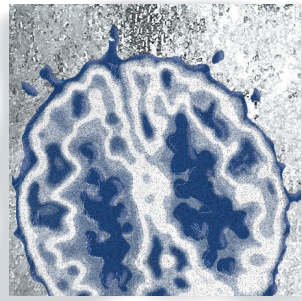# Genetics of generalized anxiety disorder and related traits

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This review serves as a systematic guide to the genetics of generalized anxiety disorder (GAD) and further focuses on anxiety-relevant endophenotypes, such as pathological worry, fear of uncertainty, and neuroticism. We inspect clinical genetic evidence for the familiality/heritability of GAD and cross-disorder phenotypes based on family and twin studies. Recent advances of linkage studies, genome-wide association studies, and candidate gene studies (eg, 5-HTT, 5-HT1A, MAOA, BDNF) are outlined. Functional and structural neuroimaging and neurophysiological readouts relating to peripheral stress markers and psychophysiology are further integrated, building a multilevel disease framework. We explore etiologic factors in gene–environment interaction approaches investigating childhood trauma, environmental adversity, and stressful life events in relation to selected candidate genes (5-HTT, NPSR1, COMT, MAOA, CRHR1, RGS2). Additionally, the pharmacogenetics of selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor treatment are summarized (5-HTT, 5-HT2A, COMT, CRHR1). Finally, GAD and trait anxiety research challenges and perspectives in the field of genetics, including epigenetics, are discussed.

Introduction

Anxiety, experienced as excessive, uncontrollable worry about a variety of topics in the absence of respective stimuli or in a manner disproportionate to their potentially posed risk, is the key diagnostic criterion of generalized anxiety disorder (GAD).[1] GAD poses an epidemiological challenge, and with a comparably late age at which sufferers receive a correct diagnosis and a considerable comorbidity with other anxiety disorders, depressive disorders, as well as trauma- and stressor-related disorders.[2] Its etiological interrelatedness with dimensional measures of trait anxiety, such as pathological worry, fear of uncertainty, or neuroticism, and its high rate of treatment resistance have attracted the attention of psychiatric geneticists aiming at identifying biomarkers of disease risk and treatment response.

Clinical genetics

A population-based family study of GAD reported a significant odds ratio (OR; ranging from 2.1 to 2.6) for

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Translational research

GAD diagnoses in children of parents with GAD, after excluding offspring with major depressive disorder (MDD) or adjusting for MDD and non-GAD anxiety disorder diagnoses.[3] Meta-analytical integrations of family and twin studies calculated a recurrence OR of 6.1 and a genetic heritability of 31.6%, with the same predisposing genes across sexes, a small influence of common familial environment in females, and the remaining variance due to individual-specific environment.[4]

Evaluating GAD's molecular cross-disorder position, a general community twin study on the genetic and environmental structure of anxiety spectrum disorders suggested two independent genetic factors for GAD, one more associated with panic disorder (PD), agoraphobia, and social anxiety disorder, and one factor with higher loading for specific phobias. Together, these account for 23% of the genetic variance in liability to GAD, the rest being represented by unique environmental factors.[5] Further exploration of the developmental phenotypic association between depression and anxiety disorder symptoms provided evidence that in childhood, a common factor accounted for most of the genetic influence on generalized anxiety, separation anxiety, social phobia, and panic, but not depression.[6] In adolescence, a high genetic correlation was suggested between depression and generalized anxiety (0.71-0.74) and other forms of anxiety, whereas in young adulthood, a common genetic factor influenced all variables, yet unique genetic influences emerged, one shared between generalized anxiety and depression and one shared among the remaining anxiety subscales.[6] Overall, it has been proposed that a common underlying genetic additive factor links GAD to a cluster of internalizing conditions, including, but not limited to, MDD,[7-9] social anxiety disorder,[7,8] PD,[7,10] agoraphobia,[7] posttraumatic stress disorder,[10] and burnout.[9] Additionally, there is evidence for a genetic correlation between GAD and anorexia nervosa of 0.20, indicating a modest genetic contribution to their comorbidity.[11] Also, a relationship between pathological gambling and GAD was attributable predominantly to shared genetic contributions (r=0.53).[12]

Unsurprisingly, twin studies have reported high genetic correlations between GAD and several dimensional traits related to GAD. For instance, high genetic correlations in males (1.00) and females (0.58) have been estimated for lifetime GAD and neuroticism, with an overall correlation of 0.80, the remaining 0.20 contributed by individual-specific environmental correlations.[13] Notably, the best-fitting model suggested a complete overlap of shared genes between GAD and neuroticism (Eysenck Personality Questionnaire [EPQ]).[13] As yet, combined explorations of categorical and dimensional phenotypes has shed the most conclusive light on the clinical genetics of GAD. Considering a potential shared genetic factor among internalizing disorders relating to neuroticism and one that is independent of neuroticism, both were discovered to influence GAD.[14] A shared genetic factor with neuroticism (EPQ) (0.17) and a genetic factor independent of neuroticism (0.12, mainly shared with MDD and PD) were found, while a unique environmental factor shared with MDD and PD, and a GAD-specific unique environmental factor were implicated explaining the remaining proportion of variance in liability.[14] This is further supported by another study indicating that approximately one-third of the genetic influences on GAD were in common with genetic influences on neuroticism.[15]

Molecular genetics

Given the substantial evidence for a (partly cross-disorder) genetic component in the pathophysiology of GAD and other anxiety-related traits as described above, molecular genetic studies such as linkage and association studies have been pursued to identify chromosomal risk loci and susceptibility genes for GAD.

Linkage studies

To the best of our knowledge, there is no linkage study available focusing on GAD proper. However, genome-wide linkage analysis of extreme neuroticism personality traits (highest scoring 10th percentile on the Neuroticism-Extraversion-Openness Personality Inventory [NEO]) in 2657 individuals revealed suggestive evidence for loci on chromosomes 19q13, 21q22, and 22q11.[16] Additionally, a meta-analytical combination of eight independent neuroticism (EPQ) genome-wide linkage studies in 14 811 individuals found nominally significant risk loci on chromosomes 9, 11, 12, and 14.[17]

Association studies

Principally, two main approaches have been applied to elucidate patterns of genetic association in GAD or cross-disorder phenotypes related to anxiety. Either the methodology of non–hypothesis-driven genome-wide association studies (GWAS) was followed, utilizing the statistical power emerging from thousands of samples without an a priori selection of risk genes or hypothesis-driven studies focused on candidate genes that have previously been implicated to be of specific significance in a phenotype of interest.

Genome-wide association studies

By creating a GAD symptoms score with modest heritability (h^2=7.2%), based on three items of the State-Trait Anxiety Inventory – Trait Anxiety Scale (STAI-T) and reflecting diagnostic criteria of GAD outlined by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, a GWAS in a community-based sample of 12 282 individuals with Hispanic and Latin American ancestry identified the intronic rs78602344 polymorphism on chromosome 6 in the thrombospondin-2 gene (*THBS2*) as the most significant hit.[18] However, this was not supported by a replication meta-analysis of 7785 samples.[18] Alternatively, on the basis of nine GWAS studies of European ancestry combined into one meta-analysis (n=17 310) to identify pleiotropic genetic effects shared among anxiety disorders, the intronic rs1709393 minor C allele of an uncharacterized noncoding RNA locus (*LOC152225*) on chromosomal band 3q12.3 was associated with a lifetime diagnosis of GAD, PD, ago-raphobia, social anxiety disorder, or specific phobias.[19] Furthermore, the most significant single-nucleotide polymorphism (SNP) in a linear regression model for an overall latent anxiety disorder factor score in the same study was the intronic rs1067327 polymorphism on chromosome 2p21 within the region coding for the calmodulin-lysine *N*-methyltransferase (*CAMKMT*).[19]

In adherence to the insights derived from clinical genetic approaches as reported above, researchers targeted GAD-related dimensional traits on the genome-wide level. A meta-analysis of GWAS across 29 cohorts from Europe, America, and Australia (n=63 661) revealed a significant intronic hit for the membrane-associated guanylate kinase, WW and PDZ domain–containing protein 1 (*MAGI1*) rs35855737 minor C allele on chromosome 3p14.1, and increased neuroticism (NEO) scores, while the overall variance of neuroticism explained by common (minor allele frequency >0.05) SNPs (h^2) was estimated at 14.7%.[20] Also, in a combined set of three GWAS cohorts totaling 106 716 individual samples, genome-wide significant hits were obtained for nine neuroticism-related (EPQ) loci, with the rs12682352 C allele of an inversion polymorphism on chromosome 8 as the strongest marker, representing a larger genomic region containing at least 36 different known genes.[21] Finally, a pooled GWAS from two large cohorts (n=170 910) for EPQ-rated neuroticism yielded 16 significant loci, with six SNPs residing in the previously described inversion polymorphism on chromosome 8.[22] Remarkably, in this study, the correlation between the neuroticism phenotype and anxiety disorders was estimated at 0.86, by far the largest genetic correlation of any neuropsychiatric phenotype examined, hinting at the highly interconnected molecular network GAD is a part of within the anxiety spectrum.[22]

Candidate gene studies

Picking up on individual nodes of this putative network, candidate gene studies have gathered considerable evidence in regard to the serotonergic and catecholaminergic systems and neurotrophic signaling and their impact on GAD and anxiety-related endophenotypes.

The frequency of the less active serotonin transporter (*SLC6A4*) polymorphic region (*5-HTTLPR*) S/S (commonly "S" denotes the short allele) genotype has been observed to be significantly higher in patients with GAD than in healthy subjects (OR, 2.3).[23] Males,

but not females, with the S/S genotype have been shown to also score significantly higher in neuroticism (Maudsley Personality Inventory) than L allele carriers of the same sex, both in a bi- and tri-allelic approach evaluating the *5-HTTLPR*-rs25531.[24] Meta-analyses of anxiety-related personality traits reported increased NEO neuroticism to be linked to the S allele[25] (effect size, *d*, ranging between 0.18[26] and 0.23[27]).

In further work on serotonergic receptors, the minor G allele of the functional 5-hydroxytryptamine receptor 1A (*5-HT1A*) C-1019G polymorphism (rs6295), conferring overall diminished serotonergic signaling via increased negative feedback, was associated with a significant excess of GAD diagnoses in a case-control design.[28]

Moreover, in a community sample of early adolescents, the high-activity, longer alleles of the monoamine oxidase A (*MAOA*) upstream variable number of tandem repeats (uVNTR) polymorphism were associated with higher scores in generalized anxiety (assessed with the Screen for Childhood Anxiety and Related Emotional Disorders [SCARED]) explaining 12.6% of the variance in anxiety severity.[29] Additionally, a significantly higher frequency of the more active T allele of the *MAOA* T941G polymorphism was found in female, but not male GAD patients compared with healthy controls, adding to the converging evidence that serotonin holds a central role in the pathophysiology of GAD.[30]

In line with the current pharmacotherapy of GAD and anxiety states, additional studies assessed genes related to catecholaminergic neurotransmission and neurotrophin family members. The short variant of the D_4 dopamine receptor (*DRD4*) VNTR in exon 3 has been associated with increased neuroticism (NEO) in healthy individuals,[31] and the less active Met/Met genotype of the catechol-*O*-methyltransferase (*COMT*) rs4680 polymorphism was associated with increased female harm avoidance (Temperament and Character Inventory [TCI]), particularly with regard to the subscales "anticipatory worry" and "fear of uncertainty."[32]

Similarly, the less active Met allele of the functional brain-derived neurotrophic factor (*BDNF*) rs6265 (Val66Met) polymorphism has been shown to be associated with higher scores of "anticipatory worry" and "fear of uncertainty" as subscales of harm avoidance (TCI).[33] Accordingly, GAD patients displayed an increased frequency of the *BDNF* 66Met allele as compared with a control population, along with an increase

in serum BDNF levels.[34] In an Asian study of 108 patients with GAD, however, no association of the *BDNF* Val66Met polymorphism with GAD could be detected, while in GAD patients, BDNF plasma levels were significantly lower than those in healthy controls.[35]

As with GWAS results, candidate gene studies come with the need for independent replication, and at the same time, potential causative links toward their phenotypical presentation have to be investigated (see below), as well as their interaction with each other. It has, for example, been proposed that the *5-HTTLPR* and *BDNF* Val66Met genotype interact in their effect on trait worry (Penn State Worry Questionnaire [PSWQ]), with *5-HTTLPR* short alleles predicting increased worry in a dose-response fashion in *BDNF* Val66Met allele carriers.[36]

Genetics of intermediate phenotypes

Gathering further insight into the genetic contribution toward potential pathophysiological hallmarks, investigators have studied GAD and intermediate phenotypes related to GAD, focusing on imaging genetic, endocrinal, and behavioral readouts. Intermediate phenotypes are hypothesized to be closer to the underlying genotype and therefore contribute to a better understanding of gene function.

Neuroimaging

The so-called "imaging genetics" approach associates genetic polymorphisms with physiological correlates of cerebral activity or connectivity, and is a powerful tool for elucidating genetic effects on higher levels of neuronal functioning.

Following up on a key locus of serotonergic signaling, a resting-state functional magnetic resonance imaging (fMRI) study revealed that healthy individuals with low-expression-activity polymorphisms of the *5-HTTLPR*-rs25531 displayed an increased functional connectivity between the right amygdala and fusiform gyrus (a brain region particularly associated with facial information processing), which also correlated with heightened trait neuroticism scores (NEO).[37]

However, tribute has not only been paid to established anxiolytic drug targets. In psychiatrically healthy probands, low expression diplotypes comprised of SNPs (rs3037354, rs17149106, rs16147, rs16139, rs5573, and

rs5574) within the pro-neuropeptide Y gene (*NPY*) were associated with increased amygdala and hippocampus activation to threat-related facial expressions; lower pain-induced endogenous µ-opioid release in the ventrolateral thalamus, ventral basal ganglia, and amygdala; and higher scores on subscales of the Tri-dimensional Personality Questionnaire (TPQ) harm avoidance construct related to "fear of uncertainty" and "anticipatory worry."[38]

Notably, however, only very few imaging genetic studies have investigated GAD directly: a multimodal twin design using magnetic resonance spectroscopy and diffusion tensor imaging associated the genetic GAD risk (contrast between concordant affected and unaffected twin pairs) with increased bilateral amygdala myoinositol and right hippocampus glutamic acid/glutamine levels.[39] At the same time, an estimated genetic risk factor score of GAD and other internalizing disorders correlated negatively with increased fractional anisotropy of the right inferior longitudinal fasciculus (connecting temporal and occipital areas).[39] On a candidate gene level, a study in 50 patients with GAD revealed that individuals with low-expression-activity polymorphisms of the *5-HTTLPR*-rs25531 showed less activity in both the amygdala and anterior insula than patients carrying the L_A/L_A genotype in a paradigm designed to elicit responses in these brain areas during the anticipation of and response to aversive pictures.[40]

Peripheral stress markers and psychophysiology

Further association studies have combined candidate markers with peripheral, eg, physiological, readouts as relevant intermediate phenotypes of GAD.

The *5-HTTLPR* S allele has been shown to predict higher salivary cortisol levels in an interaction with a latent anxiety trait (Childhood Trauma Questionnaire [CTQ], Trier Inventory for Chronic Stress [TICS], neuroticism [NEO], Perceived Stress Scale [PSS] and STAI-T) in older but not younger adults.[41]

Furthermore, a peripheral biological stress marker has been explored by measuring leukocyte telomere length in internalizing disorders in a prospective longitudinal fashion, with persistence of internalizing disorder negatively predicting telomere length.[42] This still remained significant after accounting for psychiatric medication, substance dependence, childhood maltreatment, physical health, and socioeconomic status.[42]

GAD diagnoses predicted a more severe telomere erosion than depression and posttraumatic stress disorder across a monitored time interval of 12 years in males, but not in females.[42]

Complex behavioral evaluations on the other hand have been focused on solely in healthy populations, but nevertheless have contributed toward our understanding of key processes with relevance to anxious apprehension. A multimodal, multicohort investigation of the functional promoter region brain-type nitric oxide synthase (*NOS1*) ex1f-VNTR (exon 1f length polymorphism) in healthy individuals has, for example, linked the less active short allele to increased trait anxiety (STAI-T) and worry (PSWQ) and increased subjective anxiety and valence ratings in unpredictable, predictable, and safety contexts in a fear conditioning paradigm.[43] Autonomic readouts measured by fear-potentiated startle and fMRI suggested a genotype effect of increased startle, as well as neuronal activation that was unaffected by morphological differences in the right amygdala and hippocampus during the unpredictable context, the latter showing an allele-dose response.[43]

Gene–environment interaction

Given the multi-etiological origin of risk patterns related to anxiety in general and GAD in particular, gene–environment studies have analyzed a plethora of candidate genes and their environmental modification. Such studies have specifically focused on developmental disturbances in childhood and adolescence, as well as other types of autobiographical adversities and stressors.

Childhood trauma

Along the lines of candidate gene screenings as described above, gene–environment studies including traumatic childhood experiences mostly centered on neurotransmitter systems, but also included neuropeptide and hormone signaling.

Hierarchical multiple regression analysis in healthy individuals genotyped for their *5-HTTLPR*-rs25531 haplotype discerned a significant gene–environment interaction of the *5-HTT* haplotype, characterized by higher transcriptional activity/enzymatic activity (L_A/L_A) and childhood trauma intensity (CTQ), predicting increased anxiety sensitivity (Anxiety Sensitivity Index [ASI]).[44] This effect was observed independent

of sex-specific effects and notably, of a gene–environment correlation (rGE) between the *5-HTTLPR* genotypes and childhood traumata.[44] Moreover, a significant gene–environment interaction was found for childhood trauma (CTQ) and *COMT* rs4680 Met allele homozygosity, significantly explaining a proportion of the observed increased anxiety sensitivity (ASI).[45] Similarly, an interaction of the *MAOA*-uVNTR short variants and increased exposure to childhood maltreatment predicted heightened scores of anxious apprehension (PSWQ) in the male sample subgroup; thus, early developmental adversities might interact with SNPs associated with decreased monoamine degradation, contributing toward psychiatric vulnerability.[45]

Additionally, for the functional neuropeptide S receptor (*NPSR1*) rs324981 polymorphism, a significant gene–environment interaction was observed for the high-transcription T/T genotype and childhood trauma (CTQ), explaining increased anxiety sensitivity (ASI).[46] Finally, a haplotype comprised of three corticotropin-releasing hormone receptor 1 (*CRHR1*) SNPs (rs110402, rs242924, rs7209436) significantly interacted with childhood maltreatment, predicting increased neuroticism.[47] Interestingly, the haplotype interacted differently with the quantity and type of maltreatment, mediating increased neuroticism scores in homozygous carriers of the T-A-T haplotype that experienced emotional maltreatment, neglect, or physical abuse.[47] Yet, there was a noted exception for experiencing more than two different types of abuse or sexual abuse, in which case it was related to decreased neuroticism.[47]

Environmental adversity and stressful life events

Besides childhood traumata, gene–environment approaches have explored a variety of external factors potentially influencing GAD incidence rate or intermediate phenotype intensity, ranging from daily stressors and family environment to natural disasters.

A significant gene–environment interaction was described in a group of hurricane victims, linking a degree of high catastrophic exposure and the *NPY* rs16147 T/T genotype to a 3.6 OR to be diagnosed with post-hurricane GAD.[48] This was especially the case in females and was independent of social support, whereas low hurricane exposure predicted a reduced GAD incidence rate in T/T homozygotes.[48] Furthermore, in the same cohort, the regulator of G-protein signaling 2 (*RGS2*) rs4606

major C allele showed a dose-response relation to post-hurricane GAD diagnoses, in addition to main effects of female sex and hurricane exposure, however, without a gene–environment interaction.[49]

In the context of everyday environmental triggers, a gene–environment interaction study collecting ratings twice, separated by 1 year over a 1-month daily range, observed a significant association between daily event stress and the *5-HTTLPR*-rs25531 genotype.[50] Carriers of the shorter S or the functionally similar L_G alleles reported increased anxiety ratings after days of more intense stress across both years whereas these alleles did not influence ratings in hostile or depressed mood.[50] Also, in carriers of the *5-HTTLPR* short allele within a healthy nonclinical sample (n=118), more recent negative life events were related to greater neuroticism scores (Big Five International Personality Scale), whereas more positive life events correlated with lower neuroticism scores.[51]

In addition to the detrimental synergy with childhood trauma mentioned above, the *NPSR1* rs324981 polymorphism has been discerned to affect a variety of psychiatric readouts in the context of environmental adversity. In a longitudinal study following the development of Estonian adolescents, the low-transcription-activity A/A genotype was shown to interact with exposure to a low-warmth family environment (Tartu Family Relationships Scale) in females, predicting elevated rates of neuroticism, anxiety, and affective disorders lifetime diagnoses and suicide attempts.[52]

Finally, when confronted with environmental adversity, females with a short allele of the *NOS1* ex1f-VNTR displayed higher scores of neuroticism (NEO), anxiety (STAI-T), and depressiveness (Montgomery–Åsberg Depression Rating Scale) than individuals homozygous for the long allele.[53]

Pharmacogenetics

The drug classes of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have generally been considered part of the first-line pharmacotherapies for GAD, whereupon the SSRI escitalopram and the SNRIs venlafaxine and duloxetine (both approved by the US Food and Drug Administration for the treatment of GAD) have received the most attention in studies exploring the potential of genetic markers to predict treatment response or side effects.

Escitalopram

In a randomized controlled trial (RCT) of 12-week escitalopram treatment in primary GAD (n=125), low-transcription-activity haplotypes of the *5-HTTLPR*-rs25531 predicted no efficacy compared with placebo, as measured by the Clinical Global Impressions-Improvement Scale (CGI), as well as no significant improvement on the PSWQ.[54] Also, *a higher tendency toward worsening anxiety symptoms* regardless of assigned treatment arm was noted.[54] Similarly, a neurophysiological follow-up of 24-hour total cortisol and daily peak cortisol release after treatment in the same double-blind RCT demonstrated reduced cortisol levels for both endocrinological stress parameters in the high-transcription-activity group, whereas the low-transcription-activity group failed to show decreased cortisol levels.[55] Interestingly, cross-correlation of further treatment outcomes targeting SNPs in the 5-hydroxytryptamine receptors 1A (*5-HT1A*), 1B (*5-HT1B*), and 2B (*5-HT2A*) showed that carriers of the *5-HT1B* rs11568817 G allele or the *5-HT2A* rs6311 A allele (both linked to high transcription activity) displayed significantly decreased Hamilton Anxiety Rating Scale (HAM-A) scores irrespective of receiving escitalopram or placebo after the 12-week study, whereas SSRI treatment reduced the digit span to a greater extent in the high-transcription allele carriers.[56]

Venlafaxine

As part of a relapse prevention study in 112 genotyped individuals with primary GAD and without relevant depressive symptomatology, a significantly decreased clinical response to 6 months of venlafaxine pharmacotherapy, as measured by HAM-A reduction, was reported in carriers of at least one low-transcription allele of the combined *5-HTTLPR*-rs25531 haplotype.[57] Efficacy differences were apparent from the twelfth treatment week onwards.[57] Additionally, in the same cohort, the *5-HT2A* rs7997012 major G allele displayed a significant dominant effect linked to an enhanced HAM-A response to venlafaxine from the twelfth week onwards.[58] Interestingly, upon combining the pharmacogenetic information of *5-HTTLPR*-rs25531 and *5-HT2A* rs7997012 genotypes, an additive prediction model emerged, with an improved HAM-A treatment response and remission rate associated with the two

genotypes labeled as beneficial for SNRI therapy outcome.[57] Furthermore, the rs4680 Met allele of the *COMT* Val158Met polymorphism has been linked to clinical response to venlafaxine in GAD after 6 months of treatment, as scored by the CGI (but not the HAM-A), with an overall dominant effect of the A allele.[59] Additionally, an evaluation neither of the pharmacogenetic properties of the functional *BDNF* Val66Met,[60] nor of genes related to the dopaminergic system, encompassing SNPs in the D_2 dopamine receptor (*DRD2*; rs1076560, rs1800497) and the sodium-dependent dopamine transporter (*SLC6A3*; rs2550948)[61]—both previously implicated in antidepressant therapy response in MDD—resulted in significant associations with the response to venlafaxine treatment in GAD, as quantified via HAM-A and CGI.

Duloxetine

A pharmacogenomic investigation encompassing 825 SNPs in 61 candidate genes previously functionally related to antidepressant mechanisms of action in a 12-week double-blind, placebo-controlled RCT in 259 individuals suffering from GAD detected 12 SNPs after post hoc correction via a gene set–based association analysis with HAM-A changes.[62] These were distributed among the genes coding for the *CRHR1* (rs4792888, rs12942254, rs242925), D_3 dopamine receptor (*DRD3*; rs963468, rs1486009, rs324026, rs324023, rs167770), glucocorticoid receptor (*NR3C1*; rs258747, rs6196, rs6198), and calcium/calmodulin-dependent 3',5'-cyclic nucleotide phosphodiesterase 1A (*PDE1A*; rs1549870).[62] Notably, rs4792888 in intron 1 of *CRHR1* also significantly predicted decreases in the anxiety subscale of the Hamilton Depression Rating Scale (HAM-D) in patients with MDD (241 individuals) after 6 weeks of duloxetine treatment, with the minor G allele predicting worse therapy outcome in the GAD and MDD cohorts in an additive manner.[62]

Future directions

Given the state-of-the-art psychiatric genetics evidence collected above, novel pathophysiological insights arise, pointing toward the challenges upcoming studies have to face. Due to the high phenotypic—and thus probably also etiological—heterogeneity of classic categorical diagnoses, dimensional evaluations of

complementary cross-cutting and intermediate dimensional symptom measures, such as worrying and neuroticism, might provide a needed gain in statistical power to disentangle the complex pathogenesis of GAD. Nevertheless, the consequences genetic variations exert on higher levels of functioning—such as neuronal activity and, ultimately, behavior—will only be elucidated in combination with neuroimaging and neurophysiological follow-up evaluations. Also, the tissue-specific effects of SNPs on gene expression, RNA translation, and protein activity, should be considered within a systems-biological awareness. Deep sequencing approaches enabling whole-genome coverage will aid in the effort to identify structural or rare risk variants influencing GAD incidence rate or worry severity.[63] Moreover, in light of the diathesis stress model, the influence of environmental factors along the individual's developmental path to dysfunctional anxiety cannot be overestimated. In this context, because most gene–environment studies to date have relied solely on the investigation of vulnerability factors without accounting for potential beneficial protective/resilience factors, future efforts should consider coping-related measures in multidimensional assessments of GAD risk.[64] Accordingly, the field of epigenetics, representing the functional interface between genetic architecture and external stimuli, has only begun to change our understanding of neuropsychiatric disorders.[65] As a result of growing efforts in epigenetics, we are starting to see a potential molecular correlate of therapy effects with relevance to the prediction of treatment responses and clinical need for individualized patient stratification in anxiety disorders.[66] Furthermore, the conservative view that "risk" variants lead to a determinate threat of psychopathology comes into question, as such epigenetics finding promote an understanding of genetic "plasticity" factors, mediated by structural chromatin changes and DNA modifications. Such alterations dynamically regulate the susceptibility toward protective and maladaptive environmental catalysts alike (for a systematic overview of genetic and epigenetic mechanisms of anxiety, see Gottschalk and Domschke[67]).

Conclusions

GAD is a heritable condition with a moderate genetic risk (heritability of approximately 30%). Within the anxiety spectrum, it is closely related to childhood separation anxiety, social phobia, and panic, whereas during later developmental stages, a shared genetic origin with other internalizing disorders, especially MDD, becomes apparent. This overlap with PD and MDD can partially be explained by genetic contributions toward neuroticism. The most promising GWAS on trait anxiety severity or latent anxiety disorder factor scores detected encouraging hits in *THBS2* and *CAMKMT*, in addition to studies centered around neuroticism, pointing repeatedly toward SNPs in an inversion polymorphism on chromosome 8, which showed extended genetic correlation with an anxiety disorder phenotype. Moreover, in candidate gene studies—partly combined with imaging and physiological readouts—converging evidence has been gathered for GAD susceptibility genes within the serotonergic and catecholaminergic systems (*5-HTT*, *5-HT1A*, *MAOA*) as well as for the *BDNF* gene. Furthermore, gene–environment studies have highlighted the importance of early developmental trauma and recent stressful life events in interaction with molecular plasticity markers and their combined relevance to GAD, trait anxiety, and anxiety sensitivity (*5-HTT*, *NPSR1*, *COMT*, *MAOA*, *CRHR1*, *RGS2*). Finally, pharmacogenetic approaches applied to SSRI and SNRI treatment of GAD point to a potentially predictive role of serotonergic candidate genes (*5-HTT*, *5-HT2A*), as well as the *COMT* and *CRHR1* genes. Broader predictive investigations of the GAD disease course development and trait anxiety therapy response might benefit from the growing impact of epigenetics in neuropsychiatry, defining a compelling cross-link between genomic load and personal history. In summary, this line of research is expected to aid in the identification of neurobiological disease risk and treatment response markers for indicated preventive and individualized therapeutic approaches in the overall effort to more effectively lower the individual and socioeconomic burden of GAD. ❏

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Genética del trastorno de ansiedad generalizada y características asociadas

Esta revisión propone una orientación sistemática para la genética del trastorno de ansiedad generalizada (TAG) y además se enfoca en los endofenotipos relevantes para la ansiedad, como las preocupaciones patológicas, el temor por la incertidumbre y el neuroticismo. Se revisan las evidencias clínico genéticas del carácter familiar/hereditario del TAG y los fenotipos de los trastornos cruzados en base a estudios familiares y de gemelos. Hay avances recientes de estudios de ligamiento, estudios de asociaciones de todo el genoma y de genes candidatos (por ejemplo, 5-HTT, 5-HT1A, MAOA, BDNF) que se han integrado en el contexto de neuroimágenes funcionales y estructurales, y de lecturas neurofisiológicas relacionadas con marcadores periféricos de estrés y psicofisiológicos. Los efectos del trauma infantil, la adversidad ambiental y los acontecimientos de vida estresantes son explorados desde la perspectiva de la interacción genes-ambiente (5-HTT, NPSR1, COMT, MAOA, CRHR1, RGS2). Además se resume la farmacogenética del tratamiento con ISRS y ISRN (5-HTT, 5-HT2A, COMT, CRHR1). Por último, se discuten los problemas y las perspectivas de la investigación en el campo de la genética, incluyendo la epigenética, del TAG y de los rasgos de ansiedad.

Génétique de l'anxiété généralisée et caractères associés

Cet article, qui se propose comme recommandation systématique pour la génétique des troubles anxieux généralisés (TAG), se concentre ensuite sur les endophénotypes pertinents pour l'anxiété, comme les craintes pathologiques, la peur de l'inconnu et le neuroticisme. Nous analysons les données génétiques cliniques, basées sur des études familiales ou de jumeaux, montrant le caractère familial/héréditaire des TAG et des phénotypes d'anxiété présents dans d'autres troubles. Les progrès récents des études de couplage, d'association pangénomique et de gènes candidats (par ex. 5-HTT, 5-HT1A, MAOA, BDNF) sont soulignés dans le contexte de la neuro-imagerie fonctionnelle et structurale et des lectures neurophysiologiques liées aux marqueurs de stress périphériques et à la psychophysiologie. Les traumatismes subis pendant l'enfance, l'adversité environnementale, et les événements stressants de la vie sont étudiés à l'aide d'approches d'interaction gène-environnement (5-HTT, NPSR1, COMT, MAOA, CRHR1, RGS2). De plus, nous résumons la pharmacogénétique des traitements inhibiteurs sélectifs de la recapture de la sérotonine/inhibiteurs de la recapture de la sérotonine et de la noradrénaline (5-HTT, 5-HT2A, COMT, CRHR1). Enfin, nous analysons les problèmes et les perspectives de recherche dans le domaine de la génétique, y compris de l'épigénétique, du TAG et du caractère anxieux.