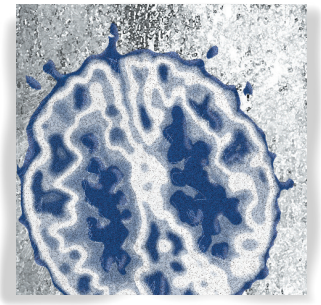
Imaging genetics of schizophrenia

Andreas Meyer-Lindenberg, MD, PhD, MSc



Recent years have seen an explosive growth of interest in the application of imaging genetics to understand neurogenetic mechanisms of schizophrenia. Imaging genetics applies structural and functional neuroimaging to study subjects carrying genetic risk variants that relate to a psychiatric disorder. We review selected aspects of this literature, starting with a widely studied candidate gene—the catechol-0-methyltransferase gene (COMT)—discussing other candidate genes in the dopaminergic system, and then discussing variants with genome-wide support. In future perspectives, approaches to characterize epistatic effects, the identification of new risk genes through forward-genetic approaches using imaging phenotypes, and the study of rare structural variants are considered.

Dialogues Clin Neurosci. 2010;12:449-456.

Keywords: *schizophrenia; imaging genetics; polymorphism; COMT; ZNF804A; dopamine; prefrontal cortex; neuroimaging*

Author affiliations: Central Institute of Mental Health, Mannheim, Germany

Address for correspondence: Andreas Meyer-Lindenberg, Central Institute of Mental Health, J5, 68159 Mannheim, Germany
(e-mail: a.meyer-lindenberg@zi-mannheim.de)

It is a daunting task to try to understand how genetic and environmental risk factors are translated into clinical symptoms, course of illness, and response to therapy of the complex disease, schizophrenia. Neuroimaging research has transformed the way we conceptualize schizophrenia. In this review, we are specifically concerned with the contribution of neuroimaging to understanding genetic risk. Since schizophrenia is a highly heritable disorder,[1] understanding how genes act to confer risk for this devastating disease is an obvious strategy in biological psychiatry. Clearly, genes can act on several levels, from the gene product itself through cellular, systems-level, and behavioral levels of description, all the way to complex phenotypes such as therapeutic response or impaired social interactions. The impact of genes is not necessarily the same on each of these levels. A proposal that has found a sizeable following in psychiatry is to move away from disease entities such as schizophrenia to more biologically defined levels, such as cellular, systems-level, or neurocognitive measures, in the hope that the effects of genes would be more prominent on these levels, and that the work of psychiatric research, including the finding of new genetic variants conferring risk for the disorder, would be easier. This is the so-called "endophenotype" or intermediate phenotype concept.[2,3] While there is evidence that this concept does not hold in general (in the sense that there are phenotypes, for example in the domain of cognition, that do not show higher genetic penetrance, at least for some genes that have been studied), the intermediate phenotype approach has had remarkable success when neuroimaging is used as the method of quantifying brain structure and function. Two meta-analyses now provide convergent support for the assertion that the penetrance of genetic variations is high in neuroimaging.[4,5] From these studies, estimates of

effect sizes of 0.7 to 1.0 can be derived, corresponding to sample sizes to detect genetic effects at 80% power of around 80 participants, which is much less than would be necessary with clinical data.

In this review, we will first discuss a paradigmatic example of a candidate genetic variant with clear impact on neural function related to dopamine: COMT rs4680 val/met. This is supplemented by a brief discussion of other dopaminergic risk variants related to schizophrenia. We then move on to the emerging field for variants with genome-wide association support. In conclusion, we discuss areas of merit for further study in imaging genetics of schizophrenia, both from the genetics and neural systems-level perspective: epistasis and structural variations in the human genome.

COMT

Starting with the classic 2001 study by Egan and coworkers,[6] the catechol-0-methyltransferase (COMT) gene, *COMT*, has been by far the most-studied gene in the schizophrenia imaging genetics literature. COMT degrades catecholamines, including dopamine (DA).[7,8] The *COMT* gene consists of two promoters and six exons which encode both the membrane-bound (MB-COMT) and soluble (S-COMT) forms of COMT and is located on chromosome 22q11.22-23. This region is implicated in schizophrenia by linkage studies,[9] as well as in 22q11.2 deletion syndrome, which is associated with strongly increased risk for psychosis.[10] Of the two confirmed isoforms, MB-COMT is predominantly expressed in the central nervous system at neuronal dendritic processes throughout the cortex, cerebellum, amygdala, putamen, thalamus, spinal cord, and hippocampus.[11,12] Postmortem studies have shown that COMT is particularly concentrated in the extrasynaptic spaces of the prefrontal cortex and hippocampus.[13] Since prefrontal dopamine transporters are scarce, COMT is thought to play a key role in clearing dopamine in the prefrontal cortex.[14] An evolutionarily recent functional single nucleotide polymorphism (SNP) in *COMT* results in the amino acid substitution of valine (val) with methionine (met) at codon 158 of MB-COMT (rs4680, GenBand accession no. Z26491, Savitz et al 2005). This substitution leads to a significant (38%) decrease in enzymatic activity in the brain and lymphocytes[15] of the polypeptide containing the met allele compared with the val allele. Consequently, met carriers have a higher level of prefrontal extracellular dopamine.[16,17]

A large body of work has demonstrated an impact of this genetic variant on cognitive and affective processing. The literature on the functional aspects of the common rs4680 val/met polymorphism in *COMT* has been recently reviewed.[5] In a meta-analysis of all available functional neuroimaging studies of rs4680 up to the end of 2008 (which are consequently not covered again in the present review), a significant association between the *COMT* genotype and prefrontal activation was found. The effect size was large (d=0.73) without evidence for publication bias. In the next step, studies were subdivided into studies relating to executive cognition paradigms and those that were related to emotional processing. Strong and opposing effects were found for executive cognition paradigms (in which more efficient activation was found for homozygous and heterozygous met allele carriers) and emotional paradigms (in which the opposite was seen, more efficient activation for val homozygotes). Effect sizes were now even larger (d=0.92 for cognitive studies and d=-1.0 for emotional paradigms). The studies thus provided evidence for a neural substrate for the pleiotropic behavioral effects of *COMT* genetic variation, the so-called "warrior/worrier" hypothesis which posits evolutionary significance for a tradeoff between emotional processing and cognitive stability during executive function.

Further support for a phasic/tonic dopamine distinction in understanding the effects of *COMT* genetic variation comes from a recent study in which sustained and transient brain activity during working memory use were dissociated using a mixed blocked/event-related design.[18] Albeit in a small sample (22 participants), the authors showed that met carriers displayed a greater transient medial temporal lobe response in the updating phase of working memory, whereas val carriers showed a less efficient sustained prefrontal cortex (PFC) activation in the maintenance phase. Similar conclusions were reached in a saccade task, with met carriers again more efficient during maintenance, and val carriers during phasic task components.[19] Importantly, rs4680 also predicted prefrontal activation changes under antipsychotic therapy with olanzapine in conjunction with parallel improvements in working memory performance and negative symptoms in met-allele carriers.[20] Similarly, smokers were more sensitive to an abstinence challenge to working memory activation in dorsolateral PFC (DLPFC) when they were val homozygotes.[21] *COMT* was also associated with an activation parameter during a fluid

intelligence test (the capacity to think logically and solve problems in novel situations) in LPFC, pre-supplementary motor area/anterior cingulate cortex, and intraparietal sulcus in a small sample.[22]

Compared with the functional findings, investigation of the effects of genetic variation in *COMT* on brain structure has been less consistent. Multiple lines of evidence show that extracellular dopamine is a modulator of neuronal growth and survival (see ref 23 for discussion). Two studies reported no associations between genotype and brain volume in healthy controls,[24,25] and two reported genotype effects in patients with schizophrenia[26] or subjects at risk for psychosis[27] but in discrepant locations, while Ho and coworkers found no differences in a group of patients. A possible reason for these discrepancies was identified in a recent study[23] which found a regionally specific impact of rs4680 that differed in directionality in PFC and hippocampus, as well as significant interactions of this risk SNP with another putatively functional SNP in the promoter region (reviewed below). A further source of variance was suggested by a study showing that IQ modulates the effects of rs4680 in prefrontal and hippocampal white matter fractional anisotropy,[28] mirroring the lateral PFC (LPFC) results observed in function.[22]

Other dopaminergic risk genes

Three risk single nucleotide polymorphisms (SNPs) in the gene for the dopamine D2 receptor, *DRD2*, showed opposite effects in patients and controls during a working memory task: enhanced engagement of prefronto-striatal pathways in controls and reduced activity in patients,[29] presumably because patients and controls are positioned on opposite sides of the inverted-u-shaped curve governing the relationship of dopaminergic simulation and prefrontal activity. On the postsynaptic side, Regulator of G-protein signaling 4 (RGS4) modulates dopamine signal transduction by affecting G alpha-GTP binding. Allelic variation in *RGS4* by itself modulated frontoparietal and frontotemporal activation during working memory and was associated with frontal gray and white matter structural volume reductions.[30] Further into the postsynapse, the pivotal integrator of information in dopaminoceptive neurons for the so-called canonical signal transduction pathway is dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 kDa (DARPP-32), encoded by the gene *PPP1R1B*. A frequent *PPP1R1B* haplotype related to risk for schizophrenia predicted reduced striatal volume and activation (in good agreement with the expression profile of DARPP-32) and increased structural and functional connectivity of striatum with lateral prefrontal cortex in a large sample of genotyped healthy controls.[31] Interestingly, genetic variation in *AKT1*, encoding another key signal transduction pivot, but now for the non-canonical, beta-arrestin mediated dopaminergic pathway, similarly predicted reduced frontostriatal volume as well as inefficient prefrontal activation during working memory.[32] Taken together, these two studies provide strong support for the prefronto-neostriatal system as a core circuit for dopaminergic variation related to schizophrenia risk. Investigating a panel of dopamine-related genes during a reward task,[33] polymorphisms in *DRD2* (141C deletion), *DAT1* (9-repeat) and *DRD4* (7-repeat), were related to ventral striatal activity, while *COMT* rs4680 was not, in agreement with its predominant role in prefrontal cortex activity.

Genome-wide significant variants

Despite their clear and often convergent impact on imaging phenotypes, the usefulness of candidate genes for understanding schizophrenia is debated because these a-priori hypothesized variants often show an inconsistent effect on the categorical disease phenotype itself. Genome-wide association studies (GWAS) offer an alternative, hypothesis-free way to identify genetic variants associated with the disease. While it is in our view unlikely that GWAS will provide all answers about common genetic variants impacting on schizophrenia, any variant that does survive the extreme amount of statistical thresholding that this method requires certainly merits study using intermediate imaging phenotypes. Several such variants have been forthcoming in schizophrenia, in particular *ZNF804A*, Neurogranin, *TCF4*, and genes located in the major histocompatibility complex.[34-36] Of those variants, the one with the strongest support is *ZNF804A*, encoding a zinc-finger protein of unknown, but possibly regulatory function. Interestingly, like the *COMT* candidate gene variant discussed here, *ZNF804A* appeared to be promiscuous on the level of psychiatric diagnoses, also being associated with bipolar disorder. In functional neuroimaging with an n-back working memory probe,[37] healthy carriers of *ZNF804A* rs1344706 risk genotypes exhibit no changes in regional activity. However, they did exhibit pronounced gene

dosage-dependent alterations in functional connectivity, which was measured by correlating the time series of activity across regions. Functional connectivity was decreased from DLPFC across hemispheres and increased with hippocampus. Both of these connectivity profiles mirrored findings in patients and carriers of candidate risk variants, providing translational genetic support for the contention first put forward by Wernicke more than 100 years ago that abnormal functional coupling between brain areas is an important mechanism of schizophrenia. Interestingly, cognitive performance of patients with the *ZNF804A* risk genotype has been linked to working and episodic memory specifically, highlighting to core functions to which DLPFC and hippocampus contribute.[38]

New frontiers in imaging genetics of schizophrenia

Work discussed so far has concerned the effects of single genetic variants on brain phenotypes. While imaging genetics has proven itself to be a sensitive and specific assay of such effects, the present data do not allow the prediction of phenotypes using these genetic findings, largely due to the fact that the amount of variance attributable to each common genetic variant in isolation is too small. The application of imaging genetics is therefore evolving to address key questions posed by the genetic complexity of schizophrenia. Here, we will discuss three of these research frontiers: epistasis, the study of rare structural variants in the genome, and discovery science using imaging genetics.

Epistasis

The genetics of schizophrenia is complex; while heritability is high, recent results from GWAS strongly suggest that no frequent variant exists that by itself increases disease risk by more than 30%.[34-36] In fact, simulation studies indicate that thousands of risk alleles may be related to heritability in this genetically complex disorder.[34] This implies that interactions between genes, "epistasis," may play an important role in the disorder, and may also contribute to the interactions with the environment. A convenient starting point for investigating epistasis is again provided by *COMT*, since this gene harbors several functional or likely functional polymorphisms. A *cis* functional variant (rs2097603) linked upstream in the P2 promoter, driving transcription of the predominant form of COMT in the brain (MB-COMT), affects COMT activity in lymphocytes and postmortem brain tissue.[15] Another variant in the 3' untranslated region (rs165599), highly associated with schizophrenia in a large sample of Israelis of Ashkenazi descent,[39] was found to differentially affect expression of rs4680 alleles in human brain tissue.[40] A further variant impacting on *COMT* transcription, through an alteration of mRNA structure, has been identified. Using probabilistic haplotype mapping in a large sample of healthy controls studied during working memory,[41] evidence for functional interactions of rs4680 with rs2097603 and rs165599 was indeed found, with a neural response that conformed to the inverted-u model. Similarly in brain structure, interactions between rs4680 and rs2097603 in hippocampal gray matter volume were found that were again consistent with a nonlinear (inverted u) effect.[23] For function, Bertolino and coworkers,[42] studying working memory in healthy subjects, showed that the *COMT* met158 allele and the *DAT* 3' variable number of tandem repeat 10-repeat allele were independently associated in healthy humans with more efficient BOLD response in the prefrontal cortex, and that these effects were additive (subjects homozygous for the *COMT* met allele and the *DAT* 10-repeat allele had the most efficient response, whereas the combination of the *COMT* val and the *DAT* 9-repeat alleles the least). Very similar results were obtained by Caldu and coworkers.[43] Conversely, during response inhibition, greater activation (reduced efficiency) was observed in carriers of the *DAT* 9-allele or the *COMT* met-allele as compared with carriers of the *DAT* 10/10 genotype and *COMT* val/val homozygotes,[44] a finding that could reflect differing processing demands during inhibition, which is a more phasic process, as compared with working memory maintenance, which requires tonic activity.[17] A true interaction between these variants was also found in a multimodal imaging study using a reward paradigm,[45] measuring midbrain dopamine synthesis with F-DOPA positron emission tomography (PET) and activation during reward anticipation in the ventral striatum, lateral prefrontal and orbitofrontal cortices as well as in the midbrain at the time of reward delivery, with carriers of the *DAT1* 9-repeat allele and *COMT* met/met allele exhibiting the least efficiency, similar to the finding during inhibition and presumably reflecting functional changes consequent to higher synaptic dopamine availability in the

context of processing phasic information. Both during working memory and episodic memory (retrieval), Bertolino and coworkers found nonlinear, true epistatic interactions between the same genetic variants in hippocampus, conforming to an inverted-u model, suggesting that epistatic phenomena vary by region (and possibly cognitive condition).[46] The modulator of postsynaptic dopamine signaling, RGS4, showed an interaction with *COMT* rs4680 genotype in DLPFC and midbrain during working memory: val/val subjects demonstrated a significant allele-dosage effect (increasing linearly with the number of minor alleles) of *RGS4* on prefrontal BOLD, while the effect of *RGS4* was attenuated in met-carrying subjects.[47] A risk variant in another postsynaptic signaling molecule gene, *AKT1*, similarly showed interactions with *COMT* rs4680 genotype during working memory,[32] with risk carriers for both genes showing especially inefficient lateral prefrontal activation.

While the papers reviewed above are limited to interactions between a maximum of four SNPs, the complexity of common genetic variation related to schizophrenia, which is likely to include effects of thousands of variants, will require a methodological effort to characterize interactions between larger sets of genes as they impact on imaging data. Calhoun and coworkers employed parallel independent component analysis, applied to auditory oddball task fMRI data, and extracted a set of 10 SNPs that were significantly related to imaging data and differed between a sample of patients and controls.[48] While selection of SNPs and small sample size preclude conclusions about the specific genes they highlighted, their study provides proof of concept of the applicability of multivariate methods in imaging genetics.

Copy number variants

An important insight that has emerged from the last waves of genome-wide studies of schizophrenia concerns structural variations of the genome, where larger segments (up to several megabases) of genetic material are either duplicated (microduplications) or missing (microdeletions).[49,50] Convergent evidence now shows that such copy number variants (CNVs) are more common in schizophrenia than in the general population. In contrast to frequent genetic variants such as SNPs, the risk associated with some CNVs is much higher, and can correspond to a tenfold increase in disease risk. There is evidence that the presence of these variants is deleterious since they are under negative selection.[51] Several specific regions now have strong evidence for conferring risk for schizophrenia, mapping on chromosome regions at 22q11, 15q13.3, 1q21.1, 15q11.2, 17p12, 2p16.3, 16p13.1, and 16p11.2. One of these, 22q11, has been known for a longer time since this microdeletion causes a clinical syndrome (velocardiofacial, DiGeorge, or 22q11 deletion syndrome) that is recognizable by a pattern of somatic symptoms, such as heart defects or cleft palate, in addition to the increased risk for psychosis.[52] An important research frontier will be to understand, using imaging genetics, how these microdeletions impact on brain structure and function. This work is farthest in 22q11DS, which has been known for the longest time. Here, convergent evidence implicates reductions in hippocampus and cerebellum, abnormal white matter connectivity, especially in the posterior corpus callosum, and reduced prefrontal activation (possibly compensated by parietal activation) during working memory tasks.[53] For the other microdeletions, only recently identified, evidence is emerging that they also cause complex neurodevelopmental syndromes whose psychiatric manifestations include, not only psychosis, but also intellectual impairment, and features of autism and attention deficit–hyperactivity disorder.[53] While these are therefore not monocausally related to schizophrenia, they are one of the best genetic clues yet for a genetical high-risk state that deserves intensive further study. This applies both to chartacterizing brain phenotypes in subjects carrying or not carrying the disorder, and to trying to further dissect why these, and not any of the many other microdeletions present in the human population, increase risk for psychosis. For the former approach, the main problem is that due to the relative rarity of these variants even in clinical populations, large numbers will have to be screened and characterized. Nevertheless, this work is ongoing and promises insights not only in studying the phenotypes of each of these variants by itself, but also in examining whether there are overlaps in structural or neurofunctional impairments across these microdeletions that would identify core systems related to a high-risk state. For the latter attempt of trying to understand why these specific microdeletions are high-risk, complex cis- and trans-acting genetic effects (ie, those that concern the genes affected by the microdeletion itself, or outside of it) will have to be considered. However, a simple hypothesis that can be tested is whether there could be, by chance, several common risk

variants for schizophrenia located in spatial proximity that are jointly affected by a microdeletion, causing a superadditive effect. Some preliminary evidence for this idea comes from 22q11DS, which includes the much-studied risk gene *COMT*, discussed above, but also several other genes where schizophrenia risk variants have been studied. One of these, *PRODH*, encoding proline oxidase (POX), has been associated with schizophrenia through linkage and association. A recent study showed that functional polymorphisms had opposite effects on schizophrenia risk depending on whether they increased or decreased POX activity.[54] In multimodal genetic imaging, both functional (working memory and emotional recognition) and structural (VBM) datasets showed dissociable genetic effects: risk haplotype carriers had decreased striatal volume and increased striatal-frontal functional connectivity, while the protective haplotype was associated with decreased striatal-frontal functional connectivity, mirroring findings in patients and suggesting that functional genetic variation in POX impacts on neostriatal-frontal circuits mediating risk and protection for schizophrenia. Since, as reviewed above, the biochemically unrelated *COMT* gene on overlapping circuitry in human brain, this suggests a neural mechanism whereby deletion of both genes in 22q11 syndrome could have a superadditive impact on schizophrenia risk. Further work, which needs to take epistatic and transacting effects into account, is necessary to extend these findings.

Forward genetics—discovery science

Finally, an important future perspective of imaging genetics is to use it to find new variants associated with brain phenotypes, as a forward genetics method. Since the penetrance of common genetic variants is higher on the level of neuroimaging, this approach, which requires a combination of neuroimaging with genome-wide association data, is feasible with a considerably smaller number of subjects than when using clinical phenotypes. First examples of this approach have appeared[55]; with regard to structural variants, some are now close to genome-wide significance.[56] It is likely that samples from several groups will have to be combined to bring this approach to full fruition; in this sense, imaging genetics will follow the trend of psychiatric genetic in general. This research strategy has considerable potential to identify new molecular targets affecting given brain systems; if these systems (and ideally also the genetic variants) can be linked to schizophrenia, this would provide a much-needed impetus for drug discovery in this still insufficiently treatable psychiatric disorder.

Conclusion

In summary, we have provided an overview of the results obtained from studying both candidate and genome-wide supported common genetic variants using neuroimaging. Those results converge on effects in lateral prefrontal cortex and subcortical structures with which it is densely interconnected, in particular striatum and hippocampus, highlighting a core neural system for genetic risk for schizophrenia. Future work will increasingly consider epistatic effects of multiple common variants, characterize rare high-risk structural variants, and use imaging data to discover new genetic contributions to neural structure and function that can lead to new treatments. ❑

REFERENCES

1. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*. 2003;60:1187-1192.
2. Gottesman, II, Shields J. A polygenic theory of schizophrenia. *Proc Natl Acad Sci U S A.* 1967;58:199-205.
3. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160:636-645.
4. Munafo MR, Attwood AS, Flint J. Bias in genetic association studies: effects of research location and resources. *Psychol Med*. 2008;38:1213-1214.
5. Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Mol Psychiatry*. 2010;15:918-927.
6. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98:6917-22.
7. Bertocci B, Miggiano V, Da Prada M, Dembic Z, Lahm HW, Malherbe P. Human catechol-O-methyltransferase: cloning and expression of the membrane-associated form. *Proc Natl Acad Sci U S A.* 1991;88:1416-1420.
8. Grossman MH, Emanuel BS, Budarf ML. Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1----q11.2. *Genomics*. 1992;12:822-825.
9. Owen MJ, Williams NM, O'Donovan MC. The molecular genetics of schizophrenia: new findings promise new insights. *Mol Psychiatry*. 2004;9:14-27.
10. Zinkstok J, van Amelsvoort T. Neuropsychological profile and neuroimaging in patients with 22Q11.2 Deletion Syndrome: a review. *Child Neuropsychol*. 2005;11:21-37.
11. Masuda M, Tsunoda M, Imai K. High-performance liquid chromatography-fluorescent assay of catechol-O-methyltransferase activity in rat brain. *Anal Bioanal Chem*. 2003;376:1069-1073.
12. Hong J, Shu-Leong H, Tao X, Lap-Ping Y. Distribution of catechol-O-methyltransferase expression in human central nervous system. *Neuroreport*. 1998;9:2861-2864.

Imagenología de la expresión genética en la esquizofrenia

En los últimos años ha habido un explosivo interés en la aplicación de la imagenología vinculada con la genética para comprender los mecanismos neurogenéticos de la esquizofrenia. La imagenología de la genética aplica neuroimágenes estructurales y funcionales al estudio de sujetos portadores de variantes de riesgo genético relacionadas con un trastorno psiquiátrico. Se revisan aspectos seleccionados de esta literatura, comenzando con un gen candidato ampliamente estudiado –el gen de la catecol-O-metiltransferasa (COMT)- luego se discuten otros genes candidatos en el sistema dopaminérgico y finalmente se analizan variantes sustentadas en el genoma completo. A futuro hay que considerar las aproximaciones que permitan caracterizar los efectos epistáticos, la identificación de nuevos genes de riesgo mediante propuestas de genética avanzada que emplea imagenología de fenotipos y el estudio de variantes estructurales raras.

Imagerie génétique de la schizophrénie

L'intérêt pour les applications de l'imagerie génétique a explosé ces dernières années dans le but de comprendre les mécanismes neurogénétiques de la schizophrénie. L'imagerie génétique utilise la neuro-imagerie fonctionnelle et structurelle pour étudier les sujets porteurs de variants de risque génétique lié à un trouble psychiatrique. Nous analysons dans cet article une sélection de la littérature, en commençant par celle concernant un gène candidat très étudié, la catéchol-0-méthyltransférase (COMT), puis en discutant l'implication d'autres gènes candidats du système dopaminergique et enfin de variants à l'échelle du génome entier. Dans les perspectives futures, nous analyserons la manière de caractériser les effets épistatiques, l'identification de nouveaux gènes de risque à l'aide d'approches génétiques modernes utilisant l'imagerie des phénotypes et l'étude de variants structuraux rares.

13. Lipska BK, Mitkus S, Caruso M, et al. RGS4 mRNA expression in postmortem human cortex is associated with COMT Val158Met genotype and COMT enzyme activity. *Hum Mol Genet*. 2006;15:2804-2812.

14. Gogos JA, Morgan M, Luine V, et al. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc Natl Acad Sci U S A.* 1998;95:9991-9996.

15. Chen J, Lipska BK, Halim N, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet*. 2004;75:807-821.

16. Chen X, Wang X, O'Neill AF, Walsh D, Kendler KS. Variants in the catechol-o-methyltransferase (COMT) gene are associated with schizophrenia in Irish high-density families. *Mol Psychiatry*. 2004;9:962-967.

17. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*. 2004;29:1943-1961.

18. de Frias CM, Marklund P, Eriksson E, et al. Influence of COMT gene polymorphism on fMRI-assessed sustained and transient activity during a working memory task. *J Cogn Neurosci*. 2010;22:1614-1622.

19. Ettinger U, Kumari V, Collier DA, et al. Catechol-O-methyltransferase (COMT) val158met genotype is associated with BOLD response as a function of task characteristic. *Neuropsychopharmacology*. 2008;33:3046-3057.

20. Bertolino A, Caforio G, Blasi G, et al. Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. *Am J Psychiatry*. 2004;161:1798-1805.

21. Loughead J, Wileyto EP, Valdez JN, et al. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. *Mol Psychiatry*. 2009;14:820-826.

22. Bishop SJ, Fossella J, Croucher CJ, Duncan J. COMT val158met genotype affects recruitment of neural mechanisms supporting fluid intelligence. *Cereb Cortex*. 2008;18:2132-2140.

23. Honea R, Verchinski BA, Pezawas L, et al. Impact of interacting functional variants in COMT on regional gray matter volume in human brain. *Neuroimage*. 2009;45:44-51.

24. Zinkstok J, Schmitz N, van Amelsvoort T, et al. The COMT val158met polymorphism and brain morphometry in healthy young adults. *Neurosci Lett*. 2006;405:34-39.

25. Ho BC, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC. Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Mol Psychiatry*. 200;10:229,87-98.

26. Ohnishi T, Hashimoto R, Mori T, et al. The association between the Val158Met polymorphism of the catechol-O-methyl transferase gene and morphological abnormalities of the brain in chronic schizophrenia. *Brain*. 2006;129(Pt 2):399-410.

27. McIntosh AM, Baig BJ, Hall J, et al. Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. *Biol Psychiatry*. In press.

28. Li J, Yu C, Li Y, et al. COMT val158met modulates association between brain white matter architecture and IQ. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B:375-380.

29. Bertolino A, Fazio L, Caforio G, et al. Functional variants of the dopamine receptor D2 gene modulate prefronto-striatal phenotypes in schizophrenia. *Brain*. 2009;132(Pt 2):417-425.

30. Buckholtz JW, Meyer-Lindenberg A, Honea RA, et al. Allelic variation in RGS4 impacts functional and structural connectivity in the human brain. *J Neurosci*. 2007;27:1584-1593.

31. Meyer-Lindenberg A, Straub RE, Lipska BK, et al. Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. *J Clin Invest*. 2007;117:672-682.

32. Tan HY, Nicodemus KK, Chen Q, et al. Genetic variation in AKT1 is linked to dopamine-associated prefrontal cortical structure and function in humans. *J Clin Invest*. 2008;118:2200-2208.

33. Forbes EE, Brown SM, Kimak M, Ferrell RE, Manuck SB, Hariri AR. Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Mol Psychiatry*. 2009;14:60-70.
34. Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748-752.
35. Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*. 2009;460:753-757.
36. Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. *Nature*. 2009;460:744-747.
37. Esslinger C, Walter H, Kirsch P, et al. Neural mechanisms of a genome-wide supported psychosis variant. *Science*. 2009;324:605.
38. Walters JT, Corvin A, Owen MJ, et al. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Arch Gen Psychiatry*. 2010;67:692-700.
39. O'Donovan MC, Craddock N, Norton N, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet*. 2008;40:768-775.
40. Bray NJ, Buckland PR, Williams NM, et al. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. *Am J Hum Genet*. 2003;73:152-161.
41. Meyer-Lindenberg A, Nichols T, Callicott JH, et al. Impact of complex genetic variation in COMT on human brain function. *Mol Psychiatry*. 2006;11:867-877, 797.
42. Bertolino A, Blasi G, Latorre V, et al. Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. *J Neurosci*. 2006;26:3918-3922.
43. Caldu X, Vendrell P, Bartres-Faz D, et al. Impact of the COMT Val108/158 Met and DAT genotypes on prefrontal function in healthy subjects. *Neuroimage*. 2007;37:1437-1444.
44. Congdon E, Constable RT, Lesch KP, Canli T. Influence of SLC6A3 and COMT variation on neural activation during response inhibition. *Biol Psychol.* 2009;81:144-152.
45. Dreher JC, Kohn P, Kolachana B, Weinberger DR, Berman KF. Variation in dopamine genes influences responsivity of the human reward system. *Proc Natl Acad Sci U S A*. 2009;106:617-622.
46. Bertolino A, Di Giorgio A, Blasi G, et al. Epistasis between dopamine regulating genes identifies a nonlinear response of the human hippocampus during memory tasks. *Biol Psychiatry*. 2008;64:226-234.
47. Buckholtz JW, Sust S, Tan HY, et al. fMRI evidence for functional epistasis between COMT and RGS4. *Mol Psychiatry*. 2007;12:893-895.
48. Liu J, Pearlson G, Windemuth A, Ruano G, Perrone-Bizzozero NI, Calhoun V. Combining fMRI and SNP data to investigate connections between brain function and genetics using parallel ICA. *Hum Brain Mapp*. 2009;30:241-255.
49. Walsh T, McClellan JM, McCarthy SE, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science*. 2008;321:690.
50. International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*. 2008;455:237-241.
51. Stefansson H, Rujescu D, Cichon S, et al. Large recurrent microdeletions associated with schizophrenia. *Nature*. 2008;455:232-236.
52. Karayiorgou M, Simon TJ, Gogos JA. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nat Rev Neurosci*. 2010;11:402-416.
53. Ben-Shachar S, Lanpher B, German JR, et al. Microdeletion 15q13.3: a locus with incomplete penetrance for autism, mental retardation, and psychiatric disorders. *J Med Genet*. 2009;46:382-388.
54. Kempf L, Nicodemus KK, Kolachana B, et al. Functional polymorphisms in PRODH are associated with risk and protection for schizophrenia and fronto-striatal structure and function. *PLoS Genet*. 2008;4:e1000252.
55. Potkin SG, Macciardi F, Guffanti G, et al. Identifying gene regulatory networks in schizophrenia. *Neuroimage*. 2010;53:839-847.
56. Stein JL, Hua X, Morra JH, et al. Genome-wide analysis reveals novel genes influencing temporal lobe structure with relevance to neurodegeneration in Alzheimer's disease. *Neuroimage*. 2010;51:542-554.