Genetic predisposition to schizophrenia: what did we learn and what does the future hold?

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Schizophrenia is a complex, devastating brain disorder with clear genetic and environmental contributions to the emergence of the disease. In the last several decades of research hundreds of millions of dollars were spent of the elusive search for schizophrenia susceptibility genes, but the results have been meager. Researchers have identified a number of genetic variants that predispose the brain to developing the disease, yet alone they can explain only a very small number of the schizophrenia occurrence. Vulnerability in DISC1, NRG1, DTNBP1, RGS4, KCNH2, COMT, AKT1 and other putative schizophrenia genes, together with copy number variants, leave unexplained the vast majority of diseased cases. Furthermore, most of the uncovered disease-associated genetic variants have been inconsistently replicated across multiple cohorts and do not lead to altered protein structure. In summary, we argue that large-scale genetic studies will not provide us with the answers we seek: we have to accept that there are no schizophrenia-predisposing genes with large effect sizes, and due to the diversity of findings, genetics-based novel therapies of schizophrenia are not realistic. The new treatments will have to come from functional studies of intracellular pathways and understanding the confluence of environmental influences and genetic predisposition, and their combined effects on developmental mechanisms and intracellular cascades.
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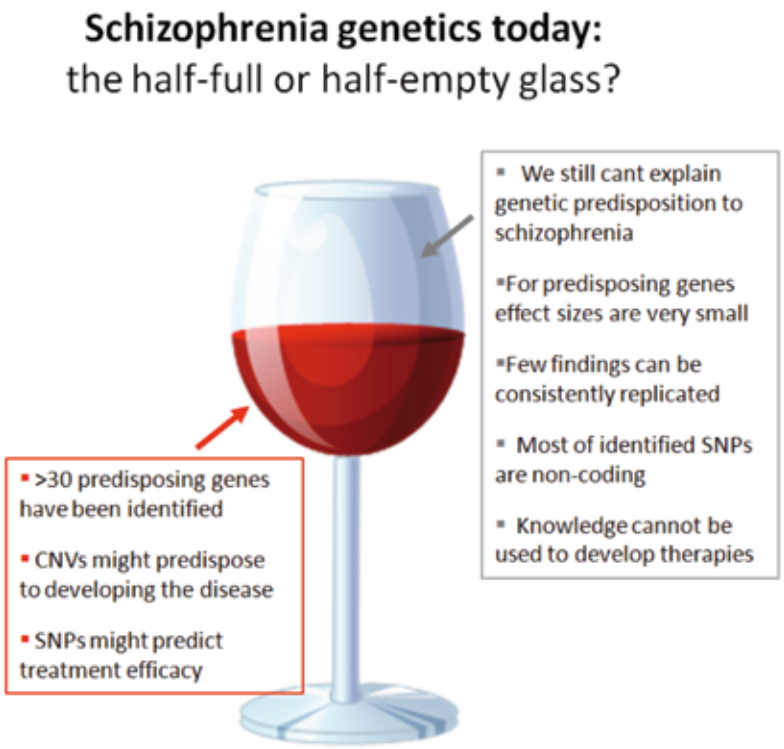
Schizophrenia is a complex, debilitating psychiatric disorder with a median lifetime prevalence of 4 per 1000 and lifetime morbidity of 7.2 per 1000 (McGrath et al., 2008). Both genetic and environmental factors contribute to the development of the disease (Must et al., 2011). The biology of schizophrenia encompasses various structural and molecular brain abnormalities (Balla and Frecska, 2011), changes in neuronal connectivity (Tenyi, 2011), with various therapeutic approaches (Gazdag and Ungvari, 2011), clinical outcomes (Kalman and Kalman, 2011) and forensic implications (Baran and Gazdag, 2011).

Genetics plays a major role in the etiology of schizophrenia with an estimated heritability of 81% (Sullivan et al., 2003). Evidence for common or shared environmental influences on liability to schizophrenia is estimated of 11% (Sullivan et al., 2003), although the exact ratio between the environmental and genetic contribution to developing schizophrenia is somewhat debatable. During the past decades many associations between schizophrenia and genetic risk factors have been reported, but only a very few can be considered schizophrenia susceptibility genes. This "candidate gene approach" tested >800 genes for association with developing schizophrenia (Harrison and Weinberger, 2005; Gogos and Gerber, 2006), suggesting that various DNA elements in DISC1 (disrupted in schizophrenia 1) (Ekelund et al., 2004; Hennah et al., 2003; Hodgkinson et al., 2004); NRG1 (neuregulin 1) (Stefansson et al., 2002; Stefansson et al., 2003; Williams et al., 2003; Corvin et al., 2004; Yang et al., 2003; Tang et al., 2004; Zhao et al., 2004; Li et al., 2004); DTNBP1 (dysbindin, also known as dystrobrevin binding-protein 1)(Kirov et al., 2004; Straub, 2002; Schwab et al., 2003; Williams et al., 2004); RGS4 (regulator of G-protein signaling 4) (Mirnics et al., 2001; Chowdari et al., 2002; Morris

Figure 1 "When it comes to the treatment of patients with chronic schizophrenia, the glass is only half-full." Jeffrey A. Lieberman, Columbia University.



et al., 2004), KCNH2 (potassium voltage-gated channel, subfamily H, member 2) (Huffaker et al., 2009), COMT (catechol-O-methyltransferase) (Shifman et al., 2002; Glatt et al., 2003a), AKT1 (v-akt murine thymoma viral oncogene homolog 1) (Emamian et al., 2004; Schwab et al., 2005), DRD2 (dopamine receptor D2) (Schindler et al., 2002; Glatt et al., 2003b; Jonsson et al., 2003; Arranz and de Leon, 2007), HTR2A (5-hydroxytryptamine (serotonin) receptor 2A) (Williams et al., 1996) contribute to the emergence of the disease. However, none of these findings were replicated across all the studied cohorts, and the effect sizes of these putative schizophrenia-susceptibility genes were very low in all cases, never explaining more than a few percent of the disease cases.

More recently, several schizophrenia-focused genome-wide association (GWA) studies have been carried out, analyzing genetic predisposition across the whole human genome. Among these, only two GWA studies have reported genome-wide levels of significance, while the rest have failed to detect real susceptibility factors (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Sullivan et al., 2008; Lencz et al., 2007; Need et al., 2009). From the positive GWA studies, two leads appeared to be most promising: the association with the MHC region (Shi et al., 2009) and with zinc-finger protein ZNF804A (O'Donovan et al., 2008) (although only with and odds ratio of 1.09). Some of the subsequent meta-analyses (Steinberg et al., 2011; Williams et al., 2011) and case-control studies (Riley et al., 2010) provided support for the initial GWA findings, but in some cases the results have only been partially reproduced (e.g. only female-dependent association) (Zhang et al., 2011).

After recognition that both the candidate gene and GWA approaches failed to provide strong evidence for the 'common disease, common variant' hypothesis, a 'common disease, multiple rare variants' hypothesis became a focus of follow-up investigation. The assessment of "copy number variations" (CNVs) (DNA deletions and duplications from about one kilobase

to several megabases in size) across the human genome found that these variants were more frequently found in schizophrenic patients than healthy controls (Walsh et al., 2008; Stone et al., 2008). Unfortunately, just like the 'common disease, common variant' hypothesis, the 'common disease, multiple rare variants' was also unable to account for the heritability of the majority of the schizophrenia cases.

So, if schizophrenia shows 81% heritability, where are the major schizophrenia susceptibility genes? The answer is simple: there are none that will account for a large proportion of disease cases. And it doesn't take a visionary to conclude that the new whole genome sequencing studies will also find none of them. Expanding the genetic studies to hundreds of thousands of patients will also fail. The best proof of this is a recent assessment of body height (Visscher, 2008), which is also a trait with a heritability of approximately 80%. In this GWA study, assessing approximately 63,000 adults identified a number of highly significant genetic factors associated with the height of the individual – yet, all these factors together could account for less than 10% of phenotypic variability.

The problem is the complexity of the biology, not the deficiency of the technical methods to identify the major genetic susceptibility factors. We should accept that investigation of schizophrenia genetics will not identify major susceptibility genes, meaningful drug targets or reliable genetic tests for predicting who will develop schizophrenia. The genetics is so diverse, so complex that the genetic makeup of each individual (coupled with environmental influences and the broadness of the clinical diagnosis) will make it extremely difficult to generalize individual conclusions to the whole population of schizophrenics. After all, the existing antipsychotic therapies did not develop out of our genetic findings: dysfunction of the dopaminergic neurotransmission in schizophrenia is a physiological explanation for the efficacy of D2-agents, and not a result of genetic vulnerability.

Ultimately, personalized medicine and treatment should take center stage; we should tailor therapies to be best suited for individual patients. And this is where the future of psychiatric genetics lies: by predicting the relationship between genetics and pharmacokinetics/pharmacodynamics, pharmacogenetics can already forecast therapeutic responses and adverse effects for many treatments. For example, most of the used antipsychotic drugs are metabolized by variable enzymes, including the cytochrome P450 system (e.g. CYP2D6, CYP2C9, CYP2C19) (Kirchheiner et al., 2004). Based on the genetic profile, patients can be classified as poor, intermediate, extensive or ultrarapid metabolizers (Nebert and Dieter, 2000) and the genetic variants of these enzymes predict the way drugs are metabolized and inform us about the likelihood of treatment success (Maier and Zobel, 2008). Furthermore, there is emerging evidence that RGS4 polymorphisms can also predict clinical manifestations and responses to risperidone treatment in patients with schizophrenia (Lane et al., 2008), and that treatment with perphenazine is more effective than treatment with quetiapine or ziprasidone in individuals of inferred African ancestry (Campbell et al., 2008).

Hollow, undeliverable promises of psychiatric genetics to identify novel drug targets or uncovering major schizophrenia susceptibility genes must end. We should accept that therapeutic targets will be identified primarily using non-genetic knowledge, knowledge that will focus on convergence of molecular pathways and altered physiology, and will understand how molecular events translate to altered behavior, cognition and emotion.

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REFERENCES

1. Arranz, M. J., de Leon, J. (2007) Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Mol Psychiatry, 12:707-47.
2. Balla, P., Frecska, E. (2011) Changes in the brain with schizophrenia: postmortem findings. Neuropsychopharmacol Hung, 13:219-227.
3. Baran, B., Gazdag, G. (2011) Relationship between schizophrenia and crime. Neuropsychopharm Hung, 13:257-261.
4. Campbell, D. B., Ebert, P. J., Skelly, T., Stroup, T. S., Lieberman, J., Levitt, P., Sullivan, P. F. (2008) Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in schizophrenia. Biol Psychiatry, 63:32-41.
5. Chowdari, K. V., Mirnics, K., Semwal, P., Wood, J., Lawrence, E., Bhatia, T., Deshpande, S. N., B, K. T., Ferrell, R. E., Middleton, F. A., Devlin, B., Levitt, P., Lewis, D. A., Nimgaonkar, V. L. (2002) Association and linkage analyses of RGS4 polymorphisms in schizophrenia. Human Molecular Genetics, 11:1373-80.
6. Corvin, A. P., Morris, D. W., McGhee, K., Schwaiger, S., Scully, P., Quinn, J., Meagher, D., St Clair, D., Waddington, J. L., Gill, M. (2004) Confirmation and refinement of an 'at-risk' haplotype for schizophrenia suggests the EST cluster, Hs.97362, as a potential susceptibility gene at the Neuregulin-1 locus. Mol Psychiatry, 9:208-212.

7. Ekelund, J., Hennah, W., Hiekkalinna, T., Parker, A., Meyer, J., Lonnqvist, J., Peltonen, L. (2004) Replication of 1q42 linkage in Finnish schizophrenia pedigrees. Mol Psychiatry, 9:1037-41.
8. Emamian, E. S., Hall, D., Birnbaum, M. J., Karayiorgou, M., Gogos, J. A. (2004) Convergent evidence for impaired AKT1-GSK3beta signaling in schizophrenia. Nature Genetics, 36:131-7.
9. Gazdag, G., Ungvari, G. S. (2011) Non-pharmacological biological therapies in schizophrenia. Neuropsychopharmacol Hung, 13:233-238.
10. Glatt, S. J., Faraone, S. V., Tsuang, M. T. (2003a) Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. The American journal of psychiatry, 160:469-76.
11. Glatt, S. J., Faraone, S. V., Tsuang, M. T. (2003b) Meta-analysis identifies an association between the dopamine D2 receptor gene and schizophrenia. Mol Psychiatry, 8:911-5.
12. Gogos, J. A., Gerber, D. J. (2006) Schizophrenia susceptibility genes: emergence of positional candidates and future directions. Trends in Pharmacological Sciences, 27:226-233.
13. Harrison, P. J., Weinberger, D. R. (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry, 10:40-68; image 5.
14. Hennah, W., Varilo, T., Kestila, M., Paunio, T., Arajarvi, R., Haukka, J., Parker, A., Martin, R., Levitzky, S., Partonen, T., Meyer, J., Lonnqvist, J., Peltonen, L., Ekelund, J. (2003) Haplotype transmission analysis provides evidence of association for DISC1 to schizophrenia and suggests sex-dependent effects. Human Molecular Genetics, 12:3151-9.
15. Hodgkinson, C. A., Goldman, D., Jaeger, J., Persaud, S., Kane, J. M., Lipsky, R. H., Malhotra, A. K. (2004) Disrupted in schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. American Journal of Human Genetics, 75:862-72.
16. Huffaker, S. J., Chen, J., Nicodemus, K. K., Sambataro, F., Yang, F., Mattay, V., Lipska, B. K., Hyde, T. M., Song, J., Rujescu, D., Giegling, I., Mayilyan, K., Proust, M. J., Soghoyan, A., Caforio, G., Callicott, J. H., Bertolino, A., Meyer-Lindenberg, A., Chang, J., Ji, Y., Egan, M. F., Goldberg, T. E., Kleinman, J. E., Lu, B., Weinberger, D. R. (2009) A primate-specific, brain isoform of KCNH2 affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia. Nature Medicine, 15:509-18.
17. Jonsson, E. G., Sillen, A., Vares, M., Ekholm, B., Terenius, L., Sedvall, G. C. (2003) Dopamine D2 receptor gene Ser311Cys variant and schizophrenia: association study and meta-analysis. Am J Med Genet B Neuropsychiatr Genet, 119B:28-34.
18. Kalman, J., Kalman, S. (2011) The conceptual re-evaluation and therapeutic success in schizophrenia. Neuropsychopharmacol Hung, 13:249-256.
19. Kirchheiner, J., Nickchen, K., Bauer, M., Wong, M. L., Licinio, J., Roots, I., Brockmoller, J. (2004) Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry, 9:442-73.
20. Kirov, G., Ivanov, D., Williams, N. M., Preece, A., Nikolov, I., Milev, R., Koleva, S., Dimitrova, A., Toncheva, D., O'Donovan, M. C., Owen, M. J. (2004) Strong evidence for association between the dystrobrevin binding protein 1 gene (DTNBP1) and schizophrenia in 488 parent-offspring trios from Bulgaria. Biol Psychiatry, 55:971-975.
21. Lane, H. Y., Liu, Y. C., Huang, C. L., Chang, Y. C., Wu, P. L., Huang, C. H., Tsai, G. E. (2008) RGS4 polymorphisms predict clinical manifestations and responses to risperidone treatment in patients with schizophrenia. J Clin Psychopharmacol, 28:64-8.
22. Lencz, T., Morgan, T. V., Athanasiou, M., Dain, B., Reed, C. R., Kane, J. M., Kucherlapati, R., Malhotra, A. K. (2007) Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. Mol Psychiatry, 12:572-580.
23. Li, T., Stefansson, H., Gudfinnsson, E., Cai, G., Liu, X., Murray, R. M., Steinthorsdottir, V., Januel, D., Gudnadottir, V. G., Petursson, H., Ingason, A., Gulcher, J. R., Stefansson, K., Collier, D. A. (2004) Identification of a novel neuregulin 1 at-risk haplotype in Han schizophrenia Chinese patients, but no association with the Icelandic/Scottish risk haplotype. Mol Psychiatry, 9:698-704.
24. Maier, W., Zobel, A. (2008) Contribution of allelic variations to the phenotype of response to antidepressants and antipsychotics. European Archives of Psychiatry and Clinical Neuroscience, 258 Suppl 1:12-20.
25. McGrath, J., Saha, S., Chant, D., Welham, J. (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews, 30:67-76.
26. Mirnics, K., Middleton, F. A., Stanwood, G. D., Lewis, D. A., Levitt, P. (2001) Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. Mol Psychiatry, 6:293-301.
27. Morris, D. W., Rodgers, A., McGhee, K. A., Schwaiger, S., Scully, P., Quinn, J., Meagher, D., Waddington, J. L., Gill, M., Corvin, A. P. (2004) Confirming RGS4 as a susceptibility gene for schizophrenia. Am J Med Genet B Neuropsychiatr Genet, 125B:50-3.
28. Must, A., Janka, Z., Horvath, S. (2011) Schizophrenia, environment and epigenetics. Neuropsychopharm Hung, 13:211-217.
29. Nebert, D. W., Dieter, M. Z. (2000) The evolution of drug metabolism. Pharmacology, 61:124-35.
30. Need, A. C., Ge, D. L., Weale, M. E., Maia, J., Feng, S., Heinzen, E. L., Shianna, K. V., Yoon, W., Kasperaviciute, D., Gennarelli, M., Strittmatter, W. J., Bonvicini, C., Rossi, G., Jayathilake, K., Cola, P. A., McEvoy, J. P., Keefe, R. S. E., Fisher, E. M. C., St Jean, P. L., Giegling, I., Hartmann, A. M., Moller, H. J., Ruppert, A., Fraser, G., Crombie, C., Middleton, L. T., St Clair, D., Roses, A. D., Muglia, P., Francks, C., Rujescu, D., Meltzer, H. Y., Goldstein, D. B. (2009) A Genome-Wide Investigation of SNPs and CNVs in Schizophrenia. Plos Genetics, 5:-.
31. O'Donovan, M. C., Craddock, N., Norton, N., Williams, H., Peirce, T., Moskvina, V., Nikolov, I., Hamshere, M., Carroll, L., Georgieva, L., Dwyer, S., Holmans, P., Marchini, J. L., Spencer, C. C. A., Howie, B., Leung, H. T., Hartmann, A. M., Moller, H. J., Morris, D. W., Shi, Y. Y., Feng, G. Y., Hoffmann, P., Propping, P., Vasilescu, C., Maier, W., Rietschel, M., Zammit, S., Schumacher, J., Quinn, E. M., Schulze, T. G., Williams, N. M., Giegling, I., Iwata, N., Ikeda, M., Darvasi, A., Shifman, S., He, L., Duan, J., Sanders, A. R., Levinson, D. F., Gejman, P. V., Cichon, S., Nothen, M. M., Gill, M., Corvin, A., Rujescu, D., Kirov, G., Owen, M. J., Coll, M. G. O. S. (2008) Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nature Genetics, 40:1053-1055.
32. Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., Sklar, P., Ruderfer, D. M., McQuillin, A., Morris, D. W., O'Dushlaine, C. T., Corvin, A., Holmans, P. A., Macgregor, S., Gurling, H., Blackwood, D. H. R., Corvin, A., Craddock, N. J., Gill, M., Hultman, C. M., Kirov, G. K., Lichtenstein, P., Muir, W. J., Owen, M. J., Pato, C. N., Scolnick, E. M., St Clair, D., Craddock, N. J., Holmans, P. A., Williams, N. M., Georgieva, L., Nikolov, I., Norton, N., Williams, H., Toncheva, D., Milanova, V., Hultman, C. M., Lichtenstein, P., Thelander, E. F., Sullivan, P., Kenny, E., Quinn, E. M., Gill, M., Corvin, A., Choudhury, K., Datta, S., Pimm, J., Thirumalai, S., Puri, V., Krasucki, R., Lawrence, J., Quested, D., Bass, N., Crombie, C., Fraser, G., Kuan, S. L., Walker, N., Blackwood, D. H. R., Muir, W. J., McGhee, K. A., Pickard, B., Malloy, P., Maclean,

A. W., Van Beck, M., Wray, N. R., Macgregor, S., Visscher, P. M., Pato, M. T., Medeiros, H., Middleton, F., Carvalho, C., Morley, C., Fanous, A., Conti, D., Knowles, J. A., Ferreira, C. P., Macedo, A., Azevedo, M. H., Kirby, A. N., Ferreira, M. A. R., Daly, M. J., Chambert, K., Kuruvilla, F., Gabriel, S. B., Ardlie, K., Moran, J. L., Daly, M. J., Scolnick, E. M. (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature, 460:748-752.

33. Riley, B., Thiselton, D., Maher, B. S., Bigdeli, T., Wormley, B., McMichael, G. O., Fanous, A. H., Vladimirov, V., O'Neill, F. A., Walsh, D., Kendler, K. S. (2010) Replication of association between schizophrenia and ZNF804A in the Irish Case-Control Study of Schizophrenia sample. Mol Psychiatry, 15:29-37.
34. Schindler, K. M., Pato, M. T., Dourado, A., Macedo, A., Azevedo, M. H., Kennedy, J. L., Pato, C. N. (2002) Association and linkage disequilibrium between a functional polymorphism of the dopamine-2 receptor gene and schizophrenia in a genetically homogeneous Portuguese population. Mol Psychiatry, 7:1002-5.
35. Schwab, S. G., Hoefgen, B., Hanses, C., Hassenbach, M. B., Albus, M., Lerer, B., Trixler, M., Maier, W., Wildenauer, D. B. (2005) Further evidence for association of variants in the AKT1 gene with schizophrenia in a sample of European sib-pair families. Biol Psychiatry, 58:446-50.
36. Schwab, S. G., Knapp, M., Mondabon, S., Hallmayer, J., Borrmann-Hassenbach, M., Albus, M., Lerer, B., Rietschel, M., Trixler, M., Maier, W., Wildenauer, D. B. (2003) Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. American Journal of Human Genetics, 72:185-190.
37. Shi, J. X., Levinson, D. F., Duan, J. B., Sanders, A. R., Zheng, Y. L., Pe'er, I., Dudbridge, F., Holmans, P. A., Whittemore, A. S., Mowry, B. J., Olincy, A., Amin, F., Cloninger, C. R., Silverman, J. M., Buccola, N. G., Byerley, W. F., Black, D. W., Crowe, R. R., Oksenberg, J. R., Mirel, D. B., Kendler, K. S., Freedman, R., Gejman, P. V. (2009) Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature, 460:753-757.
38. Shifman, S., Bronstein, M., Sternfeld, M., Pisante-Shalom, A., Lev-Lehman, E., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L., Schiffer, R., Kotler, M., Strous, R. D., Swartz-Vanetik, M., Knobler, H. Y., Shinar, E., Beckmann, J. S., Yakir, B., Risch, N., Zak, N. B., Darvasi, A. (2002) A highly significant association between a COMT haplotype and schizophrenia. American Journal of Human Genetics, 71:1296-302.
39. Stefansson, H., Ophoff, R. A., Steinberg, S., Andreassen, O. A., Cichon, S., Rujescu, D., Werge, T., Pietilainen, O. P. H., Mors, O., Mortensen, P. B., Sigurdsson, E., Gustafsson, O., Nyegaard, M., Tuulio-Henriksson, A., Ingason, A., Hansen, T., Suvisaari, J., Lonnqvist, J., Paunio, T., Borglum, A. D., Hartmann, A., Fink-Jensen, A., Nordentoft, M., Hougaard, D., Norgaard-Pedersen, B., Bottcher, Y., Olesen, J., Breuer, R., Moller, H. J., Giegling, I., Rasmussen, H. B., Timm, S., Mattheisen, M., Bitter, I., Rethelyi, J. M., Magnusdottir, B. B., Sigmundsson, T., Olason, P., Mason, G., Gulcher, J. R., Haraldsson, M., Fossdal, R., Thorgeirsson, T. E., Thorsteinsdottir, U., Ruggeri, M., Tosato, S., Franke, B., Strengman, E., Kiemeney, L. A., Melle, I., Djurovic, S., Abramova, L., Kaleda, V., Sanjuan, J., de Frutos, R., Bramon, E., Vassos, E., Fraser, G., Ettinger, U., Picchioni, M., Walker, N., Toulopoulou, T., Need, A. C., Ge, D., Yoon, J. L., Shianna, K. V., Freimer, N. B., Cantor, R. M., Murray, R., Kong, A., Golimbet, V., Carracedo, A., Arango, C., Costas, J., Jonsson, E. G., Terenius, L., Agartz, I., Petursson, H., Nothen, M. M., Rietschel, M., Matthews, P. M., Muglia, P., Peltonen, L., St Clair, D., Goldstein, D. B., Stefansson, K., Collier, D. A., Group (2009) Common variants conferring risk of schizophrenia. Nature, 460:744-U99.
40. Stefansson, H., Sarginson, J., Kong, A., Yates, P., Steinthorsdottir, V., Gudfinnsson, E., Gunnarsdottir, S., Walker, N., Petursson, H., Crombie, C., Ingason, A., Gulcher, J. R., Stefansson, K., St Clair, D. (2003) Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. American Journal of Human Genetics, 72:83-87.
41. Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Brynjolfsson, J., Gudmundsdottir, E., Gunnarsdottir, S., Ivarsson, O., Mutel, V., Harvey, R., Bjornsson, A., Sigfusson, S., Frigge, M., Gurney, M., Kong, A., Gulcher, J., Petursson, H., Stefansson, K., Lemke, M. (2002) Neuregulin 1 and susceptibility to schizophrenia. American Journal of Human Genetics, 71:185-185.
42. Steinberg, S., Mors, O., Borglum, A. D., Gustafsson, O., Werge, T., Mortensen, P. B., Andreassen, O. A., Sigurdsson, E., Thorgeirsson, T. E., Bottcher, Y., Olason, P., Ophoff, R. A., Cichon, S., Gudjonsdottir, I. H., Pietilainen, O. P. H., Nyegaard, M., Tuulio-Henriksson, A., Ingason, A., Hansen, T., Athanasiu, L., Suvisaari, J., Lonnqvist, J., Paunio, T., Hartmann, A., Jurgens, G., Nordentoft, M., Hougaard, D., Norgaard-Pedersen, B., Breuer, R., Moller, H. J., Giegling, I., Glenthoj, B., Rasmussen, H. B., Mattheisen, M., Bitter, I., Rethelyi, J. M., Sigmundsson, T., Fossdal, R., Thorsteinsdottir, U., Ruggeri, M., Tosato, S., Strengman, E., Kiemeney, L. A., Melle, I., Djurovic, S., Abramova, L., Kaleda, V., Walshe, M., Bramon, E., Vassos, E., Li, T., Fraser, G., Walker, N., Toulopoulou, T., Yoon, J., Freimer, N. B., Cantor, R. M., Murray, R., Kong, A., Golimbet, V., Jonsson, E. G., Terenius, L., Agartz, I., Petursson, H., Nothen, M. M., Rietschel, M., Peltonen, L., Rujescu, D., Collier, D. A., Stefansson, H., St Clair, D., Stefansson, K., Group (2011) Expanding the range of ZNF804A variants conferring risk of psychosis. Mol Psychiatry, 16:59-66.
43. Stone, J. L., O'Donovan, M. C., Gurling, H., Kirov, G. K., Blackwood, D. H. R., Corvin, A., Craddock, N. J., Gill, M., Hultman, C. M., Lichtenstein, P., McQuillin, A., Pato, C. N., Ruderfer, D. M., Owen, M. J., St Clair, D., Sullivan, P. F., Sklar, P., Purcell, S. M., Scolnick, E. M., Holmans, P. A., Georgieva, L., Nikolov, I., Norton, N., Williams, H., Williams, N. M., Toncheva, D., Milanova, V., Thelander, E. F., Morris, D. W., O'Dushlaine, C. T., Kenny, E., Waddington, J. L., Choudhury, K., Datta, S., Pimm, J., Thirumalai, S., Puri, V., Krasucki, R., Lawrence, J., Quested, D., Bass, N., Curtis, D., Crombie, C., Fraser, G., Kwan, S. L., Muir, W. J., McGhee, K. A., Pickard, B., Malloy, P., Maclean, A. W., Van Beck, M., Visscher, P. M., Macgregor, S., Pato, M. T., Medeiros, H., Middleton, F., Carvalho, C., Morley, C., Fanous, A., Conti, D., Knowles, J. A., Ferreira, C. P., Azevedo, M. H., McCarroll, S. A., Gates, C., Daly, M. J., Sklar, P., Consortium, I. S. (2008) Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature, 455:237-241.
44. Straub (2002) Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia (vol 71, pg 337, 2002). American Journal of Human Genetics, 71:1007-1007.
45. Sullivan, P. F., Kendler, K. S., Neale, M. C. (2003) Schizophrenia as a complex trait - Evidence from a meta-analysis of twin studies. Arch Gen Psychiatry, 60:1187-1192.
46. Sullivan, P. F., Lin, D., Tzeng, J. Y., van den Oord, E., Perkins, D., Stroup, T. S., Wagner, M., Lee, S., Wright, F. A., Zou, F., Liu, W., Downing, A. M., Lieberman, J., Close, S. L. (2008) Genomewide association for schizophrenia in the CATIE study: results of stage 1. Mol Psychiatry, 13:570-584.
47. Tang, J. X., Chen, W. Y., He, G., Zhou, J., Gu, N. F., Feng, G. Y., He, L. (2004) Polymorphisms within 5 ' end of the Neuregulin

1 gene are genetically associated with schizophrenia in the Chinese population. Mol Psychiatry, 9:11-12.
48. Tenyi, T. (2011) Neurodevelopment and schizophrenia: data on minor physical anomalies and structural brain imaging. Neuropsychopharmacol Hung, 13:229-232.
49. Visscher, P. M. (2008) Sizing up human height variation. Nature Genetics, 40:489-90.
50. Walsh, T., McClellan, J. M., McCarthy, S. E., Addington, A. M., Pierce, S. B., Cooper, G. M., Nord, A. S., Kusenda, M., Malhotra, D., Bhandari, A., Stray, S. M., Rippey, C. F., Roccanova, P., Makarov, V., Lakshmi, B., Findling, R. L., Sikich, L., Stromberg, T., Merriman, B., Gogtay, N., Butler, P., Eckstrand, K., Noory, L., Gochman, P., Long, R., Chen, Z., Davis, S., Baker, C., Eichler, E. E., Meltzer, P. S., Nelson, S. F., Singleton, A. B., Lee, M. K., Rapoport, J. L., King, M. C., Sebat, J. (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science, 320:539-43.
51. Williams, H. J., Norton, N., Dwyer, S., Moskvina, V., Nikolov, I., Carroll, L., Georgieva, L., Williams, N. M., Morris, D. W., Quinn, E. M., Giegling, I., Ikeda, M., Wood, J., Lencz, T., Hultman, C., Lichtenstein, P., Thiselton, D., Maher, B. S., Malhotra, A. K., Riley, B., Kendler, K. S., Gill, M., Sullivan, P., Sklar, P., Purcell, S., Nimgaonkar, V. L., Kirov, G., Holmans, P., Corvin, A., Rujescu, D., Craddock, N., Owen, M. J., O'Donovan, M. C., Schizophrenia, M. G., ISC, SGENE-Plus, GROUP (2011) Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol Psychiatry, 16:429-441.
52. Williams, J., Spurlock, G., McGuffin, P., Mallet, J., Nothen, M. M., Gill, M., Aschauer, H., Nylander, P. O., Macciardi, F., Owen, M. J. (1996) Association between schizophrenia and T102C polymorphism of the 5-hydroxytryptamine type 2a-receptor gene. European Multicentre Association Study of Schizophrenia (EMASS) Group. Lancet, 347:1294-6.
53. Williams, N. M., Preece, A., Mortis, D. W., Spurlock, G., Bray, N. J., Stephens, M., Norton, N., Williams, H., Clement, M., Dwyer, S., Curran, C., Wilkinson, J., Moskvina, V., Waddington, J. L., Gill, M., Corvin, A. P., Zammit, S., Kirov, G., Owen, M. J., O'Donovan, M. C. (2004) Identification in 2 independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (DTNBP1). Arch Gen Psychiatry, 61:336-344.
54. Williams, N. M., Preece, A., Spurlock, G., Norton, N., Williams, H. J., Zammit, S., O'Donovan, M. C., Owen, M. J. (2003) Support for genetic variation in neuregulin 1 and susceptibility to schizophrenia. Mol Psychiatry, 8:485-487.
55. Yang, J. Z., Si, T. M., Ruan, Y., Ling, Y. S., Han, Y. H., Wang, X. L., Zhou, M., Zhang, H. Y., Kong, Q. M., Liu, C., Zhang, D. R., Yu, Y. Q., Liu, S. Z., Ju, G. Z., Shu, L., Ma, D. L., Zhang, D. (2003) Association study of neuregulin 1 gene with schizophrenia. Mol Psychiatry, 8:706-709.
56. Zhang, F. Y., Chen, Q., Ye, T. Z., Lipska, B. K., Straub, R. E., Vakkalanka, R., Rujescu, D., St Clair, D., Hyde, T. M., Bigelow, L., Kleinman, J. E., Weinberger, D. R. (2011) Evidence of Sex-Modulated Association of ZNF804A with Schizophrenia. Biol Psychiatry, 69:914-917.
57. Zhao, X., Shi, Y., Tang, J., Tang, R., Yu, L., Gu, N., Feng, G., Zhu, S., Liu, H., Xing, Y., Zhao, S., Sang, H., Guan, Y., St Clair, D., He, L. (2004) A case control and family based association study of the neuregulin1 gene and schizophrenia. Journal of Medical Genetics, 41:31-34.

A szkizofrénia és a genetikai hajlam: mit tudunk, és mit hoz a jövő?

A szkizofrénia súlyos, komplex agyi betegség, egyértelmű genetikai és környezeti befolyásoltsággal. Az elmúlt évtizedekben dollármilliókat költöttek a megfoghatatlannak tűnő szkizofréniára hajlamosító gének kutatására, ám ezen kutatások igen csekély eredménnyel jártak. A kutatók számos genetikai variánst azonosítottak, amely hajlamossá tehet ugyan a betegség kialakulására, ám ezen variánsok önmagukban a betegség jelenlétét csak igen kis mértékben magyarázzák. A DISC1, NRG1, DTNBP1, RGS4, KCNH2, COMT, AKT1, és más, lehetségesnek vélt szkizofrénia-hajlamosító gén, a kópiaszám-variációkkal (copy number variations) együttesen sem képes a szkizofrén esetek legnagyobb részének magyarázatára. Továbbá a legtöbb, betegséggel összefüggésbe hozható genetikai variánst vizsgáló tanulmány gyakran nem reprodukálható és nem vezet megváltozott fehérjeszerkezethez sem. Mivel a széleskörű genetikai vizsgálatok nem hozták meg a kívánt eredményt, ma már biztosra vehetjük, hogy nincsenek erős hatású szkizofrénia-hajlamosító gének, és a genetikára alapozott terápia sem tűnik megvalósíthatónak. A fejlődéstani folyamatok és intracelluláris kaszkádmechanizmusok zavarai jelentik a szkizofrénia biológiai alapját, és ezért az új kezelések kifejlesztése a szkizofrén agyállomány funkcionális vizsgálataitól, valamint a genetikai és környezeti hatások között fellépő interakciók megértésétől függ.

Kulcsszavak: szkizofrénia, genetikai hajlam, hajlamosító gének, kópiaszám-variáció, copy number variation, genome-wide association studies