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# Phenotype in Psychiatric Genetic Research

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## 1. Introduction

Mental illnesses differ from medical conditions in their lack of objectively assessable biological markers for the establishment of a diagnosis. In the absence of clear external validators such as laboratory tests or radiological examinations, accurate assessment of the clinical picture and phenomenology becomes crucial. Common diseases with successful genetic mapping studies are generally characterized by diagnostic assessments that are objective, have a clear biological basis, and measure phenotypic features shared relatively uniformly among affected individuals. For example, type 2 diabetes is diagnosed based on elevation in blood glucose above a generally accepted threshold, as assessed by a simple assay. This phenotypic feature is at the core of the diagnosis, even though other disease components may vary between affected individuals. For mental illness, however, no biological assays are currently available for diagnostic purposes; the phenotypic features are generally assessed by subjective ratings, and individuals are assigned a diagnosis based on report of symptoms, no one of which is present in all individuals assigned that diagnosis. There is now considerable interest in identifying quantitative assessments, which may provide a more objective means of rating psychopathology.

Many researchers on psychiatric genetics have given attention to populations that are more genetically homogeneous due to historical reasons. These isolated populations have been useful for the identification of genes for disorders in other medical fields. In addition to the genetic homogeneity, these unique groups may also help in the definition of the phenotype. Particularly, psychiatric disorders with psychosis such as schizophrenia (SZ), schizoaffective disorder (SCA) and bipolar disorder type I with psychosis (BPI) are major public health burdens and their biology is still largely unknown. It is unlikely that these disorders represent a single illness, however they overlap on many dimensions, including symptoms, neurocognition, and treatment. Families of individuals with SZ very often have other members with BPI and SCA (Kendler et al., 2010). Many authors argue that modifying genes may determine why one person develops SZ and another develops BPI or SCA (Van Erp et al., 2002). Nevertheless, the question whether or not phenotype uncertainty is responsible of the presumed genetic overlap remains unanswered.

The use of multiple sources of information in the diagnostic process is essential in genetic studies of mental illness. A best-estimation diagnostic approach ensures diagnostic precision and reduces misclassifications getting better phenotype characterization of the study subjects. Along with the clinical complexity and the assumed genetic heterogeneity, environmental factors play an important role in the final outcome of most psychiatric disorders. In this instance, stressful environmental factors have been clearly associated with

increased risk for suicidal behaviour (Perez-Olmos et al., 2007). In this way, external factors interact with genetic predisposition in the occurrence of suicide. Likewise, subjects with chronic psychosis who experience a high number of adverse life events could be at particular risk to develop depression depending of their genetic susceptibility.

## **2. Psychiatric genetic research in the Central Valley of Costa Rica**

The isolated Costa Rican Central Valley population (CRCV) was founded by approximately 86 Spanish families. These families colonized the area between 1569 and 1575 and intermarried with indigenous Amerindians. By the beginning of the 18th century, the population grew rapidly with little subsequent emigration for almost 200 years (Escamilla et al., 1996). Psychiatric genetic research in CVCR began on mid-1990s. Participants have been selected with regard to their ancestry by completing a genealogical search. Thus, the majority of the great-grandparents of each subject are descended from the original founding population of the CVCR. Documentation of the birthplace of the great-grandparents is possible due to the centralization of birth records. This yield to link up approximately half of these subjects to a founder couple who came into Costa Rica in the 17th century, which demonstrates the founder effects in this population.

At present, more studies are being conducted for SZ, SCA and BPI in the CVCR. It has been found that subjects recruited independently of each other within this population can be linked together once genealogies are studied. This suggests that accurate genealogical screening is crucial for selecting subjects whose ancestors are predominantly from the founder population. This research approach represents an advantage for fine mapping and the identification of susceptibility genes. Because both linkage and association approaches depend on the probability that affected individuals will share disease-susceptibility genetic variants and marker loci identical due to descent from a common ancestor, human geneticists have long been interested in identifying study samples characterized by relative genetic homogeneity.

## **3. The phenotype in psychiatric genetic studies**

Segregation analyses, adoption studies and twin studies have consistently shown that regardless of the population studied, genetic factors play an important role in determining the risk of developing SZ, SCA and BPI. Evidence suggests that these disorders share common genes (Badner & Gershon, 2002). Although genetic studies of these disorders have made progress in recent years, the field lags behind other complex diseases in the identification of disease-related genes. SCA patients have increased familial risk of SZ and mood disorders. Relatives of SZ probands have increased risk for SCA and major depressive disorders. Many patients with SZ have concomitant major depression at some point in their illness, and the longitudinal course of this depression (which is difficult to accurately assess) is often the determining factor in assignation of a diagnosis of SCA versus SZ. A clinical characterization study from a Costa Rican sample reported that more than half of the patients with SZ have mood symptoms particularly depressive symptoms (Contreras et al., 2008). Conversely, many patients with BPI endorse lifetime history of psychotic symptoms. As illustrated in figure 1, SZ, SCA and BPI with psychosis share a common domain, psychosis. Another report from the same population found that 97.6% of the bipolar I patients have history of psychosis which might explain the clinical similarities found between patients with SZ versus BPI (Pacheco et al., 2009).

Their clinical complexity is not well considered in the current diagnostic system, which may explain some of the misclassification biases yielding to misleading research findings. Categorical diagnosis appears to be a poor predictor of correlation between the phenotype and the specific genotypic variants that contribute to an individual’s risk of developing these mental disorders. In the absence of measurable biomarkers for most of these conditions, accurate assessment of the clinical picture and phenomenology of patients becomes even more crucial. It is now generally agreed that phenotypes (diagnoses) are best made by comprehensive characterization of lifetime clinical symptomatology based on information gathered from several sources (Maziade et al., 1992). The scientific rationale for such a recommendation is that systematic evaluation of all sources of information conduct to a best-estimate diagnosis that reduces diagnostic error (Merikangas et al., 1989).

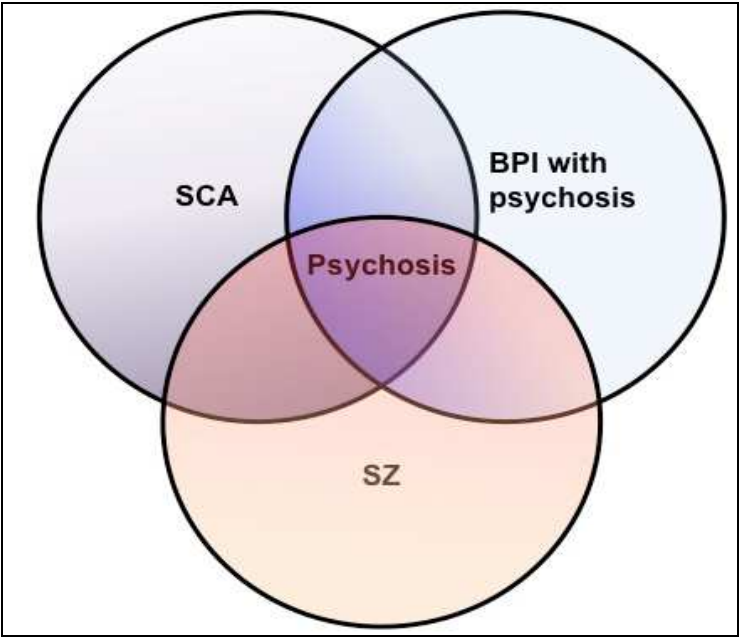


Fig. 1. Psychosis: the shared domain in SZ, SCA and BPI with psychosis.

**3.1 Best estimation and consensus diagnostic process**

The best estimation process uses a consensus-based approach to arrive at final diagnosis (Leckman et al., 1982). Clinical information is gathered from the Diagnostic Interview for Genetic Studies (DIGS), (Nurnberger et al., 1994), a Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) and medical records.

The DIGS was developed by the National Institute of Mental Health (NIMH) in 1994. Its polydiagnostic capacity enables a detailed assessment of the course of the illness, chronology of the affective and psychotic disorders and comorbidity, as well as an additional description of symptoms including the possibility of an algorithmic scoring. The DIGS is an diagnostic instrument that allow psychiatrist form around the world to speak the same language; it includes a section describing the temporal relationships between affective disorders, anxiety disorders, psychosis and substance abuse disorders. It is reliable and valid instrument for genetic studies and has been used as a research instrument in other biological marker studies, given its diagnostic capacity for both the current and previous episodes. The direct interviews (DIGS) are conducted by trained psychiatrists and inter-rater

reliability is evaluated to ensure consistency of the instrument. The psychiatrist is blind to family history, medical records, or any other information other than that they derived from the direct interview.

Final diagnoses is obtained through a consensus process where two independent psychiatrists review all available information, arrive at independent diagnoses, discuss the case and then arrive at consensus diagnoses. Each best estimate rater also score each affected subject for lifetime dimensions of psychosis using the Lifetime Dimensions of Psychosis Scale (LDPS) developed by Levinson et al; 2002. The LDPS creates a profile of the lifetime characteristics of each case based on retrospective ratings, encompassing dimensions of positive psychotic, depressive and manic symptoms, complicating factors and deterioration. Dimensional information allows researchers to capture subsyndromic symptoms used to define spectrum conditions like SZ, SCA, BPI. For instance, LDPS has been used to study disorganization and negative symptoms (dimension for hebephrenia) in a Costa Rican sample. It was found that prominent lifetime scores for disorganization and negative symptoms are associated with the cannabinoid receptor 1 gene (CNR1) (Chavarría-Siles et al., 2008). The defined dimension for hebephrenia resembles the chronic cannabinoid-induced psychosis.

In spite of a good research instrument such as the DIGS, additional sources of information are required to accurately capture the diagnosis of patients with psychotic disorders. A study comparing direct interview and consensus based multi-source methods found that the DIGS alone have low agreement for the diagnosis of SZ (Contreras et al., 2009). Disagreement is more commonly observed on those diagnoses involving mixed symptomatology (psychotic and affective symptoms). The lack of clarity in the DSM-IV criteria for SCA, the difficulty of accurately assessing the duration of mood symptoms and/or psychotic symptoms and their overlap may explain the poor agreement rate in this disorder. This finding provides more evidence on the importance of a final best-estimate and consensus diagnostic process for psychiatric genetic research.

#### 4. Endophenotype

While psychiatric nosology defines SZ, SCA and BPI as unique illnesses with distinctive clinical characteristics, and presumably separated aetiologies, there is growing evidence that they share common susceptibility genes (Walss-Bass et al., 2005). Although it is unlikely that they are a single illness, there is an overlap on many dimensions, including symptoms, neurocognition, and effective treatment. To date, most genetic research has been focused on the categorical classification and few have explored quantitative phenotypes. Imprecision of psychiatric phenotyping might explain the failure of genetic research to identify susceptibility genes of these disorders where research diagnoses is attained by subjective assessments. Growing evidence supports the study of quantitative processes mediating between the genotype and gross clinical phenotype (endophenotype) (Preston et al., 2005). Imprecision of psychiatric phenotyping might explain the failure of genetic research to identify genes that contribute to susceptibility of these disorders (Bearden et al., 2004). It is assumed that genes involved in endophenotypic variation are likely to represent more elementary phenomena than those involved in complex psychiatric diagnostic entities. It is also used interchangeably with the term 'intermediate trait,' describing a heritable quantitative phenotype believed to be closer in the chain of causality to the genes underlying the disease (Bearden & Freimer, 2006).



Clinical heterogeneity occurs when more than one clinical condition can be brought about by the same cause; causal heterogeneity occurs when two or more causes can, on their own, lead to the same clinical syndrome. Some individuals will have the “full disorder”, which mean a clinical syndrome meets diagnostic criteria for a specific diagnosis. Others will not meet criteria for the full disorder yet will show the abnormalities that are called “spectrum conditions”. There is a third group, cases of illness that mimic a genetic disorder but are not caused by genes, “phenocopies”. It is likely that phenocopies account for many diagnostic errors whereby a patient is diagnosed with a genetic condition but actually has some other disorder. Hence, phenocopies are a dramatic form of causal heterogeneity where disease genes cause some cases and others are not. Most probably, the “other” cases are caused by some environmental event. Defining disorders as “genetic” and “nongenetic” can lead to controversial position. Some authors argue that it would make more sense to view the genetic and environmental contributions to illness as varying among people. By chance, some patients will have primarily genetic disorders and others will have primarily environmental disorders. Most of them are likely to have a mix of both types of causes as seen in clinical daily practice.

Gottesman proposed that SZ does not have a single cause but it is caused by the combination of many genes and environmental factors, each having a small additive effect on the expression of SZ. This view has been called “the multifactorial theory of SZ” because it proposes that multiple causes lead to illness. This theory posits that it is possible to separate patients into groups with greater and smaller genetic contributions to their disorder but most of them will fall between the two extremes of “primarily genetic” and “primarily environmental.” This approach result of help for patients and their family members to better understand the causes of mental illness. It shows the role of environmental circumstances and how psychosocial therapies can help people with mental disorders even though many of these disorders are believe to be biologically based conditions reflecting the dysregulation of brain systems.

The “spectrum conditions” are used to describe mild psychopathology or other abnormalities of unknown clinical significance that occur among the otherwise well relatives of psychiatric patients. It supports the theory that most psychiatric disorders are not a discrete condition. Instead, it places many mental disorders within a continuum of psychopathology where genes and environmental insults determine the susceptibility to develop a psychiatric disorder. Figure 2 illustrates how this vulnerability is viewed as a quantitative or continuous trait. Many psychiatric disorders display a signature of complex inheritance. The liability to develop the disease is defined by a particular threshold of phenotypic severity. Milder forms of the illness are defined by less severe phenotypic features, and so there is familial aggregation of a spectrum of conditions that vary in severity. This pattern is consistent with models of inheritance that include multiple genes that interact with each other and environmental factor to confer susceptibility to illness.

An endophenotype is a heritable quantitative trait that is genetically correlated with disease liability, can be measured in affected and unaffected family-members and provides greater power to localize disease-related genes than affection status alone (Gottesman & Shields, 1973). They are less dependent on diagnostic certainty than more traditional genetic designs. Currently, an increasing number of researchers are using quantitative endophenotypes in extended pedigrees, which is considered the most powerful approach for localizing genes for affective and psychotic illnesses. Nevertheless, some geneticists argue against the endophenotype-based approach in psychiatry, noting the lack of evidence that such

intermediate phenotypes are more closely related to risk genes than are the diseases themselves.

Personality traits and neurocognitive measures are inexpensive endophenotypes that can be collected in large-scale family-based studies. Many candidate endophenotypes for BPI (e.g. neurocognitive functions, behavioural traits, sleep abnormalities) have been proposed (Gottesman & Gould, 2003; Hasler et al., 2006). Research of candidate endophenotypes for SZ and BP has also been conducted in the population of the CVCR. It was observed that neurocognitive traits are strong candidate endophenotypes for SZ and BP separately. For instance, a processing speed measure (Digit-Symbol Coding) was a strong candidate endophenotype for both illnesses (Glahn et al., 2010) and closely related to genetic liability for SZ (Glahn et al., 2007).

A study of quantitative measure of anxiety as a candidate endophenotype for BPI in the CVCR was also performed. It was found that quantitative measurements of both, state and trait anxiety are highly heritable and share some genetic factors but only anxiety trait is associated with Costa Rican BPI (Contreras et al., 2010). Hence, quantitative trait of anxiety meets criteria for a candidate endophenotype in the studied sample. The relevance of this work can be summarized as follows: (1) Quantitative anxiety measures as an endophenotype may facilitate the identification of genes that predispose individuals to develop BPI. (2) Confirmation of this result will aid researchers to understand the essential pathophysiology underlying bipolar spectrum disorders. (3) If this trait is proven to be an endophenotype, it will be of help in diagnosing and treating BPI patients in a more reliable and biologically valid manner than our current classification allows. This will also have direct epidemiological implication on public health policies. (4) As for other bipolar endophenotypes, anxiety traits can be modelled in animal research. Several genetic, pharmacological, and behavioural animal models have long been used to establish animal anxiety-like phenotypes, as well as to assess their memory, learning, and other cognitive functions (Ennaceur et al., 2006; Kalueff & Murphy, 2007; Waikar & Craske, 1997; Wang et al., 2007; Yokoyama et al., 2009). Specifically, chronic oxytocin has been used to attenuate the high level of trait anxiety in rats (Slattery and Neumann, 2009). Some innate fear responses may also underlie the type of elevated anxiety levels found in the subjects with BPI.

Factor analysis of this trait in subjects with lifetime history of manic/hypomanic syndrome led to the classification of these individuals in two groups, worry and rumination, based on the nature of the symptoms (Contreras et al., 2011). Comorbid obsessive compulsive disorder in BP is characterized by episodic course, higher rates of certain obsessions (e.g. aggressive/impulsive, sexual, religious, and obsessional doubts) that require more frequent hospitalizations and complex pharmacological interventions (Perugi et al., 2002). A defining characteristic of obsessive compulsive disorder is unsuccessful suppression of unwanted thoughts. Obsessive symptoms have else been positively associated with rumination and inversely associated with perceived thought control ability (Grisham & Williams, 2009). Rumination involves repetitive thought about past events, current mood states, or failure to achieve goals (Martin & Tesser, 1996). Evidence suggests that rumination predicts the future occurrence of anxiety in anxious depressed comorbid conditions (Nolen-Hoeksema, 2000). In subjects with history of mania/hypomania, rumination may play an important role in triggering depressive episodes too. This analysis represents an important contribution to the understanding of underlying constructs in bipolar patients with sub-syndromic anxiety.

Further research will test whether these component factor scores are heritable, whether they share the same genetic factors, which (if they are not highly correlated) may further help define the components underlying BPI and other psychiatric disorders with a history of mania/hypomania.

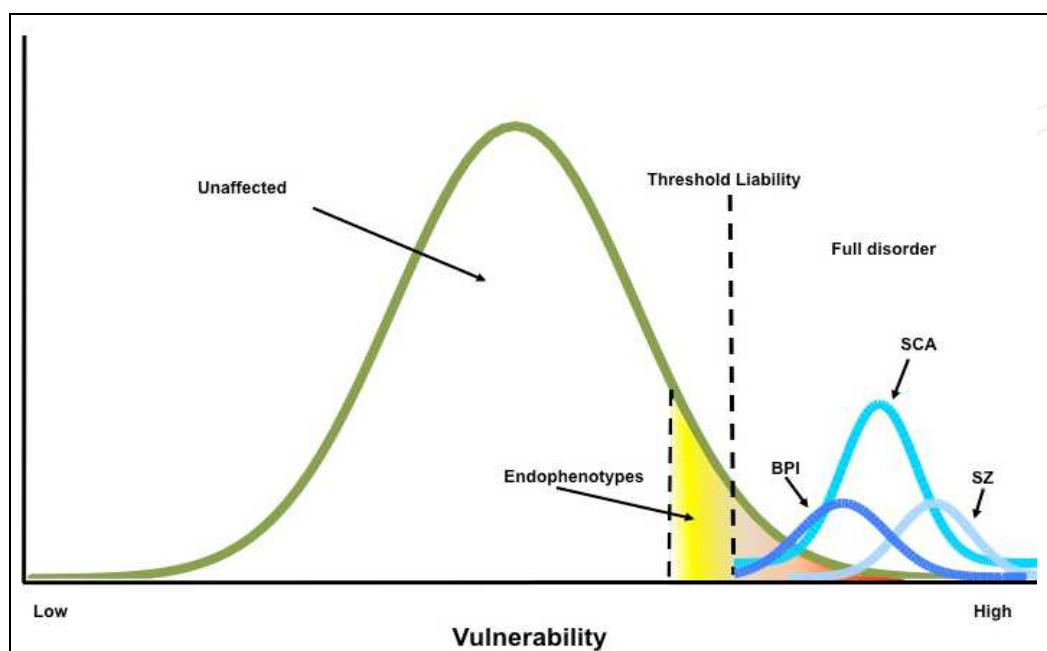


Fig. 2. Multifactorial vulnerability model for complex disorders.

## 5. Gene/environmental interaction

Gene-environment interactions result when genetic polymorphisms alter the ability of a specific region of the genome to be epigenetically altered in response to an environmental factor. Interaction between genes and environment plays an important role when studying the underlying etiological process of these psychiatric disorders (Kim et al., 2007). Many candidate genes have been studied, especially those directly implicated in the monoamines pathways. For example, allele-specific epigenetic modifications have been associated with “risk” polymorphisms in psychiatric candidate genes including the C/T(102) polymorphism in the serotonin receptor 2A gene (Polesskaya et al., 2006) and the Val66met polymorphism in the brain-derived neurotrophic factor gene (BDNF) (Mill et al., 2008). Increasing evidence suggests that epigenetic processes can be influenced by external environmental factors (Sutherland et al., 2003). Epigenetic events such as DNA methylation has been shown to vary as a function of nutritional, chemical, physical, and even psychosocial factors. As epigenetic changes are inherited mitotically in somatic cells, they provide a possible mechanism by which the effects of external environmental factors at specific stages in the life course can be propagated through development, producing long-term phenotypic changes. Epigenome seems to be particularly susceptible to disruption during rapid cell replication (Dolinoy et al., 2007).

In the same way, the polymorphism of the gene that codes for the serotonin transporter protein has been associated with specific clinical outcomes when interacting with environmental factors. This single gene (SLC6A4, Locus Link ID: 6532) has been mapped to



chromosome 17q11.1-q12 (Murphy et al., 2004). This protein plays a crucial role in regulating the intensity and duration of serotonergic signalling at synapses and has been a target for many psychiatric drugs (Alessandro et al., 2008). There are at least two polymorphic variants that play a role in differential expression of the SLC6A4 gene. The short allele of these variants results in decreased expression of the serotonin transporter protein (Glatz et al., 2003). Several studies have analyzed the role of these variants in anxiety and depression (Uher et al., 2008). Depressive symptoms and suicidality have been associated with having one or two copies of the “s” allele, but only in the context of stressful life events (Caspi et al., 2003). Kendler and colleagues were able to replicate Caspi’s finding showing in an independent sample that individuals with two “s” alleles showed an increased risk for depressive episodes in the context of stressful life events (Kendler et al., 2005).

Patients with SZ and SCA are at great risk for lifetime history of a full depressive syndrome or episode. One can hypothesize several potential pathways that might explain the high rates of depression in persons with a psychotic disorder. Lack of personal security, living conditions potentially harmful to the patients, psychological wellbeing, persecution and discrimination, bad peer relationships and unemployment are all potential consequences of interaction between the psychotic individual and his/her environment. For persons whose psychosis carries a paranoid element, the presumed threat from persecutors to the individuals’ wellbeing may be sufficient to trigger depression and fear. For those patients who have sufficient insight to be aware of their illness and how it impacts their life, awareness of illness may be a direct trigger for a potentially dysphoric response. Postpsychotic depression, for instance, is a common occurrence in persons who are treated for first-break psychosis. By this mean, chronic psychosis might itself act as a “stressor” which interact with the “s/l” serotonin transporter variant to increase depression in persons with at least one copy of the “s” variant.

There is increasing evidence supporting the role of this gene in the course of mood symptoms in the context of psychosis (Contreras et al., 2008). A replication of the previous work was conducted using a narrower phenotype. Only subjects with SZ from the CVCR were included in the analysis. It was found that schizophrenic subjects carrying at least one short allele have higher risk for depressive syndromes (Contreras et al., 2010). Contrary to other scientific reports the authors did not find association between suicidal behaviour and the genetic variant.

## 6. Conclusion

Mental illnesses pose significant economic burdens, are associated with substantial morbidity and mortality rates and their etiological factors are poorly understood. Isolated populations such as the CVCR are essential for conducting studies of complex disorders. A centralized of health care; large family sizes and high rate of compliance of patients make this population ideal for genetic studies on mental illness. Within founder populations, genetic variants that are rare in other populations may also account for a greater proportion of the genetic cases, thus increasing the opportunity to identify predisposition genes of these common disorders.

Although genetic studies of SZ, SCA and BPI have made progress in recent years, the field lags behind other complex diseases in the identification of disease-related genes. The difficulty in finding genetic loci most likely derives from the complex nature of the illnesses.

The observed differences in social and functional decline among these psychiatric conditions support the original dichotomy described by Kraepelin based on chronicity and periodicity. By following this dichotomic concept some researchers have focused their work on a more severe and homogeneous phenotype. In this case, the categorical classification of the current diagnostic system has been utilized to define narrow phenotypes. Another group of researchers prefer to combine the traditional diagnostic approach with quantitative measurements. Thus, the measurement of more sophisticated dimensions such as neurocognitive endophenotypes and personality traits in multiplex multigenerational families have gained importance. Regardless of the diagnostic approach, a best estimation process is vital to avoid misclassification biases. The use of direct interview together with information from family members can help to identify problematic symptoms during diagnostic process. All efforts are oriented not only to the improvement of genotyping techniques and clinical classification but else to the understanding of the interaction of genes with environment. Some of the main limitations in this field of research are explain by the clinical and genetic complexity of psychiatric disorders, the lack of large sample sizes needed to detect associations at appropriate levels of statistical significance, the underlying stratification of study groups and the effect of medications on behavioural measurements. In order to overcome those obstacles, research is moving toward a more quantifiable and dimensional rating system. This will allow scientist to understanding the pathophysiology of mental illness that is of great public health significance. Identifying genes that contribute to risk of these diseases will provide critical information leading to the development of novel diagnostic and therapeutic strategies.

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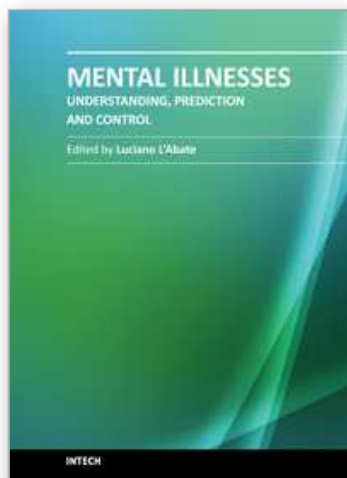
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## **Mental Illnesses - Understanding, Prediction and Control**

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In the book "Mental Illnesses - Understanding, Prediction and Control" attention is devoted to the many background factors that are present in understanding public attitudes, immigration, stigma, and competencies surrounding mental illness. Various etiological and pathogenic factors, starting with adhesion molecules at one level and ending with abuse and maltreatment in childhood and youth at another level that are related to mental illness, include personality disorders that sit between mental health and illness. If we really understand the nature of mental illness then we should be able to not only predict but perhaps even to control it irrespective of the type of mental illness in question but also the degree of severity of the illness in order to allow us to predict their long-term outcome and begin to reduce its influence and costs to society. How can we integrate theory, research evidence, and specific ways to deal with mental illness? An attempt will be made in the last conclusive chapter of this volume.

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