A new clinical evidence-based gene-environment interaction model of depression

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In our current understanding of mood disorders, the role of genes is diverse including the mediation of the effects of provoking and protective factors. Different or partially overlapping gene sets play a major role in the development of personality traits including also affective temperaments, in the mediation of the effects of environmental factors, and in the interaction of these elements in the development of depression. Certain genes are associated with personality traits and temperaments including e.g., neuroticism, impulsivity, openness, rumination and extroversion. Environmental factors consist of external (early and provoking life events, seasonal changes, social support etc.) and internal factors (hormones, biological rhythm generators, comorbid disorders etc). Some of these environmental factors, such as early life events and some prenatal events directly influence the development of personality traits and temperaments. In the NEWMOOD cohort polymorphisms of the genes of the serotonin transporter, 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A} and endocannabinoid CB_1 receptors, tryptophan hydroxylase, CREB1, BDNF and GIRK provide evidence for the involvement of these genes in the development of depression. Based on their role in this process they could be assigned to different gene sets. The role of certain genes, such as promoter polymorphisms of the serotonin transporter (5-HTTLPR) and CB_1 receptor has been shown in more than one of the above factors. Furthermore, gene-gene interactions of these promoters associated with anxiety suggest the application of these polymorphisms in personalized medicine. In this review we introduce a new model including environmental factors, genes, trait and temperament markers based on human genetic studies.

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NATURE AND NURTURE: THE INTERACTION BETWEEN GENETIC VARIATION IN THE SEROTONIN TRANSPORTER AND ENVIRONMENTAL INFLUENCES, AND ITS EFFECT ON MOOD AND MOOD DISORDERS

Depression is a common mental disorder contributing to significant burden and is expected to be among the most frequent causes of morbidity by 2020 in the developed world (Swartz and Rollman 2003). Studies indicate that the contribution of genetic factors to the development of depression is 30-40% (Dick et al., 2010) and there is an increasing number of studies trying to establish the substrate of this genetic component, with a vast array of methodologies including candidate gene to whole genome association studies.

Due to its well-known role in the regulation of mood and also other symptoms and features associated with depressive illnesses as well as anxiety, one major target of research is the serotonergic system and especially the serotonin transporter protein responsible for the reuptake of serotonin after release and being the target molecule of major antidepressants, and its gene SLC6A4. In humans, the s (short) allele of the 5-HTTLPR polymorphism of the serotonin transporter gene was found to be associated with anxiety-related traits (Lesch et al., 1996; Gonda et al., 2007) and neuroticism, which conveys increased attention and sensitivity to environmental adversities and experiencing neutral stimuli as negative, as well as less effective coping mechanisms in the face of stress therefore increasing risk for the development of de-

pression (Gonda et al., 2009). Subsequently, in human studies a vast variation of methodological approaches, including various stressors, self-report questionnaire methods, imaging studies, stress hormone activation, and post mortem brain studies supported a similar association between the s allele and stress-induced reactivity (Caspi et al., 2010). S allele carriers were found to show increased and faster developing activation in the amygdala, which is known to play a role in modulating vegetative and behavioural responses to environmental stressors and fearful stimuli, and alteration in the functional and microstructural connectivity of the amygdala and the medial prefrontal cortex was also reported in s allele carriers. 5-HTTLPR was also found to be associated with other possible affective disease precursor states or phenomena including subthreshold depression (Gonda et al., 2005) and affective temperaments (Gonda et al., 2006). In a landmark longitudinal study in 2003 Caspi et al. (Caspi et al., 2003) demonstrated the effect of the s allele of the 5-HTTLPR polymorphism in the development of depressive symptoms in the face of stressful life events, a finding which has been subsequently confirmed by the largest metaanalysis, which included 54 studies on altogether 41 thousand subjects (Karg et al., 2011). While some of the earlier contradictory results concerning the association between life events, 5-HTTLPR genotype, and depression were attributed to differences regarding the definition, assessment, inclusion of, and differentiation between distinct types of stressors and life events, this latter study also indicated that childhood and adolescent maltreatment, recent life events, or serious medical conditions are all more likely to lead to depression in those carrying the s allele or the ss genotype of the serotonin transporter gene. In a study in a large Hungarian population sample we observed similar and strongly significant associations in ss subjects and a moderate significant association in sl subjects between threatening life events and mood symptoms as measured by the Zung Self-rating Depression Scale (Lazary et al., 2008; Lazary 2010). While severe life events on their own explained 2.4% of the variance in mood symptoms, this ratio nearly doubled to 4.2% upon including the interaction effect of 5-HTTLPR genotype, and rose to 5.9% when genotype data of other polymorphisms of the serotonin transporter gene were also included in the model clearly indicating that genetic variability and environmental influences interact in regulating mood (Lazary et al., 2008).

To support the universalness of the role of the s allele in mediating the effect of environmental stressors, stress vulnerability has been found to be associated with the serotonin transporter gene and compromised serotonin transporter function not only in human studies but also in multiple nonhuman experiments including rodents and all investigated mammalian species as well (Kantor et al., 2000; Lesch et al., 2003; Caspi et al., 2010). An association between the s allele and stress hormone levels as a function of stressful environment were reported in rhesus macaques, while increased anxiety was observed in serotonin transporter deficient rodent models (Lesch et al., 2003; Caspi et al., 2010).

THE UNIVERSAL ROLE OF THE 5-HTTLPR IN MEDIATING REACTIVITY TO ENVIRONMENTAL FACTORS: THE GOOD AND THE BAD SIDE OF THE SAME COIN

Although the association between the 5-HTLPR s allele and increased susceptibility towards mood symptoms when encountering adverse environmental events seems to be obvious, it must be borne in mind that the frequency of the s allele and s allele carriers in the general population is relatively high in spite of the obvious disadvantages it contributes to, which provokes the question why this variant did not become extinct over evolution (Bagdy 2012). One possible answer is the fact that presence of the s allele increases susceptibility towards not only negative, but also positive environmental events, hindering or promoting adaptation. S allele carriers were found to perform better in several cognitive tasks and were also found to manifest increased social conformity, with similar results in nonhuman primates, and it has been postulated that s allele-related hyperactivity of corticolimbic structures may characterise both anxiety-related traits and the better social and cognitive skills of s allele carriers leaving it up to given environmental conditions to determine if the outcome will be positive or negative (Homberg and Lesch 2011). In our previously quoted study we observed better mood and lower depression scores in ss carriers compared to ll subjects if persons only without any exposure to threatening life events were included, a finding also reported in some other international studies, shedding light on the possible adaptive qualities associated with this variant (Lazary et al., 2008; Bagdy 2012). These results suggest that this gene conveys a general increased reactivity towards the environment thus strengthening adaptive capacities or plasticity which may be evolutionally valuable. This hypothesis is also supported by the fact that among primates,

humans and rhesus macaques could adapt best to diverse ecological challenges, and these are the two primate species carrying this polymorphism (Belsky et al., 2009).

OUR CURRENT UNDERSTANDING AND PAST, PRESENT AND FUTURE MODELS OF DEPRESSION

Understanding the complexity of and the complex interaction between environmental and genetic factors in the background of depression contributes to the evolution of a new model of depression. Previous models postulated that in the presence of inherited disposition, life events encountered during childhood or adolescence contribute to increased vulnerability for developing depression in the face of severe or stressful life events during adulthood. In accordance with this model, in the presence of the s allele there is an increased susceptibility towards the mood deteriorating effects of childhood or later severe stressful life events. Our studies, however, pinpoint important pitfalls of this model, as our results indicate no association between seasonality (encompassing an increased susceptibility towards seasonal affective disorder) and the 5-HTTLPR s allele (Molnar et al., 2010). Similarly, rumination, a trait-like cognitive style associated with risk of depression was found to be associated with an interaction of 2 genes (CREB1, KCNJ6) and separately with the gene of BDNF playing a role in the neural regulation of cognitive processes, but not with the 5-HTTLPR (Lazary et al., 2011). These examples indicate that everyday stressors are varied and manifold, including childhood maltreatment and abuse, regular adversities including losses and health problems, but also hormonal changes or change of seasons, and each individual has a distinct vulnerability profile towards them, just as everyone has a different susceptibility towards protective factors and events as well. Thus, different genes may have distinct actions in the development of depression as shown in Figure 1. The sensitivity towards the individual and combined effects of these factors is determined by heritable factors, distinct combinations of genetic variants, contributing towards the proposal of a new model for depression (Bagdy 2012).

In a new depression model (Figure 1), several other genes besides the serotonin transporter gene play a role in the emergence of depression, and these candidate genes include those playing a role in serotonergic neurotransmission (HTR1A, HTR1B, HTR2A, TPH1, TPH2), dopaminergic neurotransmission (DRD2, DRD4) (Varga et al., 2011), monoamine metabolism (MAOA, COMT), genes of different neuropeptides, trophic factors and their receptors (CRH, CRHR, BDNF), proteins playing a role in other transport and transmission processes (SLC1A1, SLC6A2, P2RX7, CREB1/CREM, KCNJ6, CACNA1, GLUR7), as well as the endocannabinoid 1 receptor (CNR1), as based on human data so far (Lazary et al., 2011). Some of these have been confirmed also in the NEWMOOD studies (Table 1). CNR1, the gene of the CB1 receptor has been found to be most strongly related to depression besides the 5HTTLPR in our studies, showing an association with trait anxiety and neuroticism as well. Furthermore, the CNR1 influences trait anxiety in interaction with the 5-HTTLPR, increasing the risk of high trait anxiety 5-fold in the combined presence of the GG variant of the rs2180619 polymorphism in the regulatory region of the CNR1, and the ss variant of the 5-HTTLPR (Lazary et al., 2009), due to a sustained extremely high serotonin concentration following activation of serotonergic neurons after stress, resulting partly from a low expression of CB1 receptors exerting an inhibitory effect on serotonin release, and partly from a low expression of the serotonin transporter removing serotonin from the synaptic cleft and thus terminating its effects. Similar observation was reported in fMRI studies where increased amygdala activation was found in ss carriers also characterised by increased neuroticism. CNR1 gene polymorphisms in interaction with life events are also associated with the development of depression (Juhasz et al., 2009). These results support that candidate genes most strongly associated with depression and anxiety are the serotonin transporter gene (SLC6A4) and the CB1 receptor gene (CNR1) (Lazary et al., 2011) (Table 1), and suggest that depression manifests on the ground of various genes mediating the effects of diverse environmental influences, as well as the interaction between these genes (Bagdy 2012).

These genes could be divided into seven groups or gene sets based on their role towards the development of depression as shown in Figure 1. Some of these have a protective, others a risk type role. Different gene sets play a role in the development of personality, in the mediation of the effects of environmental factors, and in the interaction of different elements of personality with the environmental factors. Environmental factors consist of external and internal influences. Some of the early environmental factors directly influence the development of the personality traits and temperaments. The role of certain genes, such as promoter polymorphisms of the

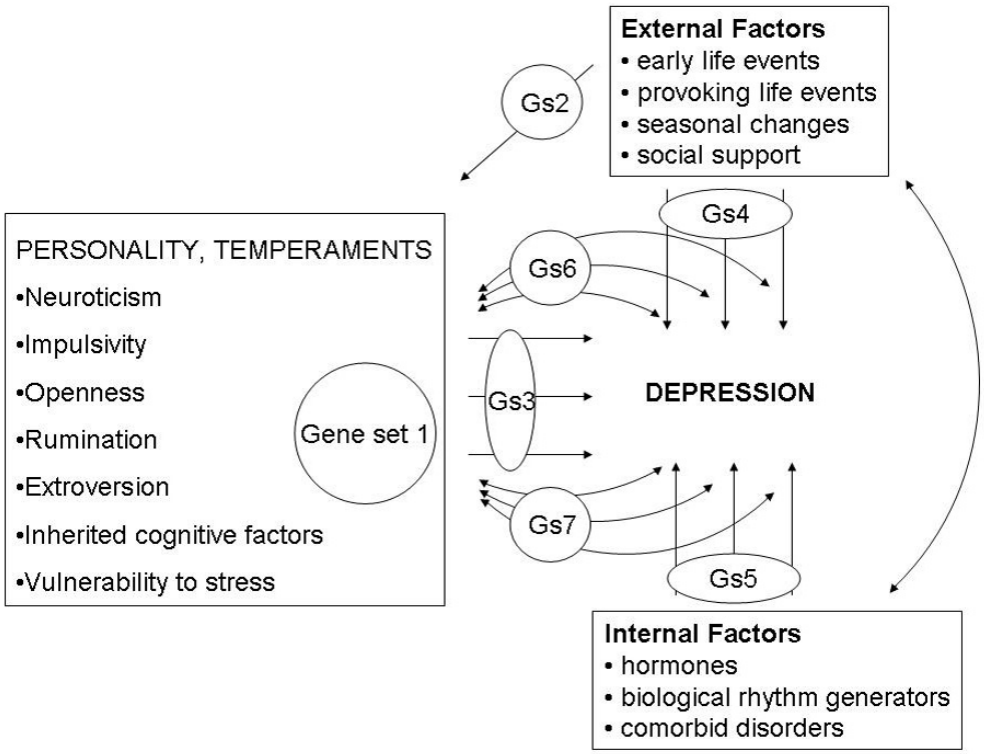

Figure 1 A new gene-environment model of the development of depression. The effect of a large number of protective (e.g., social support, openness, trust, acceptance) and risk (e.g., neuroticism, impulsivity, rumination, stress) inherited and environmental factors is mediated by various, only partly known genetic variants. The roles of individual genes could be identified only by studying each environmental factor, personality trait and temperament parallel with genetic polymorphisms in a large population. Different gene sets (Gs) play a role in the development of personality, in the mediation of the effects of environmental factors, and in the interaction of different elements of personality with the environmental factors in the development of depression. Environmental factors consist of external and internal factors. Some of the early environmental factors directly influence the development of the personality traits and temperaments. Some of the genes such as tryptophane-hydroxylase-2 (see also Table 1) are included in one gene set. The role of certain genes, such as promoter polymorphisms of the serotonin transporter (5-HTTLPR) and CB1 receptor genes have been shown in more than one of the above factors, namely in gene sets 1, 2, 4 and 6. It is interesting to note that even within one gene set, different genes may have separate roles, e.g., 5-HTTLPR has a significant effect in mediating the effects of certain provoking life events, but it has no significant role in seasonal depression. Modified from (Bagdy 2012).

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THE PRACTICAL SIDE OF SCIENCE: UTILISING OUR EXPANDING KNOWLEDGE CONCERNING THE ROLE OF THE 5-HTTLPR IN CLINICAL WORK

Implementing psychopharmacogenetics in personalised medicine

Psychopharmacogenetics has important information for personalised medicine (Weizman et al., 2012), as genotyping can be used to identify individuals who are susceptible for depression and anxiety, and are thus also more susceptible towards the anxiogenic and depressogenic side effects of certain medications. Several currently available medications have such side effects including interferon alpha, interleukin-2,

Table 1 Association between genetic variants, mood-related heritable traits and mediation of environmental factors. Genes playing a role in the background of personality traits and temperaments related to mood and depression based on large-scale general population Hungarian studies (Bagdy et al., 2001; Lazary et al., 2008; Gonda et al., 2009; Juhasz et al., 2009; Lazary et al., 2009; Lazary 2010; Molnar et al., 2010; Juhasz et al., 2011; Lazary et al., 2012; Pap et al., in press). Modified from (Bagdy 2012).

Parameters associated with mood and effects of mood-influencing medications	Protein	Gene
Depressogenic and anxiogenic effects of medications	SERT, CB1	SLC6A4, CNR1
Neuroticism, trait anxiety	SERT, CB1	SLC6A4, CNR1
Effects of stress and negative life events on mood and depression	SERT, CB1	SLC6A4, CNR1
Coping with stress	5-HT_{1A}, 5-HT_{1B}	HTR1A, HTR1B
Susceptibility towards seasonal changes, depression	5-HT_{2A}	HTR2A
Hopelessness	TPH2	TPH2
Rumination	CREB1, GIRK, BDNF	CREB1, KCNJ6, BDNF
Impulsiveness	5-HT_{1A}, COMT	HTR1A, COMT

gonadotropin releasing hormone agonists, mefloquin, certain hormonal contraceptives, propranolol, isotretinoin, montelukast, vareniclyne and oseltamivir (Lazary et al., 2011), and 2 studies already indicated an association between 5-HTTLPR genotype and psychiatric side effects in case of interferon alpha treatment. CB1 receptor agonists, including rimonabant, were considered one of the most promising classes of medications against obesity and related metabolic and cardiovascular problems, induced anxiety and depression as a side effect in about 20% of patients, and also increased risk of suicide, prompting withdrawal of rimonabant from the market. According to a model of an interaction between CB1 receptors and the serotonergic system in the amygdala playing a role in the regulation of anxiety and depression, stress-induced serotonin release activates postsynaptic 5HT2C receptors thus increasing anxiety (Kantor et al., 2000; Bagdy et al., 2001), and also leads to Gq protein activation and thus increased synthesis of the endocannabinoid 2-AG (Turu et al., 2009), which, as a retrograde neurotransmitter, activates inhibitory presynaptic CB1 receptors inhibiting further release of serotonin (Lazary et al., 2011). This inhibitory feedback circuit is more active with higher extracellular serotonin concentration characteristic of those carrying the ss genotype of the 5-HTTLPR and thus expressing less serotonin transporter proteins. CB1 antagonists such as rimonabant interfere with this inhibitory feedback circle thus leading to depression and anxiety, therefore those polymorphisms located in promoter regions and thus influencing protein expression of the serotonin transporter and the CB1 receptors will influence the anxiogenic and depressogenic effects of CB1 antagonists (Lazary et al., 2011). Based on our knowledge concerning the genetic background of depression and anxiety, screening for CB1 receptor gene (CNR1) and serotonin transporter gene (SLC6A4) variants and their combinations can be useful to identify those individuals in whom CB1 antagonists can safely be used without psychiatric side effects (Lazary et al., 2011),

Applying 5-HTTLPR related results in the treatment and prevention of psychiatric disorders

Another consequence of the significant, but relatively weak association of the 5-HTTLPR s allele with depressogenic actions of stress is that it cannot be used for direct screening for depression susceptibility, and we can also suppose that in the absence of multiple severe environmental events s allele carriers will not manifest more depressive symptomatology than those carrying other genotypes. However, in the presence of environmental adversities and stressful life events s allele carriers have an increased risk for bad mood, less effective adaptation, and in certain cases, depression. Furthermore, these same people, who are at an increased risk for depression, show worse therapeutic response to the most frequently used antidepres-

sive agents, SSRIs, due to later onset and lower rates of response and remission, worse tolerability and more frequent side effects in s allele carriers (Laje et al., 2009), while antidepressants with a different mechanism of action (for example noradrenaline selective agents) as well as psychotherapy were found to be more effective in their case (Rundell et al., 2011). However, viewing possible risk and protective factors in constellation, screening for 5-HTTLPR genotype could be part of a functional model to understand the evolving etiopathology of depression and detect those who are at a relatively high risk for mood disorders, and it could also prove to be a useful tool guiding selection of appropriate treatment (Kirilly et al., 2012).

FUTURE PERSPECTIVES

In case of most common illnesses, the role of hereditary factors is estimated to exceed 30%, however, even with our state-of-the art methods, we can map only a fraction of this variation to well-defined genetic variants and base-sequence alterations. This has drawn our attention also to epigenetic effects not affecting base sequences, but playing a role in regulating protein synthesis, and being only partially heritable but modifiable by environmental effects (Falus and Molnar 2010). Two main epigenetic mechanisms can modify the function of genes: (1) acetylation or methylation of histones that control the availability of DNA for further processes, and (2) methylation of the DNA itself, which suppresses the transcriptional activity of the CpG rich regions of the genes. Because these epigenetic changes are partially heritable, or, with other words, allele-specific, genetic polymorphisms are associated with different probability and type of epigenetic changes after environmental events and, as a consequence, considerable variances in sensitivity to environmental factors. A good example is the catechol-O-methyltransferase (COMT) gene, in which the presence of the Val^{158} allele in the rs4680 polymorphism creates a CpG site for methylation, which repressive effect can compensate the increased dopamine elimination in the prefrontal cortex in the high-activity Val allele carriers. However, life stressors decrease the methylation of this part of the gene, resulting in increased COMT activity and thus impaired working memory performance due to decreased dopamine availability in this important brain region (Ursini et al., 2011). Investigating the effect of COMT gene on depression we found that variations in the COMT gene are associated with depressive symptom scores in those who have not been depressed previously but not in those who have already suffered from depression possibly because epigenetic changes alter the gene function in patients (Pap et al., in press). Although epigenetic changes are highly dynamic during the adaptation to function and environment, these changes can persist and last for several years. This might explain why abuse in early childhood increases the risk of later depressive disorder. For example, maternal maltreatment of rats in the postnatal period elicited long-lasting methylation of the BDNF gene in the prefrontal cortex and these animals showed impaired maternal behaviour towards their offspring (Roth et al., 2009), and in line with this, the BDNF gene in a human population study was associated with increased risk of depression only in the presence of childhood maltreatment (Juhasz et al., 2011). However, the main feature of epigenetic signature is its tissue and cell specificity, meaning that different parts of the brain show different methylation and acetylation patterns thus limiting our ability to investigate it in vivo human brain (Houston et al., in press). Nevertheless, since we have no method yet to asses these directly in the living brain, in order to understand physiological and pathological central nervous functions and to predict medication effects and side effects, gathering in-depth knowledge concerning genetic base sequence and the interaction of its effects with environmental factors is still a primary target of research (Bagdy 2012).

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A depresszió új, bizonyítékokon alapuló gén-környezet interakciós modellje

Jelen ismereteink szerint a hangulatzavarok kialakulásának hátterében meghúzódó genetikai faktorok szerepe összetett. A személyiségvonások és temperamentumok kialakulásában és a környezeti hatások közvetítésében – bár ezek részben átfedést mutatnak – különböző gének csoportjai vesznek részt, ráadásul némelyik védő, mások hajlamosító tényezőként. A személyiségvonások és temperamentumok között fel kell sorolnunk a neuroticizmust, a szorongást, az impulzivitást, a nyitottságot, az extroverziót, a ruminációt és egyéb kognitív faktorokat, melyek részben a stressztűrő képesség elemeit is alkotják. A környezeti faktorokat alapvetően külső és belső tényezőkre oszthatjuk, előbbiek közé például a korai és a provokáló életeseményeket, az évszakváltást, a szociális támogatottságot, utóbbiak közé a hormonokat, biológiai ritmusgenerátorokat és a komorbid betegségeket sorolhatjuk. A környezeti tényezők közül néhány, így például a korai életesemények, vagy az intrauterin történések a személyiségjegyek és temperamentumok kialakulását is befolyásolják. A NEWMOOD adatbázisban a szerotonin transzporter, az 5-HT1A, 5-HT1B, 5-HT2A és a CB1 endokannabinoid receptor, valamint a triptofán hidroxiláz, a CREB1, a BDNF, valamint a GIRK csatorna depresszió kialakulásában játszott szerepét igazoltuk. A fentiek közül például a szerotonin transzporter és a CB1 receptor gén promoter polimorfizmusai több ponton is befolyásolják a depresszió létrejöttét, ugyanakkor ezeknek a polimorfizmusoknak a gén-gén interakciós hatása a vonás-szorongás és temperamentum kialakulásában is jelentős, így a személyre szabott orvoslásban is felhasználható. Összefoglaló közleményünk egy új depressziómodellt mutat be, melyben a gének, környezeti faktorok, személyiségvonások és temperamentumok humán genetikai vizsgálataink eredményei alapján illeszkednek.

Kulcsszavak: 5-HTTLPR, gén-környezet interakció, bizonyítékokon alapuló, személyre szabott terápia, depresszió, neuroticizmus, életesemények