Neuroendocrinology Letters Volume 36 No. 7 2015
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

The complex etiology of schizophrenia – general state of the art

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Submitted: 2015-10-28 Accepted: 2015-11-12 Published online: 2015-12-28

Key words: **schizophrenia; etiology; genetics; environment; stress; G×E interactions**

Neuroendocrinol Lett 2015; **36**(7):631–637 **PMID:** 26859583 NEL360715R01

Abstract

The etiology of schizophrenia is complex. The aim of this article is to present a global view of the causes of schizophrenia and their interconnectivity. Recent genetic research into schizophrenia is based on genome-wide association studies, the assessment of DNA copy number variations, and the concept of endophenotypes. A lot of suspected genes have already been identified, mostly relating to neurodevelopment, neuroplasticity, immunology and neuroendocrinology. Gene-environment interactions (G×E) reflect genetic variation in susceptibility to the environment. Psychosocial stress and cannabis abuse seem to be the most important environmental factors in schizophrenia etiology. Epigenetic mechanisms, particularly DNA methylation, histone modifications, and non-coding RNAs are the most important linking factor among the genetic and prenatal environmental variables in the etiology of schizophrenia. Postnatal risk factors (e.g., stress, urbanicity, cannabis use) may also affect the risk of schizophrenia via the potentiation of vulnerable brain pathways. Many questionable issues pertaining to G×E assessment of schizophrenia still persist and relate to the exact assessment of environmental agents as well as psychopathology. In future research concerning G×E in schizophrenia, the study samples should be adequately large, schizophrenia endophenotypes should be involved, prospective studies should be supported, environmental causative factors as well as psychopathology should be assessed in a quantitative way, the multiple interactions among the variety of environmental and genetic variables should be evaluated, and epigenetic factors should not be neglected. The EU-GEI project of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (2010–2015) may become a milestone in the schizophrenia G×E research.

Abbreviations:

BDNF	- brain-derived neurotrophic factor
CI	- confidence interval
CNV	- copy number variation/variant
DNA	- deoxyribonucleic acid
EU-GEI	- European Network of National Schizophrenia Networks Studying Gene-Environment Interactions
GABA	- gamma-amino butyric acid
G×E	- gene-environment interaction
GEWIS	- gene-environment wide interaction study
GWAS	- genome-wide association study
HPA	- hypothalamic-pituitary-adrenal axis
mRNA	- messenger ribonucleic acid
MUMC	- Maastricht University Medical Center
NMDA	- N-methyl-D-aspartate
OR	- odds ratio
rGE	- gene-environment correlation
RNA	- ribonucleic acid
SNP	- single nucleotide polymorphism
THC	- tetrahydrocannabinol

INVITED REVIEW

INTRODUCTION

The etiology of most of mental disorders is complex. DNA (deoxyribonucleic acid) abnormalities, epigenetic factors, prenatal physical and biological variables, perinatal noxious circumstances and biological, psychological and social environmental conditions all play a role. In a similar way, DNA polymorphisms, epigenetic regulatory mechanisms, prenatal infections and hypoxia, prenatal nutritional deprivation, drug abuse and stress are important agents in the schizophrenia etiopathogenesis (Weinberger & Harrison 2011).

It is far beyond the scope of this article to give a comprehensive review of the current scientific knowledge on the causes of schizophrenia. Instead, we try to display the possible interconnectivity of individual groups of schizophrenia etiological factors exerting their influence at different bio-psycho-social levels.

GENETIC RESEARCH INTO SCHIZOPHRENIA

Heritability of schizophrenia is stated in the range of 0.7–0.8 (Tsuang *et al.* 2001) and reflects the extent to which phenotype variation among individuals suffering from schizophrenia in a population is due to differences in their genes. The recent genetic etiological research into schizophrenia is represented by genome-wide association studies (GWASs), detection of the DNA microdeletions/microduplications (copy number variations/variants, CNVs) and the genetics of schizophrenia endophenotypes.

The basic principle of a GWAS study involves comparing at least 500,000 single nucleotide polymorphisms (SNPs) in the DNA of thousands of schizophrenia patients as against a similar number of healthy volunteers. If genetic differences between these two groups of study subjects are detected, they become suspected of causing schizophrenia. The published GWASs on schizophrenia can be found at http://www.genome.gov/gwastudies/. Up to the present, 32 schizophrenia GWASs have already been presented. The advantage of a GWAS study is that no a priori research hypothesis is necessary. On the other hand, GWASs are limited by the necessity to involve large numbers of study subjects with a significant financial cost, and the study results do not shed light on the pathogenesis of the investigated disease. Last but not least, the clinical and perhaps even etiological heterogeneity of schizophrenia is substantial, thus potentially giving rise to biased results in individual GWASs depending on the admixture of various schizophrenia subtypes. According to the GWASs published thus far, the following genes have been identified at least once as associated with schizophrenia: ACSM1, ADAM, ADAMTS6, AGBL1, ANK3, ARNTL, AS3MT, ATP5SL, BRD1,BRP44, BTN2A2, BTN3A1, BTN3A2, BUCS1, CACNA1C, CACNA1I, CCDC60, CCDC68, CDH13, CEACAM21, CENTG2, CLC, CNNM2,CNTNAP5, CSF2RA, CSMD1, CTD, CTDP1, CSCL12, DCAF6, EXOC2, FEZ1, FTSJ2, FXR1, GRIK3, HHAT, HIST-1H2AG, HIST1H2BJ, HLA-DQA1, IL3RA, ITIH3, ITIH4, LGALS17A,LSM1, MAD1L1, MHC, MIR137, MMP16, MSRA, NR, NKAPL, NOTCH4, NRGN, NRP1, NT5C2, NTSC2, NUDT1, PARD3, PCDH20, PCGEM1, PLAA, POM121L2, PPFIA2, PRSS16, PTBP2, RELN, RORA, RUNDC2A, SEC16B,SLC17A1, SLC17A3, SLCO6A1, SNX8, TCF4, TMTC1, TRIM26, TSPAN18, VRK2, WHSC1L1, ZNF184, ZNF804A and others. These genes are mostly related to neurodevelopment, neuroplasticity, immunology and neuroendocrinology. All the polymorphisms detected are relatively frequent in the population, and their individual contribution to schizophrenia etiology is exptected to be less than 1%. Using a large-scale genome-wide association study data set, the polygenic score approach is able to identify the overrepresentation of independently discovered risk alleles when compared with controls (Kong *et al.* 2015). This approach has already been used in schizophrenia research (French *et al.* 2015).

DNA microdeletions or microduplications larger than 1 000 nucleotide bases are termed copy number variations/variants (Hywel *et al.* 2009). Nevertheless, some CNVs may include up to several million bases. CNVs may occur during meiosis or as a result of insufficient DNA reparation. A copy number variation may be inherited or occur de novo in a given individual. One copy number variation covers one or more genes. This means that the expression of a given gene is increased (microduplication) or decreased (microdeletion). According to the literature, the most affected chromosomes (genes) in schizophrenia comprise for example 1q (PRKAβ2), 2p (NRXN1), 3q (BDH1, DLG1, PAK2, TFRC), 15q (CYF1P1, CHRNA7), 16p (NTAN1, NDE1) and 22q (COMT, GSTT2, PRODH). These genes are mostly related to neurodevelopment, neuroplasticity and glutamatergic neurotransmission (Hosak *et al.* 2012). In the etiology of schizophrenia, the following general rules for important CNVs apply (Bassett *et al.* 2010):

- the microdeletion/microduplication need not be very frequent but should have a high penetrance;
- microdeletion is more deleterious than microduplication;
- large CNVs are more significant than small ones;
- newly-emerged CNVs are more detrimental than inherited ones.

The advantage of CNV genetic research into schizophrenia is that no a priori hypothesis is necessary, an advantage shared with GWAS studies. On the other hand, only a very limited knowledge of schizophrenia pathogenesis can be gained using this method.

The concept of the endophenotype was introduced to psychiatry by Gottesman & Shields (1973). The following criteria should be fulfilled for a biological marker to be considered an endophenotype (Gottesman & Gould 2003):

- the endophenotype should be associated with the given disease;
- the endophenotype should not be dependent on the present stage of the disease, but rather should be a "trait marker", not a "state marker";
- the endophenotype should be heritable;
- in affected families, it should occur together with the given disease;
- the endophenotype should also be present in healthy relatives of the patients, more frequently than in the general population;
- the endophenotype should be able to predict the disease.

An endophenotype may be neurophysiological (prepulse inhibition of the startle response, P50 wave suppression, P300 component of evoked EEG potentials, mismatch negativity), neuromotoric (disorder of the smooth eye movement, antisaccadic task), neurocognitive (Continuous Performance Task, Span of Apprehension, Visual Backward Masking Test, Verbal Declarative Memory Test, Wisconsin Card Sorting Test), neuroanatomical (the global brain volume, the volume of the frontal and temporal lobes, brain white matter anomalies), neurological (soft signs) or personality-related (schizotypy, openness to new experience) in nature. Endophenotypes represent simpler clues to genetic underpinnings than the disease syndrome itself, promoting the view that psychiatric diagnoses can be decomposed or deconstructed, which can result in a more straightforward and successful genetic analysis (Gottesman & Gould 2003). The genetic research into endophenotypes does not require as many study subjects as GWAS studies. Advantageously, it is possible to study the genes suggested by the GWASs whether or not they are involved into the etiology of individual schizophrenia endophenotypes. In this way, the pathogenesis of schizophrenia may be gradually discovered. The limitation of the endophenotype concept of schizophrenia research is the extensive heterogeneity of this serious mental disorder, with the occurrence of individual endophenotypes potentially being different among individual subtypes of schizophrenia.

GENERAL ASPECTS OF THE GENE-ENVIRONMENT INTERPLAY

Gene-environment interplay related to psychopathology has been described by Rutter *et al.* (2006). Gene-environment interplay is a general term that covers several divergent concepts. Gene-environment correlations (rGE) concern genetic influences on people´s exposure to particular sorts of environment. They may be active (genetic effects serve to select the environment, e.g. reading in a library versus playing with friends on the football field) or evocative (e.g. some children irritate their parents who then act more harshly in response). On the other hand, gene-environment interactions (G×E) reflect genetic variation in susceptibility to the environment. For example, genes play a certain role in determining whether a soldier after a frightening battle experience develops posttraumatic stress disorder or not. In the recent research into schizophrenia etiology, G×E have been studied extensively, whilst rGE are considered a bias and neutralized by methods of statistics.

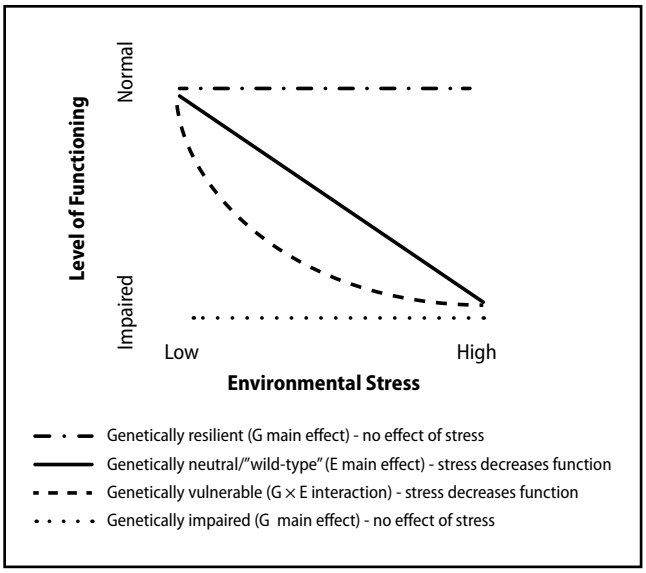

Fig. 1. Gene-environment interactions (Nugent *et al.* 2011).

An excellent model of gene-environment interactions was published by Nugent *et al.* (2011) (Figure 1). Genetically resilient individuals are able to keep a high level of functioning regardless of the influence of the environmental stress. In genetically neutral subjects, the level of functioning proportionally decreases with an increasing stress. Genetically vulnerable people evince a low level of functioning even at a low level of environmental stress. In genetically impaired persons, the level of functioning is always low due to the detrimental genetic effects, and stress does not play any role.

WHY TO STUDY GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA?

The G×E research into schizophrenia may result in

- the discovery of schizophrenia etiology;
- the early and causal treatment of this serious mental disorder;
- the effective prevention of schizophrenia;
- the decrease of stigma in schizophrenia.

G×E STUDIES IN SCHIZOPHRENIA

Van Os *et al.* (2008) presented a review of epidemiological findings in schizophrenia. As for the published environmental exposures for psychosis for which G×E was suggested, at least one positive meta-analytic estimate can be found in maternal pregnancy complications, in particular fetal hypoxia and proxies for fetal

folate deficiency, paternal age, urban environment during development, cannabis use and migration. In other variables, e.g. prenatal maternal infection, childhood trauma or traumatic brain injury, the results were inconclusive or not available at all. The authors concluded that environmental exposures have an impact on the risk for psychotic disorder in co-participation with genetic factors, and that the effects of genes and the environment in isolation are likely small or nonexistent. Urbanicity is considered as a proxy for an as yet unidentified environmental factor prevalent in urban areas which may be associated with stressful life events.

Van Winkel *et al.* (2008) comprehensively analyzed neurobiological mechanisms mediating the influence of psychosocial stress on the development of psychosis. The authors pointed out that psychosocial stress only increases the risk for positive psychotic symptoms (hallucinations, delusions), but not for the negative schizophrenia features (lack of interest, inability to act spontaneously etc.). The types of stressors may be various, for example psychotrauma in the childhood, stressful life events, discrimination, migration, social defeats, outsider status in the society or minor stressors of everyday life. The significance of the stressors for the development of psychosis in a given individual is as follows: Subjective > objective, cumulative > one-time, uncontrollable > controllable, and substantial > minor. Van Winkel *et al.* (2008) promoted the concept of the "behavioral sensitisation". This means that a repeated stress increases the neurobiological and behavioral response to the next exposure to stress in a progressive way even if this later exposure is not as severe as the previous one(s). The essence of behavioral sensitisation is the dysregulation of the activity of the hypothalamic-pituitary-adrenal axis (HPA) which increases the blood cortisol level leading to the increased dopamine release and up-regulation of dopamine receptors in the mesolimbic brain system. The magnitude of behavioral sensitisation in a given subject is influenced by several genes and their polymorphisms, for example catechol-*O*-methyltransferase gene, brain-derived neurotrophic factor (BDNF) gene, genes for various dopamine receptors and genes important in the function of HPA axis. The scheme of behavioral sensitisation is displayed in the Figure 2 (van Winkel *et al.* 2008).

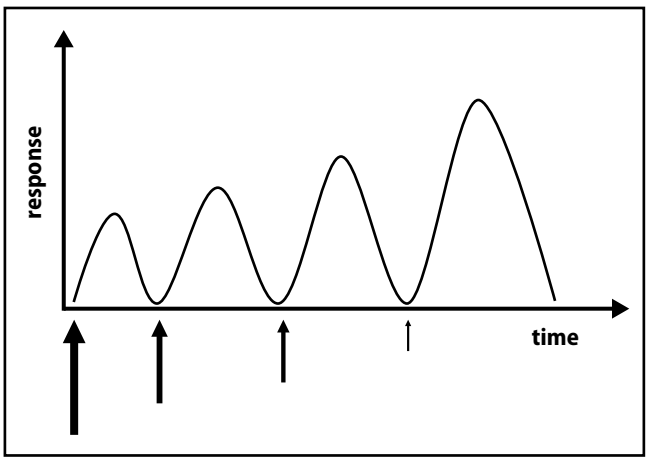

Fig. 2. A scheme of behavioral sensitisation (van Winkel *et al.* 2008). Note: Each vertical arrow represents a psychosocial stressor, with the length of the arrow representing its "objective" severity

Beards *et al.* (2013) presented a review and meta-analysis of the relationship between life events and the onset of psychotic symptoms/experiences. Sixteen studies published between the years 1968 and 2012 were included (first onset schizophrenia N=6, acute or chronic schizophrenia N=5, general population N=5). Fourteen studies reported positive associations between exposure to adult life events and subsequent onset of psychotic disorder/experiences. The meta-analysis yielded an overall weighted OR of 3.19 (95% CI 2.15–4.75). However, limitations were found in many studies (small sample sizes, methods for measuring life events without their subjective interpretation). The authors concluded that the results should be interpreted with caution and that more methodologically robust studies are warranted.

Modinos *et al.* (2013) summarized the results of molecular genetic gene-environment studies using candidate genes in schizophrenia. The authors pointed out that existing results are inconsistent, many studies face methodological problems, replication studies are missing and biological explanations of G×E are still hypothetical. They consider the influence of cannabinoids abuse and stress on the development of schizophrenia symptoms as the most significant finding.

According to an excellent recent review by Uher (2014), both genetic disposition and environmental exposures play important roles in the development of schizophrenia. Gene-environment interactions may underlie the paradox of strong environmental factors for highly heritable disorders, the low estimates of shared environmental influences in twin studies of schizophrenia, and the heritability gap between twin and molecular heritability estimates. Sons and daughters of parents with schizophrenia are more vulnerable to the effects of prenatal and postnatal environmental exposures, suggesting that the expression of genetic liability depends on environment.

EPIGENETIC MECHANISMS

Epigenetic modifications include DNA methylation, histone modifications, and non-coding RNAs (ribonucleic acids). DNA methylation in the promoter region usually silences the gene expression. Histone deacetylation induces a tight DNA turning around the nucleosome and thus reduces expression of the genes. Non-coding RNAs deactivate messenger RNA (mRNA) and reduce protein biosynthesis. Schizophrenia is associated with abnormalities in multiple epigenetic mechanisms, resulting in altered gene expression during development and adulthood. Environmental factors that lead

to epigenetic modifications may either reduce or exacerbate the expression of molecular and behavioral phenotypes associated with schizophrenia. For more information, see e.g. the review by Shorter & Miller (2015) on the current understanding of molecular dysregulation in schizophrenia, including disruption of the dopamine, NMDA, and GABA signaling pathways.

The DNA epigenetic status is broadly influenced by dietary intake, for example folic acid, other B vitamins, A and E vitamins, unsaturated fatty acids, amino acids, glucose, capsaicin, curcumin, vegetables etc. (Dominguez-Salas *et al.* 2013). Nevertheless, the influence of stress on epigenetic changes is unequivocal. Klengel & Binder (2015) reviewed epigenetic mechanisms associated with the response to stress and the development of stress-related psychiatric disorders.

THE ROLE OF CANNABINOIDS IN SCHIZOPHRENIA ETIOPATHOGENESIS

Recent scientific evidence supports a number of associations between cannabis and psychosis, including schizophrenia (Radhakrishnan *et al.* 2014). These associations based on case-studies, surveys, epidemiological studies, and experimental studies indicate that cannabinoids can produce acute transient effects, acute persistent effects and delayed persistent effects. Acute exposure to cannabis can produce transient psychotomimetic symptoms resembling schizophrenia. In the patients already suffering from schizophrenia, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. Exposure to cannabinoids in adolescence confers a higher risk for psychosis outcomes in later life and the risk is dose-related. Individuals with polymorphisms of COMT and AKT1 genes may be at increased risk for psychotic disorders in association with cannabinoids. According to Radhakrishnan *et al.* (2014), the relationship between cannabis and schizophrenia fulfills many but not all of the standard criteria for causality.

Pelayo-Teran *et al.* (2012) in their review suggested that cannabis use may be considered as an additional risk factor in a diathesis-stress model of schizophrenia where the risk of developing the illness would be higher in genetically vulnerable people. According to the authors, cannabis use has been shown to act together with other environmental factors such as childhood trauma or urbanicity producing synergistic dopamine sensitization effects. Based on the studies on gene-environment interaction, the most promising genetic variants in this field are COMT, CNR1, BDNF, AKT1 and NRG1.

Sami *et al.* (2015) presented the first systematic review of all studies examining the acute as well as chronic effect of cannabis or THC (tetrahydrocannabinol) on the dopamine system in man. They identified 25 studies reporting outcomes on over 568 participants, of whom 244 participants belonged to the cannabis/cannabinoid exposure group. According to the authors, there is as yet little direct evidence to suggest that cannabis use affects acute striatal dopamine release or affects chronic dopamine receptor status in healthy human volunteers. However some work has suggested that acute cannabis exposure increases dopamine release in striatal and pre-frontal areas in those genetically predisposed for, or at clinical high risk of psychosis.

GLOBAL VIEW OF THE G×E INTERACTIONS IN SCHIZOPHRENIA

According to Maric & Svrakic (2012), about 80% of the variance in schizophrenia is attributable to genetic factors. Thousands of common single nucleotide polymorphisms (SNPs), each with small effect, cumulatively could explain about 30% of the underlying genetic risk of schizophrenia. On the other hand, rare and large copy number variants (CNVs) with high but incomplete penetrance could explain around an additional 30% of schizophrenia cases. Environmental factors are rarely sufficient to cause schizophrenia independently, but act in parallel or in synergy with the underlying genetic liability. Epigenetic misregulation of the genome and direct central nervous system injury are probably the main mechanism to mediate prenatal environmental effects (e.g., viruses, ethanol, or nutritional deficiency). Postnatal risk factors (e.g., stress, urbanicity, cannabis use) may also affect schizophrenia risk via potentiation of vulnerable brain pathways implicated in schizophrenia. The authors argue that the epigenetic model of schizophrenia provides a framework for integrating a variety of diverse empirical data, both genetic and environmental, into a powerful etiopathogenetic synthesis.

The importance and complexity of G×E interactions in the schizophrenia etiology were described by Leboyer *et al.* (2008). Genome and epigenome induce the subsequent creation of transcriptome and proteome with several feedbacks in this process, for example the genome regulated by the epigenome or the genome regulated by transcriptome by means of interference RNA. The environment works at all levels of this cascade, thus influencing the genome (mutations), epigenome as well as proteome (diet).

QUESTIONABLE ISSUES IN THE G×E ASSESSMENT OF SCHIZOPHRENIA

Many questionable issues in the G×E assessment of mental disorders/schizophrenia still persist:

- How exactly to assess the influence of environment?
- A retrospective assessment may be vague and subjectively distorted by the respondent. A prospective assessment is time-consuming.
- Which method to use – a questionnaire or an interview? Should the data from the patient´s relatives be obtained?

- How to classify the influence of the environment – individually for each environmental factor or in a summarizing way, dichotomously or quantitatively – on which scale?
- Some environmental factors are only pathogenic in a certain time span of the brain´s development, for example in utero ("timing").
- How to assess the mental disorder/schizophrenia? Using the nosological diagnosis or syndrome scales, dichotomously or quantitatively – which dimensions should be measured?
- Should schizophrenia be evaluated as a whole or divided into its individual subtypes?
- The clinical/ethiopathogenetic heterogeneity of schizophrenia poses a problem. Schizophrenia is rather a set of syndromes than a well-defined nosological entity.

THE FUTURE OF THE G×E RESEARCH INTO SCHIZOPHRENIA

The appropriate avenues in the schizophrenia G×E research should adhere to the following suggestions:

- The study sample size should be adequate, advocated by statistical power analysis.
- GWASs may help find eligible genes for the G×E research.
- G×E research is also warranted in schizophrenia endophenotypes.
- Prospective studies are more beneficial than retrospective ones.
- It is necessary to record the severity, duration, frequency and timing of environmental causative factors in a quantitative way.
- Protective environmental variables, for example a supporting social background, should also be evaluated.
- The psychopathology should be assessed in dimensions, in a quantitative way.
- GEWISs (Gene-Environment Wide Interaction Studies), in which multiple interactions among a variety of environmental and genetic variables are assessed, seem to be full of promise, but the statistical problem of multiple comparisons should be addressed.
- rGEs should be eliminated by statistical procedures.
- Study samples should be pooled and meta-analysed.
- Epigenetic factors should not be neglected.
- The design of G×E studies should be unified.

THE EU-GEI RESEARCH INITIATIVE

The EU-GEI project of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions started in 2010 (http://www.eu-gei.eu/). The EU-GEI project has aimed to identify, over a 5-year period, the interactive genetic, clinical and environmental determinants involved in the development, severity and outcome of schizophrenia. The partners in EU-GEI represent the nationally funded schizophrenia/mental health networks of the UK, Netherlands, France, Spain, Turkey and Germany, as well as other research institutes within and outside the EU. The project is coordinated by Maastricht University (MUMC). The project coordinator is Professor Jim van Os. The results of the project may become a milestone in the schizophrenia G×E research, significantly influencing future development in the field.

ACKNOWLEDGMENTS

The work was supported by the Grant No. NT/14504 of the Internal Grant Agency of the Ministry of Health of the Czech Republic.

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