Unlocking the brain: Pioneering psychiatric genomics at the University of Arizona

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Psychiatric disorders challenge us deeply. At the University of Arizona, researchers dissect their molecular roots, focusing on genomics. They aim to decode miRNA's role in conditions like depression, using advanced analysis to forge a path towards personalized mental health care. Find out more in this exclusive Q&A:

Could you summarise the core goal of your current research in psychiatric genomics at the University of Arizona?

We are currently working in parallel on two main projects. I will primarily describe the first project here. The first project focuses on understanding the role of miRNA in the neuropathology of Major Depressive Disorder (MDD) and Bipolar Disorder (BPD). We utilise brain tissues from deceased MDD and BPD patients to achieve this goal. Specifically, by comparing miRNA expression differences in selected brain regions, such as the subgenual Anterior Cingulate Cortex (sACC) and Amygdala (AMY), we aim to identify miRNA expression differences driven by the disease processes in the brain. These differences may also arise from disease neuropathology, i.e., due to neuroadaptation to the disorder rather than being causative of the disease.

Therefore, we integrate miRNA expressions with genetic signals derived from large GWAS of MDD and BPD. This integration allows us to identify expression quantitative loci (eQTLs) that impact miRNA expression and functions. Since the genetic make-up precedes any molecular changes in the brain, any association between genetic locus and miRNA expression could be interpreted as potentially causative.

Additional analyses, such as Mendelian Randomization (MR) Analysis, can further validate this assumption. At its core, this analysis uses the genetic data associated with disease to infer the causal pathway for the outcome, i.e., gene expression (in our case, miRNA). MiRNA can be considered the RNA equivalent of Transcription Factors, i.e., they control gene expression by binding to specific, very short (approx. 5 to 8 base pair (bp) sequences (called miRNA response elements (MRE)) in the three prime untranslated region (3'UTR) sequences of protein-coding (mRNA) genes, that predominantly control mRNA stability. Once miRNA binds the 3'UTR of their respective gene targets, they can initiate either mRNA degradation or translational inhibition, all of which will ultimately lead to reduced protein expression of the miRNA target. Furthermore, miRNA can affect multiple mRNAs (in the hundreds) with various strengths. Thus, miRNA function needs to be examined in the context of their ability to control gene expression. To that end,

surveying the protein-coding transcriptome in the same MDD and BPD patients with whom we have the miRNA expression data is essential to reveal the miRNA functions in the disease etiology. More importantly, by linking the genetic data derived from patients with MDD or BPD with miRNA functions on protein-coding gene expression, we highlight a potential neurobiological mechanism that can be amenable to novel treatment therapies that currently do not exist.

What are the most promising molecular mechanisms you've identified in your research related to psychiatric disorders?

In our study, we identified significant differences in miRNA expression associated with MDD. Interestingly, we also detected considerable enrichment of our miRNA eQTL signals in the genetic (GWAS) data for MDD. Moreover, through MR analysis, we demonstrated that the differences in miRNA expression are likely causative factors in the etiology of MDD and are not confounded by disease pathology; that is, the changes in miRNA expression are unlikely to result from neuroadaptation to the condition. While these discoveries are identified in the brain, they still offer a tantalizing possibility of developing potentially novel biomarkers for disease diagnosis, evaluating drug efficacy treatment, or developing novel miRNA-based treatment approaches. For example, in the last decade, there have been numerous clinical trials attempting to use miRNA for the treatment of oncological diseases.

How does data integration, from genomics to neuroimaging, contribute to a deeper understanding of these disorders?

One could reasonably argue that there are two main challenges associated with the diagnosis and treatment of psychiatric disorders. In terms of diagnosis, both clinically and genetically, psychiatric disorders exhibit a high degree of heterogeneity. For instance, due to clinical heterogeneity, various psychiatric nosologies will present with overlapping symptoms that may hinder accurate diagnosis. This issue can be further complicated by the inconsistencies found in the diverse questionnaires and tools employed to diagnose these disorders, particularly regarding the significant overlap in symptoms between bipolar disorder and major depression. For instance, the symptoms exhibited by patients with unipolar depression and bipolar depression are quite similar, and particularly in outpatient clinics, misdiagnosis can easily occur, leading to inappropriate treatment plans.

Regrettably, mental disorders are not currently curable. As psychiatrists, all we can do is treat the symptoms and hope for the best – that the patient will respond to treatment. However, this is often not the case, leading to multiple rounds of prescribing various drugs and dosages until we find one that the patient will respond to. Furthermore, many of the drugs currently used to address psychiatric symptoms have significant side effects that may limit the patient's compliance with the treatment plan, even if the prescribed antipsychotic medication is effective. The prevailing belief in the field for our inability to find a cure for mental disorders stems from significant genetic heterogeneity and the existing complex interactions between environmental and genetic factors. Given that

miRNA expression and functions are influenced by both environmental and genetic factors, they represent excellent candidates for understanding the aetiology and molecular neuropathology of mental disorders.

In your opinion, what is the biggest challenge in translating psychiatric genomics research into practical clinical applications?

The biggest challenge in translating genomic research from the bench to the patient's bed is the considerable genetic and phenotypic variation within the human population. Until the last decade, most treatment plans have depended on the efficacy of diagnostic approaches and drug responses for "average" patients, that is, whether the treatment effect is observed across a group of individuals. This strategy has been exceptionally successful in treating infectious diseases; one could even argue that the major advancement in medicine over the past 100 years has been our capability to treat various infectious diseases.

However, when it comes to complex (i.e., chronic disorders such as cardiovascular diseases, cancer, and, of course, psychiatric disorders), this approach has had limited success. In fact, in response to this limitation, in the last decade, the "holy grail" in biomedical research has been to apply the concept of precision medicine (also known as personalized), where the efficacy of drug response is focused on the individual and not ameliorated across the "average" patient.

I would argue that the inefficiency of the classical (i.e., average) approach to treatment is most evident in the management of psychiatric disorders. For example, many antipsychotics prescribed for treating schizophrenia exhibit varying degrees of success, with some patients remaining completely resistant to these medications. This is further complicated by the fact that, frequently, even if a patient is fortunate enough to respond to antipsychotic treatment, it may come with significant side effects that hinder the patient's compliance in continuing the medication. Therefore, the goal of precision medicine is to identify the individual genetic and physiological differences and tailor the medication accordingly to enhance treatment efficacy and lessen side effects for each individual rather than for the group of patients as a whole since every patient is a unique human being.

What key message do you want to convey to the broader scientific and public community about your proposed editorials?

Science is inherently messy, and researchers, even the most brilliant among us, are, after all, merely human and susceptible to mistakes. Fortunately, science has ways to self-correct, and the correct answer will eventually emerge. Often, the media plays a negative role by attempting to sensationalize discoveries, even though the researchers involved in the study are far more cautious in their language. Thus, my key message to the scientific community is to be careful when announcing their research to the media and to be proactive in correcting the media when it overhypes their findings. Likewise, the public

must heed the simple adage that “if it sounds too good to be true, then it probably isn’t,” and be much more cautious in believing answers that promise to deliver the truth, whatever that may be. In science, the truth is as good as the next discovery.

How do you see the future of personalised psychiatry being shaped by advancements in genomics?

Our genomes shape the blueprint of our identity as human beings. Comprehending how the human genome functions on various levels – specifically, the interaction between polymorphisms coded in our DNA and gene expression – is one approach to unravelling the biological mechanisms underpinning disease aetiology. Technological advancements, combined with decreased costs, have enabled us to explore the biological origins of psychiatric disorders with increasing granularity, from the organ level down to individual cells.

What specific psychiatric disorder within your research do you feel holds the most promise for breakthroughs in the near future?

That is a tall order to answer, maybe depression, but I might be wrong.

To conclude

This exploration into the complexities of psychiatric genomics highlights both the promise and the inherent challenges of translating research into clinical practice. The University of Arizona’s focus on miRNAs and data integration underscores the importance of rigorous scientific inquiry. As we move towards personalized medicine, it’s vital to remember that scientific progress is a nuanced and ongoing process, demanding both optimism and a critical eye.

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Primary Contributor

Vladimir Vladimirov
University of Arizona

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