A public health genetic approach for schizophrenia

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SUMMARY. **Background** – Schizophrenia is a complex disease resulting from the interplay of genetic and environmental factors. However, psychiatric genetics and epidemiology have often worked as independent research fields. **Aims** – To review the evidence about the gene-environment interplay involved in the development of schizophrenia. **Methods** – Systematic review of medical and psychological databases. **Results** – On one hand, quantitative and molecular genetics showed high heritability for schizophrenia and identified genes likely to be involved in its pathophysiology. The strength of the association between candidate genes and schizophrenia is however modest, and the need for a more appropriate conceptualization of the genetic risk has been claimed. On the other hand, psychiatric epidemiology described several environmental factors liked with the onset or the course of schizophrenia. The observational nature of epidemiology, however, may hamper inference on causation. Gene-environment correlations and interactions influence the exposure and the vulnerability to the environment, respectively. Current findings suggest that gene-environment correlations and interactions may be common phenomena in the pathophysiology of schizophrenia. The consideration of gene-environment interplay may help to overcome many limitations of genetic and epidemiological studies in psychiatry and suggest innovative preventive and therapeutic strategies. **Conclusions** – Taking into account the complexity of schizophrenia pathophysiology, mental health genetics may provide a comprehensive and heuristic model of disease.

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INTRODUCTION

Schizophrenia ranks among the top 10 causes of life years lost to disability globally, accounting for 2.3% of the total burden of disease (DALY) (Murray & Lopez, 1996). Despite the efforts of national health care devoted to the direct costs of the disorder, a substantial proportion of DALY liked to schizophrenia therefore seems to be resistant to secondary and tertiary prevention. This points to the need for a public health strategy aimed at primary prevention (McGrath, 2002). The application of public health strategies in psychiatry should be based on epidemiological evidence from longitudinal population-based studies, measuring the social and economical context and evaluating services cost-effectiveness (Thornicroft & Tansella, 1999). Critically, these studies should be able to inform policy makers planning primary prevention measures about causes of disease, as opposed to risk indicators (Kraemer *et al.*, 1997). To do this, research will have to disentangle the complex interplay between genetic and environmental factors involved in the pathophysiology of schizophrenia (Andreasen, 1999).

Public health genetics is primarily interested in the interplay between genetic and environmental factors underlying human disease, with the aim of unravelling the true origin and the vulnerability to putative environmental risk factors (Khoury *et al.*, 2005). As suggested by heritability estimate, genetic factors may directly influence disease phenotypes. However, genes may also indirectly affect the development of several disorders. Genes may indeed control the exposure to environmental risk factors through gene-environment correlations. Moreover, genes may modulate individual differences in the response to environmental risk factors through gene-environment interactions. The implications of correlations and interactions between genes and environment are profound, possibly leading to processes of selection for genetically mediated environmental measures and threshold heterogeneity due to genetic predisposition (van Os & Sham, 2002). Causal inference in public health research should therefore include the evaluation of genetically mediated processes.

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Gene-environment interplay also influences psychological functioning and the pathophysiology of mental disorders, including schizophrenia (Tsuang, 2000; van Os & Sham, 2002; McGuffin, 2004). It is therefore proposed here to apply a public health genetic approach to schizophrenia research, in order to ultimately improve preventive and therapeutic interventions.

THE GENETICS OF SCHIZOPHRENIA

Quantitative genetic analysis clearly suggests a genetic contribution in the pathophysiology of schizophrenia. The risk of developing schizophrenia increases together with the genetic correlation between relatives, in a clear-cut dose-response fashion (Gottesman, 1991). Familial risk for schizophrenia cannot however be used to disentangle the gene-environment interplay underlying schizophrenia, as relatives also share variable environmental influences. It is therefore useful to consider the results of twin and adoption studies.

Monozygotic twins are genetically identical, while dizygotic twins share 50% of genes. Assuming zygosity does not affect the likelihood of exposure to a shared environmental experience (the 'equal environment assumption'), the difference in phenotypic correlations between monozygotic and dizygotic twin pairs is a function of their genetic correlation. By comparing the phenotypic correlations in monozygotic and dizygotic twins it is then possible to fraction the variance for the phenotype of interest (univariate analysis), quantifying the relative contribution of genetic, shared and non-shared environmental factors (Plomin *et al.*, 2001). Heritability estimates for schizophrenia vary between 70-90% (McGuffin *et al.*, 2002). Positional cloning techniques have been employed in order to localize and identify genetic factors contributing to the high heritability estimates (see OMIM database: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=181500).

Linkage analysis tests the co-segregation of a phenotype and a genetic marker with known chromosomal position. The probability of recombination between two loci on the same chromosome is a function of the distance between them: the linkage phenomenon. If a gene in linkage with a specific DNA marker influences a given characteristic, relatives who share the DNA marker will be more similar for the characteristic than relatives who do not (Risch, 2000). Linkage analyses suggest the role of 1q, 2q, 3p, 5q, 6p, 8p, 11q, 13q, 14p, 20q, 22q regions in the pathophysiology of schizophrenia (Badner & Gershon, 2002; Lewis *et al.*, 2003).

Allelic association studies rely on the phenomenon of linkage disequilibrium (LD) (Reich *et al.*, 2001). LD refers to a specific linkage phenomenon that is observed when two loci are so close together on a chromosome that they are not separated by recombination events over many generations (i.e. long periods of evolution). Each such pairs of loci reflects a fragment of an ancestral chromosome that remains intact despite several meioses (over multiple generations) and therefore appears to be associated even in individuals from different families (unrelated subjects). Association studies compare the frequencies of DNA marker alleles in a group of affected individuals and a sample of controls without the disorder (Risch, 2000; Tabor *et al.*, 2002). Association studies suggest a possible role of genes disbyndin (6p22), neuroregulin-1 (8p21) in the pathophysiology of schizophrenia. Data on genes D-aminoacid oxidase activator (DAOA or G72; 13q34), proline dehydrogenase (PRODH; 22q11), cathechol-O-methyltransferase (COMT; 22q11), DISC-1 (1q42) and DISC-2 (1q42) are promising but not yet compelling (McGuffin, 2004; Harrison & Weinberger, 2005; Owen *et al.*, 2005).

Quantitative genetics data suggest that schizophrenia cannot be theorized according to simple genetic models (Sullivan *et al.*, 2003). Molecular genetic findings are consistent with such a view, claiming the need for a more appropriate conceptualization of the genetic risk for schizophrenia (Kendler, 2005). The strength of the association between single candidate genes like neuroregulin-1 and dysbindin and schizophrenia is modest, with relative risk of 1.1-1.6. The specificity of the association between candidate genes and schizophrenia is low, because of the pleiotropic effect of genes, the overlapping genetic influences among different disorders and the likely biological heterogeneity underlying schizophrenia (Jablensky, 2005). Gene-gene and gene-environment interactions may be important in the pathophysiology of schizophrenia, resulting in non-contingency of the association.

THE EPIDEMIOLOGY OF SCHIZOPHRENIA

Epidemiology is the study of the distribution and determinants of disease frequency in human population. Epidemiological studies described several risk factors for the onset or the course of schizophrenia.

One of the most consistent findings is the inverse relationship between the socioeconomic status and schizophrenia (Dohrenwend & Dohrenwend, 1969). The relative risk for schizophrenia is about 3 in the lowest com-

pared to the highest class (Eaton *et al.*, 1988). In contrast to early hypothesis of social causation, subsequent data suggested that patient's functional impairment may lead to socioeconomic drift or hamper upward mobility (social selection) (Dohrenwend *et al.*, 1992). Although social selection hypothesis still stands confirmed, evidence from migration and urbanicity studies suggests caution in closing the social selection / causation debate for schizophrenia (Cooper, 2005).

Migration has also been implicated as a risk factor for the development of schizophrenia, conferring a relative risk of 2.9 (Cantor-Graae & Selten, 2005). The selection/causation issue is still debated (Selten *et al.*, 2002). Nevertheless, migration appears to be an important distal risk factor, perhaps related to experiences of discrimination, social defeat or drug abuse (Cantor-Graae & Selten, 2005).

Urbanicity appears to increase the rate of schizophrenia. Subjects from urban areas show a relative risk for schizophrenia of 1.72, independent from the effect of age, sex, ethnicity, drug use, social class, family history and season of birth (Krabbendam & van Os, 2005). The findings are consistent across countries and cultures and show a dose-response relationship, suggesting causality (Pedersen & Mortensen, 2001; McGrath *et al.*, 2004; van Os, 2004). Urbanicity has also been interpreted as a distal risk factor for schizophrenia and more proximal factors mediating the effect are under study (van Os, 2004; Krabbendam & van Os, 2005).

Expressed emotion describes criticism, hostility, warmth, positive comments and over-involvement shown by relatives of a patient while spontaneously talking about him (Vaughn & Leff, 1976). The measure has extensively been studied in the last 20 years and appears to be a reliable predictor of relapse in schizophrenic patients (Butzlaff & Hooley, 1998). Further support for the role of expressed emotion in schizophrenia relapses comes from the positive results of family-based intervention studies (Pharoah *et al.*, 2003). Findings are however heterogeneous with regard to the magnitude of the observed effects (Butzlaff & Hooley, 1998; Pharoah *et al.*, 2003).

Epidemiological studies have also described non-psychosocial putative environmental risks for schizophrenia. Obstetrical complications have been reported to increase the risk for schizophrenia to less about 2 (Cannon *et al.*, 2002). Complications of the pregnancy, abnormal foetal growth and complications of delivery appear with significantly higher frequency in the case history of schizophrenic individuals compared to healthy subject. These findings support the 'neurodevelopmental hypothesis' for schizophrenia (Rosanoff *et al.*, 1934; Murray & Lewis, 1987).

Cannabis use is a proximal risk factor associated with schizophrenia, associated with a relative risk of 2.34 (Arseneault *et al.*, 2004). The relationship between cannabis use and schizophrenia is not explained by disturbed behaviour, low IQ, place of upbringing, cigarette smoking, poor social integration, gender, age, ethnic group, level of education, unemployment, single marital status, and previous psychotic symptoms. Further evidence supporting the causal role of cannabis in the development of schizophrenia comes from longitudinal studies proving temporal priority, direction of the effect and dose-response relationship (Arseneault *et al.*, 2004). Consistently, experimental data showed cannabis-induced psychotic-like symptoms in healthy volunteers (D'Souza *et al.*, 2004). Beyond cannabis, amphetamine and cocaine abuse is also frequent in schizophrenic individuals and could be implicated in disease pathophysiology (Regier *et al.*, 1990; Kapur, 2003).

Because of its observational nature and the consequent non-random assignment of subjects to environmental risk exposure, psychiatric epidemiology has limited ability to determine the true origins of the exposure (Taubes, 1995). Selection processes may arise, with schizophrenic subjects also being more likely to be exposed to environmental factors. Selection is usually ruled out by controlling for potential intervening variables. However, the broad range of non-controlled variables and possible selection processes may flaw causal inferences (Goldman, 1994). Longitudinal study design could help to overcome these problems examining the within-individual changes in relation to changing environmental risk exposure. Heterotypic continuity (variable expression of the disorder over time during development), elements of endogeneity (co-occurrence of causation and reverse causation pathways) and the effect of omitted variables may however impair inferences from longitudinal findings (Rutter *et al.*, 2001).

Genes are likely omitted variables in epidemiological studies (Rutter *et al.*, 2001). Fair examination of disease distribution and determinants should therefore include the analysis of putative genetic influences mediating or modulating the effect of environmental risk factors (Rutter & Silberg, 2002).

A PUBLIC HEALTH GENETIC APPROACH FOR SCHIZOPHRENIA

The development of schizophrenia is likely to be due to the influence of several different genes of small effect, interacting with numerous environmental factors

(Andreasen, 1999). Genes may directly affect the development of schizophrenia or may affect it indirectly, influencing the exposure or the sensibility to the environment. Environmental influences might simply result from stochastic (or casual) events related to neurodevelopment (McGuffin *et al.*, 1994). Epidemiological studies, however, point at the effect of specific environmental factors consistently linked with the disease. Public health genetics is interested in describing whether such environmental measures are casual (that is, unrelated to individual predisposition to exposure), or rather linked to genetic origin or mediation. Moreover, public health genetics investigate whether the effect of specific environmental factor is widespread in the population, or rather dependent upon genetic vulnerability or modulation.

Gene-environment correlations

The concept of gene-environment correlation (rGE) originates from Bell's findings about reverse causation in socialization processes (Bell, 1968). Genetic influences may shape or select a related environment, therefore giving rise to putative environmentally mediated processes. In other words, an individual could be more likely to experience a particular environment or specific life events because of genetically mediated attitudes. Gene-environment correlation is also known as 'extended phenotype', because of the genetically mediated process of environment selection (Dawkins, 1982; 1989). The concept has alternatively been named 'niche-picking', because the selected environment is thought to be the most adaptive to individual genotype, therefore fulfilling a specific evolutionary function (Scarr & McCartney, 1983).

A taxonomy has been proposed to synthesize the different ways in which genes could shape the environment (Plomin *et al.*, 1977). A *passive* rGE occurs when people passively inherit specific environmental niches related to their genetic background. The passive rGE therefore refers to the influence of parental genotype on offsprings' environmental measures. For instance, because of schizophrenia or schizotypal personality in their biological parents, subjects developing schizophrenia could be more likely to experience obstetrical complications (Sacker et al., 1996; Bennedsen *et al.*, 2001). Evidence is however inconsistent (Nimgaonkar et al., 1988; O'Callaghan *et al.*, 1992; Kunugi *et al.*, 1996). Moreover, family history of schizophrenia appeared to be unrelated to urban birth, supporting social causation (Mortensen *et al.*, 1999).

The evocative rGE is observed when people evoke reactions from other people because of their own genetically mediated characteristics. Individuals developing schizophrenia, for example, may show subclinical psychopathological symptoms, therefore evoking higher expressed emotions (Goldstein, 1994; Woo *et al.*, 1997). Consistently, family history of schizophrenia correlates with the risk of experiencing stressful life events (van Os et al., 1994). Genetically influenced traits like temperament may also evoke reactions within supportive relationships, affecting social support (Kendler, 1997).

The active rGE is the genetically influenced tendency for individuals to seek or create particular kinds of environment. Personality and cognitive abilities show strong genetic influence, resulting likely genetic mediators of environmental exposure (Plomin *et al.*, 2001). In fact, subjects developing schizophrenia could have an increased probability of experiencing drug abuse because of their schizotypal personality traits (Schiffman *et al.*, 2005). In addition, cognitive impairment is thought to mediate the relationship between schizophrenia and low socioeconomic status (Dohrenwend *et al.*, 1992).

It may be predicted that passive rGE could be important overall early in life, when children passively experience their family environment. Evocative rGE are quite stable over time while active rGE may be critical from the adolescence onwards, when children begin to actively shape their environment.

Findings about gene-environment correlations therefore encourage us to reconsider the role of main environmental risk indicators previously described, taking into account the possibility of underlying genetic influences. Whatever the origin, environmental factors have an effect on the development of schizophrenia, perhaps through epigenetic mechanisms like DNA methylation (Abdolmaleky *et al.*, 2004; Champagne & Curley, 2005; Kato *et al.*, 2005). Indeed, gene-environment correlations do not deny the significance of environmental factors but may suggest alternative and possibly more effective interventions for disease prevention.

Gene-environment interactions

The idea of gene-environment interactions (GxE) was perhaps first proposed in the scientific literature by Garrod, who inferred the significance of the interaction between family history and diet on the risk for alkaptonuria (Garrod, 1902). Genetic influences may confer resilience or vulnerability to the environment, therefore modulating the effect of environmental risks.

Statistical description of gene-environment interactions does not imply biological causation. In statistical terms, GxE are defined when the risk due to the joint effect exceeds the multiplicative (relative risk) or additive

(attributable risk) model for the main effects due to gene and environment (Clayton & McKeigue, 2001). Statistical model of interactions, however, have no clear relationship with biological model of disease (Thompson, 1991). In fact, the same statistical model for disease could underlie different pathophysiological models. Therefore, biological plausibility of gene-environment interactions should always be assessed and not implied. Biological plausibility may be suggested by the evaluation of the direct gene-to-disorder associations and the relevance of the candidate gene in the reactivity to environmental pathogen. Further support comes from findings replications with heterogeneous study designs, measurements and statistical approaches (Moffitt *et al.*, 2005).

Different study designs may be used to detect gene-environment interactions (Hunter, 2005). Family studies involving twins, multigenerational pedigrees, sib-pairs and case-parents designs can quantitatively assess GxE testing whether the correlation between environmental exposure and outcome is higher in individuals with higher genetic risk. Advances in molecular genetics also enable to study GxE in groups of unrelated individuals. Case-control studies are particularly useful for rare outcomes like schizophrenia but show a major drawback in the retrospective recall of exposure, leading to misclassification then power loss. Nested case-control studies from longitudinal studies minimize misclassification due to exposure but may be inadequate for rare conditions. Finally, case-only studies could show useful preliminary GxE data assessing departures from the expected equal prevalence of exposure in genotype-positive and genotype-negative cases.

Examples of gene-environment interactions have been reported for schizophrenia. For instance, living in urban areas increases the risk for schizophrenia (Krabbendam & van Os, 2005). The effect of urbanicity on the development of schizophrenia is however restricted to a fraction of the exposed subjects. Genetic factors may therefore influence the vulnerability to the effects of urbanicity. Consistent to this hypothesis, familial vulnerability – more likely genetic factors – seems to influence the development of schizophrenia in subjects living in urban areas (van Os *et al.*, 2003).

As reported above, high expressed emotion has been frequently related to relapses in schizophrenic patients (Butzlaff & Hooley, 1998). The heterogeneity of the reported effects however suggests a role for genetic factors in modulating the vulnerability to expressed emotions (McGuffin, 2004). Direct investigation of gene-environment interactions indeed showed that the risk of developing a schizophrenic–spectrum disorder was increased in adoptees exposed to family critic and conflict with high genetic risk (biological parent with schizophrenia) compared to those without genetic risk (Tienari *et al.*, 1994). Similarly, the liability to schizophrenia – as measured by the Rorshach's primitive thought – is increased in adoptees experiencing adoptive family communication deviance with high genetic risk compared to those with lower genetic risk (Wahlberg *et al.*, 1997). Emotional reactivity to psychosocial stress also appears to be dependent on genetic factors, including family history of psychosis (Myin-Germeys *et al.*, 2001).

Obstetrical complications increase the risk of developing schizophrenia (Cannon *et al.*, 2002). However, just a fraction of individuals with obstetrical complications develop schizophrenia, suggesting a possible effect modification due to genetic influences. Consistently, subjects with both high genetic risk (offspring of schizophrenic mothers) and obstetrical complications have higher risk of developing schizophrenia compared both to individuals with high genetic risk but without complications, and individuals with low genetic risk and complications. Similarly, obstetric complications interact with genetic risk in influencing the probability of ventricular enlargement, a biological marker of schizophrenia (Cannon, 1996).

Cannabis also increases the risk of schizophrenia (Arseneault *et al.*, 2004). Again, most people smoking cannabis will not develop schizophrenia, suggesting the role for genetic factor in influencing vulnerability to environmental exposure. Recent studies support this hypothesis, reporting increased risk of developing schizophrenia in subject smoking cannabis with a high genetic risk, compared to those with low genetic load (van Os *et al.*, 2002; Verdoux *et al.*, 2003; Henquet *et al.*, 2005). Strikingly, the adoption of molecular genetics techniques allowed for the identification a specific gene polymorphism (i.e., the val 158 allele in the COMT gene) modulating the effect of cannabis abuse on the development of the schizophreniform disorder (Caspi *et al.*, 2005). Hence, cannabis is neither a necessary nor a sufficient cause of schizophrenia but act as a part of a constellation of causes including genetic predisposition (Di Forti & Murray, 2005).

Gene-environment interactions study could inform biological research in psychiatry. GxE may help to dissect causal mechanisms from complex mixture of biological processes. If the effect of environmental exposure on the outcome is conditional upon variation in a specific gene, then the stratification for gene variants could highlight the role of an environmental causal component within a complex mixture (Hunter, 2005). Limits of biological inferences from epidemiological findings of effect modification should however be considered (Thompson, 1991).

Gene-environment interactions study could also benefit public health research and practice (Khoury *et al.*, 2005). First, GxE strengthen the association between an environmental factor and disease by examining its effect in genetically vulnerable subjects. The power to detect interaction is lower than the one for main effects. However, the assessment of GxE can detect a stratum-specific effect otherwise hidden by averaging strata effects. GxE can therefore increase the positive predictive value by minimizing the dilutional effect on penetrance (Khoury, 2000). Second, GxE can detect preventable effects of great public health interest (Caspi *et al.*, 2003). Although single genes have small impact, the measurement of many different polymorphisms or environmental risks could collectively result in a substantial attributable risk (Willett, 2002). The impact of interacting factors is expected to exceed the additive model for the joint effect of two or more risk factors (Clayton & McKeigue, 2001), therefore resulting in large population attributable fraction. Higher positive predictive value and attributable risk will improve the clinical utility of molecular tools in clinical medicine (Bell, 2004).

CONCLUSION

The present review summarizes the possible application of public health genetics principles to mental health, as exemplified here by the case of schizophrenia. On one hand psychiatric genetics has quantified and initially described genetic factors influencing the pathophysiology of schizophrenia (McGuffin *et al.*, 2002). Associations between genes and schizophrenia are however often weak and inconsistent, possibly because of the modulation due to unmeasured environmental variables (Kennedy *et al.*, 2003). On the other hand, psychiatric epidemiology described environmental risks for schizophrenia (Murray *et al.*, 2002). Yet the observational nature of epidemiology often hampers conclusive inference about causality, at least partly because of the effect of omitted genetic variables (Rutter *et al.*, 2001). The application of public health genetics therefore has the potential to overcome many limitations of genetic and epidemiological studies of schizophrenia and psychiatric disorders in general. Gene-environment correlations and interactions seem to have a significant and widespread effect in the pathophysiology of schizophrenia. Their consideration is likely to lead to major advances in research and health.

Research implications of public health genetics may include an improved knowledge of the biology and the epidemiology of disease. Gene-environment correlations will help us to understand the true origin of putative environmental factors and the molecular pathways influencing the predisposition to experience specific environmental risks. With regard to schizophrenia, gene-environment correlations could be particularly helpful in better characterizing the risk associated with cannabis abuse, low socioeconomic status and stressful experiences. Gene-environment interactions will strengthen our knowledge about resilience and vulnerability factors to environmental risks influencing the development of schizophrenia. The measurement of strata-specific (allele- or haplotype-specific) effects will also improve the detection of environmental risk factors. Studying the gene-environment interplay underlying the development of schizophrenia will eventually result in a more accurate model of disease (Tsuang, 2000). For instance, describing mechanisms involved in the exposure and the vulnerability to psychosocial stressors, it will be possible to better understand the role of stress in the development of schizophrenia (Cotter & Pariante, 2002; Pariante *et al.*, 2005).

Health implications of public health genetics may include the improvement in the prevention and treatment of the disease. Public health genetics holds the potential to characterize modifiable causes of disease and promote phenotypic prevention, or the prevention of the physical manifestation of genetic traits (Khoury *et al.*, 2000). Gene-environment correlations will quantify and describe genetic influence on risk exposure, informing us about more adequate preventive strategies. Although population strategies are more effective for pure environmental (stochastic) risk factors, high-risk strategies could be useful to reduce genetically-mediated risk of exposure. For instance, interventions targeted to reduce addiction in subjects with a genetic predisposition to cannabis abuse will possibly enhance the effect of drug banning policies in reducing cannabis exposure and consequently schizophrenia risk. Gene-environment interactions will define vulnerable subjects at risk of showing pathological responses after environmental exposure. Although population strategies are more effective for population-wide causes of disease, high-risk strategies could be useful to reduce pathological consequences in vulnerable individuals, especially in relatively rare conditions like schizophrenia. Ultimately both population and at-risk strategies will be needed (Rose, 1994) and the development of valid and reliable measures of genetic risk - including family history and genomic profiling – will be critical for advancement of research (Khoury *et al.*, 2005). Gene-environment interplay study will also be relevant to schizophrenia treatment, strengthening our knowledge of disease biology (Burke, 2003), treatment response and tolerability (Roses, 2000).

The focus on the gene-environment interplay may finally stimulate a paradigm shift in the societal approach to research findings. Traditional interpretation of genetic discoveries often emphasized the deterministic role of genes in disease pathophysiology. Consequently, the possibility of genetic discrimination in health insurance and employment has been feared (Clayton, 2003). The focus on gene-environment interaction research would however challenge this position, by claiming the conditional function of genes on phenotypes according to environmental exposure, and minimizing genetic stigmatization. Moreover, the consideration of gene-environment interactions underlying common disease would improve interventions on preventable causes of health inequalities (Sankar *et al.*, 2004).

The intriguing promises of mental health genetics are now mainly speculative and need to be tested in order to enable us to take advantage of their potential.

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