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Genetic Analysis of Transdiagnostic Dimensional Phenotypes across Three Common Mental Disorders

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Thanks very much for the introduction. Thanks also to Professor Lo for the invitation and also congratulations for the anniversary of the Mental Health Association of Hong Kong. It is a great honour to be here to share some of my work and also to learn from all of you about the mental health. I'm going to switch the topic a little bit from detection and early intervention to genetic study which I have been doing for more than 30 years.

The Issue of Phenotypes

The topic change which I have mentioned is about transdiagnostic dimensional phenotypes across three common mental disorders, which are schizophrenia, bipolar disorders and depression. As a clinician and psychiatrist, I am also interested in other mental disorders. When we study and search, we need to ask which way we are studying. The first question is phenotype. At the moment most studies mainly use the current psychiatric diagnostic classification system namely DSM V and ICD 10. About ten years ago we have the success of the human genomic project, some of the researchers had suggested important questions. First, the most important for the complex disorders is not only genetic knowledge but also they need to forecast the human phenotypes according to parameters and the standard. This means we need to have some really firm phenotype to know what we have been studying. This is particularly important for mental disorders.

Also, it raises the question what we need to see when we are doing the studies, we need to see the transdiagnostic dimensional phenotypes. For example, for a patient if they have the diagnosis of schizophrenia there are psychiatric symptoms or other disorders, they might also have psychotic symptoms. For the treatment, when they use an anti-psychotic mainly for schizophrenia, they also use a second generation anti-psychotic for bipolar disorders. Clinical heterogeneity is therefore common among schizophrenia, bipolar disorder and major depressive disorder. More and more evidence has shown those common mental disorders such as schizophrenia and bipolar and also depression have obvious connections, they are genetically connected. Depression is just in the middle of those two groups. There is a very close genetic correlation, for those common disorders. For another group of disorders such as anorexia nervosa, they are genetically connected as well and there is a connection.

The Study on Three Common Mental Disorders

We know that a lot of mental disorders have cognitive impairment but when we put all these disorders together, only for schizophrenia, bipolar disorder and depression, they all have some cognitive impairment. Some are different, some shared with other disorders. Another group has also done quite a lot of similar study for cognitive function and also for schizophrenia, bipolar disorder and depression. Actually for cognitive function study, we learned how to do cognitive study for schizophrenia. We did the same cognitive study with a sample of schizophrenia and

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depression patient together to see if they could share a cognitive deficit. We found that those patients all had the cognitive deficits together. They only had difference in term of severity and it didn't matter whether they had schizophrenia or depression disorder.

So is cognitive deficits unique? Patients including schizophrenia, bipolar disorder and depression together showed some other markers in our sample including immunology, neurology, endocrine and circadian factors. Those patients all had some decrease or increase impairment in those bio-markers. This was not unique for only one patient group. We have been thinking, it is also possible for genetic studies on endophenotypes, where the brain structure may have shared changes among common mental disorders. So they can be used as a phenotype for genetic study. This is our group's design. They include 1,052 schizophrenia, bipolar disorders and major depressive disorder patients together with healthy control clinical assessment, imaging, cognitive function and also the genetic test are in place to identify the genetic basis for all these disorders (Table 1). The total sample included all those patients and the controls. We did the phenotype, different genetic assessment, including second generation sequencing and also used a public database. We used the genotype data to predict the spatial expression quantification of the target gene in the target brain region (Figure 1 to 3).

Table 1
Participants: 1052

	Sample
Diagnosis	
first-episode drug-naïve schizophrenia	262
Bipolar disorder	227
MDD (unmedicated >3 months)	160
Healthy controls	403
Age	25.99(9.40)
Sex (male)	471 (45%)
Educational years	13.32 (3.34)

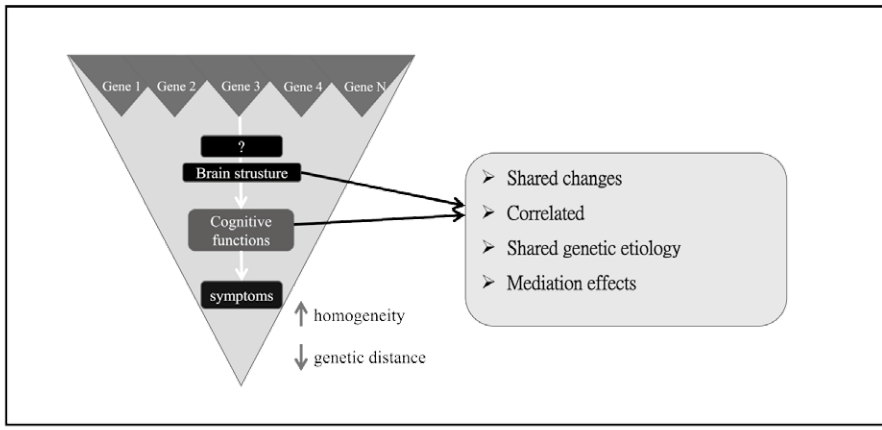

Figure 1: The Endophenotypes

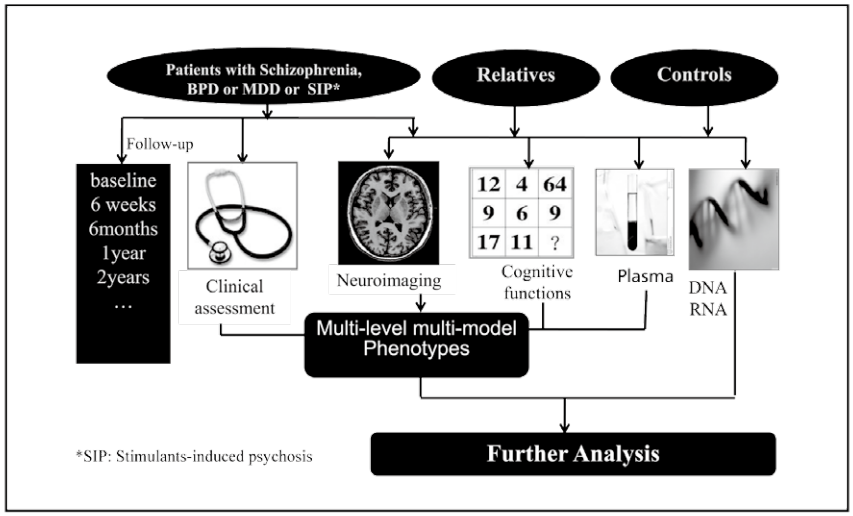

Figure 2: Research Outline

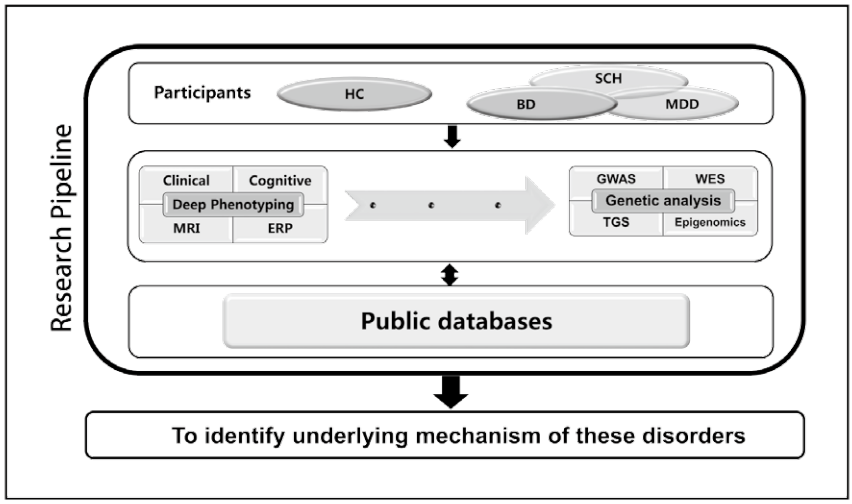

Figure 3: Research Pipeline

We firstly found a common factor for those three disorders. Then, sharing the common factor with a genome-wide significance in studies including schizophrenia and other disorders. We then did a transcriptome mapping and able to analysis and show a difference in the expression level of ZNF391. This has been expressed in popular brain regions, including some interesting regions. We put all these disorders together and used gene expression as a biomarker, three new biotypes emerge for these disorders. These three biotypes have shown different biotypes in terms of cognitive and neuroimaging attributes. There is a crucial pathway to cognitive function, partially shown here on gray matter volume when we come across the three common mental disorders. This might suggest that in future when we look at disorders with the worst outcomes, we need to think which phenotype is used in a different way. Finally I would like to thank my colleagues in Mainland, especially Professor Pak Sham and his team at the University of Hong Kong. Last but not least, all the participating patients and their families. Thank you very much.