

Changing neurophysiology with age may thus significantly impact the effect of any given genetic marker, and not necessarily in the anticipated direction. As such, the findings of the numerous neuroimaging genetic investigations to emerge in the past decade on younger psychiatric patients cannot be assumed to generalize directly to older adults. The investigation in this issue by Yi et al.⁴ is another excellent example of how changing brain physiology interacts with genetic markers to produce very different outcomes. They investigated the relationship of A β deposition, a key pathological feature of dementia, APOE-e4 status, and regional cerebral glucose metabolism in cognitively normal older adults. Yi and colleagues' study suggests that A β deposition mediates the association between the e4 allele and reduced cerebral metabolism in the temporoparietal junction, but that the association of APOE-e4 and hypermetabolism in the frontal and anterior temporal regions, is in fact independent of A β deposits. The differential findings may point to very different mechanisms or pathways underlying

the varying patterns of metabolism associated with APOE. This investigation indicates that any association of a genetic marker with brain function cannot be assumed to be uniform across brain regions, activation or metabolism, and that such relationships may be mediated differentially.

One of the significant limitations in the field of geriatric psychiatry has been the lack of longitudinal genetic investigations, making it difficult to ascertain the impact of age. Again, there have been genetic investigations of longitudinal course of cognitive impairment in late life, but far less with respect to psychiatric outcomes. Much of what has been captured longitudinally in the field of geriatric psychiatry has been conducted in the framework of a clinical trial. The paper by Garfield et al.⁵ provides a good model of such an approach, and builds upon the seminal work of the authors' examining genetic markers in clinical trials with late-life anxiety.

Garfield et al.⁵ genotyped functional variants in the promoters of the serotonin transporter and the serotonin 1A and 2A receptors in 177 participants of a 12-week, double-blind, randomized controlled trial of the selective serotonin reuptake inhibitor (SSRI) escitalopram. Because the serotonin transporter is the principal target of SSRIs, the authors hypothesized that side effects experienced by participants vary in relation to genetic variations in these genes. Indeed, they found significant associations between the occurrence of specific side effects and variations in these genes. For example, dry mouth was more common in carriers of the low expressing genotype at the serotonin transporter and diarrhea in the low expressing genotype at the serotonin 1A receptor. Interestingly, no relationship was detected between the concentration of escitalopram and any side effects. This study strongly suggests that variations in genes of the serotonergic pathway may facilitate predictions about whether a patient receiving an SSRI may experience side effects.

The Kim et al.⁶ report on serotonergic genes, stroke, and suicidal ideation represents a step further forward in terms of following subjects over a year, and also considering not only gene by gene interactions, but also gene by comorbidity interactions in older adults, for whom such medical comorbidities are highly prevalent. Findings that variations in serotonergic genes are associated with suicidal behavior and with post-stroke depression, led Kim

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