

“What a Psychiatrist Should Know About Genetics”

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Common Variants in Psychiatry – John Nurnberger, Wade Berrettini

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Why candidate gene studies are likely to be misleading.

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The most powerful common variant in neuropsychiatric disease.

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K,

Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE; Schizophrenia Working Group of the Psychiatric Genomics Consortium., Daly MJ, Carroll MC, Stevens B, McCarroll SA. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016 Feb 11;530(7589):177-83.

The MHC locus harbors one of the SZ risk alleles of largest effect. This paper demonstrates that the responsible allele is an insertion of a HERV (human endogenous retrovirus) sequence into the complement C4A and C4B genes.

Epigenetics - James Potash, Aaron Besterman, Wade Berrettini

What is gene expression? What influences it?

Razin A, Cedar H. DNA methylation and gene expression. *Microbiol Rev*. 1991 Sep;55(3):451-8.

Early description of the relationship between DNA methylation by two of the key people who first established this connection.

Felsenfeld G, Boyes J, Chung J, Clark D, Studitsky V. Chromatin structure and gene expression. *Proc Natl Acad Sci U S A*. 1996 Sep 3;93(18):9384-8. Review.

Early review of the relationship between chromatin configuration as (in part) established by histone marks and gene expression, by a key figure in that work (Felsenfeld).

How do environmental changes impact gene expression?

Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet*. 2003 Mar;33 Suppl:245-54. Review.

Well written review of how the environment impacts epigenetic marks and gene expression.

Hing B, Gardner C, Potash JB. Effects of negative stressors on DNA methylation in the brain: implications for mood and anxiety disorders. *Am J Med Genet B Neuropsychiatr Genet*. 2014 Oct;165B(7):541-54. Review.

Review of the impact of a key environmental signal for psychiatric illness—negative stressors—on epigenetic marks and gene expression in the brain.

GxG and GxE

Hall MA, Moore JH, Ritchie MD. Embracing complex associations in common traits: critical considerations for precision medicine. *Trends Genet*. 2016 Aug;32(8):470-84

Review of the importance of gene by gene and gene by environment interaction, particularly in relation to individual patient profiles.

Rakyan VK1, Down TA, Balding DJ, Beck S. Epigenome-wide association studies for common human diseases. *Nat Rev Genet*. 2011 Jul 12;12(8):529-41.

Excellent review of the key considerations for assessing epigenetic variation across the genome, and includes consideration of integration with GWAS.

How can we study changes in gene expression?

- role of peripheral cell studies

Sullivan PF, Fan C, Perou CM. Evaluating the comparability of gene expression in blood and brain. *Am J Med Genet B Neuropsychiatr Genet*. 2006 Apr 5;141B(3):261-8.

This is the first good assessment of how closely gene expression in blood correlates with expression in brain, across several brain regions.

Liu C, Marioni RE et al. A DNA methylation biomarker of alcohol consumption. Mol Psychiatry. 2016 Nov 15. [E-pub]

This is a good example of the use of DNA methylation measures derived from blood samples to create a biomarker of a psychiatrically relevant phenotype.

- brain collections and their use

Ladd-Acosta, C., J. Pevsner, S. Sabunciyar, R. H. Yolken, M. J. Webster, T. Dinkins, P. A. Callinan, J. B. Fan, J. B. Potash, and A. P. Feinberg. DNA methylation signatures within the human brain. Am J Hum Genet. 2007 81 (6):1304-15.

This paper assesses regional variation of DNA methylation in the human brain, and shows both commonalities, and also unique signatures across regions.

Hawrylycz MJ, Lein ES et al. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature. 2012 Sep 20;489(7416):391-9.

This paper from the Allen Brain Institute shows unique gene expression profiles across different brain regions.

- induced pluripotent stem cells

Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, Li Y, Mu Y, Chen G, Yu D, McCarthy S, Sebat J, Gage FH. Modelling schizophrenia using human induced pluripotent stem cells. Nature. 2011 May 12;473(7346):221-5.

This paper used iPS cells from patients with schizophrenia and compared them to those from controls. The authors converted the stem cells into neurons, and then showed a number of gene expression differences in the induced neurons from those with disease.

Mertens J...et al...Kelsoe JR, Gage FH, Yao J. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. Nature. 2015 Nov 5;527(7576):95-9.

This paper used the stem cell approach to create induced neurons from those with bipolar disorder, looking both at lithium responders and non-lithium responders. Treatment of the two sets of induced neurons with lithium yielded gene expression differences.

Methylation, acetylation, histone changes

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. Nat Neurosci. 2004 Aug;7(8):847-54.

This paper examined rats that had been exposed to "good" or "bad" mothering, and saw differences in gene expression of the glucocorticoid receptor genes, along with differences in DNA methylation in the promoter of the gene.

Tsankova, N. M., O. Berton, W. Renthal, A. Kumar, R. L. Neve, and E. J. Nestler. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci. 2006 9 (4):519-25.

Exposure of mice to a stress-induced model of depression led to changes in behavior accompanied by changes in histone modifications. The behavior and the histone changes were rescued by imipramine and fluoxetine.

Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holsboer F, Heim CM, Ressler KJ, Rein T, Binder EB. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci*. 2013 Jan;16(1):33-41.

This paper demonstrates an impact both of genetic and epigenetic variation in the HPA-axis gene FKBP5 on the relationship between childhood trauma and later stress-related psychiatric disorders.

Sun W, Poschmann J, Cruz-Herrera Del Rosario R, Parikshak NN, Hajan HS, Kumar V, Ramasamy R, Belgard TG, Elanggovan B, Wong CC, Mill J, Geschwind DH, Prabhakar S. Histone acetylome-wide association study of autism spectrum disorder. *Cell*. 2016 Nov 17;167(5):1385-1397.e11.

The authors conducted a histone acetylome-wide association study on 257 postmortem samples from autism patient and matched control brains, and found four variants related to disease.

Transgenerational epigenetic changes

Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neuroscience*. 2014 Jan;17(1):89-96.

The authors examined the inheritance of parental traumatic exposure in mice. They subjected mice to odor-invoked fear conditioning before conception and found that subsequently conceived generations had an increased behavioral sensitivity to the odor. This was associated with decreased methylation in sperm DNA for a relevant olfactory gene. This transgenerational effect appeared to be inherited via parental gametes.

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This paper demonstrate that the male rat offspring of cocaine-exposed sires display reduced propensity to self-administer cocaine and the F2 generation males display memory deficits.

Wimmer ME, Briand LA, Fant B, Guercio LA, Arreola AC, Schmidt HD, Sidoli S, Han Y, Garcia BA, Pierce RC. Paternal cocaine taking elicits epigenetic remodeling and memory deficits in male progeny. *Mol Psychiatry*. 2017 Mar 21. doi: 10.1038/mp.2017.71.

This paper demonstrate that the male rat offspring of cocaine-exposed sires display reduced propensity to self-administer cocaine and the F2 generation males display memory deficits.

Others

Epigenetic dynamics in psychiatric disorders: Environmental programming of neurodevelopmental processes - Daniel Kofinka, Marco P.M. Boksb, H.T. Marc Timmers c, Martien J. Kasa

How does the social environment 'get into the mind'? Epigenetics at the intersection of social and psychiatric epidemiology - Satoshi Toyokawa a,b, Monica Uddin c,d,*, Karestan C. Koenen Sandro Galea e

Epigenetic dynamics in psychiatric disorders: Environmental programming of neurodevelopmental processes - Daniel Kofinka, Marco P.M. Boksb, H.T. Marc Timmersc, Martien J. Kasa

Pharmacogenetics – Jim Kennedy, Gwyneth Zai, and Aaron Besterman

Bonvicini C, Faraone SV, Scassellati C. (2016) Attention-deficit hyperactivity disorder in adults: a systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies. *Mol Psychiatry* 21(7):872-84. Review

This review provides a comprehensive systematic review of all candidate gene association studies, pharmacogenetic and biochemical (metabolomics) studies in adult ADHD, in addition to a meta-analysis of a subset of these reviewed studies. The authors concluded that to date there were not enough studies to provide conclusive findings but confirmed a role of the brain-specific angiogenesis inhibitor 1-associated protein 2 (BAIAP2) in the etiology of ADHD. Future investigations are required to further elucidate the importance of genetics, pharmacogenetics, and biochemical factors in ADHD.

Fabbri C, Serretti. (2015) Pharmacogenetics of major depressive disorder: top genes and pathways toward clinical applications. *Curr Psychiatry Rep* 17(7):50. Review.

This is a review of pharmacogenetic studies of antidepressants in major depressive disorder. The authors concluded that cumulative evidence supports the involvement of several genes and molecular pathways in antidepressant response. These genes include: SLC6A4, HTR2A, BDNF, GNB3, FKBP5, ABCB1, CYP2D6, and CYP2C19.

Gressier F, Procelli S, Calati R, Serretti A. (2016) Pharmacogenetics of clozapine response and induced weight gain: a comprehensive review and meta-analysis. *Eur Neuropsychopharmacol* 26(2):163-85. Review.

This is a comprehensive review and meta-analysis of pharmacogenetics studies (published until May 2014) on clozapine efficacy, focusing on pharmacodynamic genes. The systematic review provided conflicting results and the meta-analyses detected significant findings for three genetic variants within the serotonergic system genes (HTR2A and HT3A) that were associated with clozapine response. The authors reported no conclusive results for clozapine-induced weight gain.

Hamilton SP (2015) The promise of psychiatric pharmacogenomics. *Biol Psychiatry* 77(1):29-35.

This article summarizes current pharmacogenetic results for psychotropic medication response and tolerability with stronger evidence from drug side effects including HLA loci with carbamazepine-induced dermatologic outcome and MC4R with atypical antipsychotic-induced weight gain.

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, et al. (2015) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther* 98(2):127-34. Review.

This review, published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), provides a guideline for adjusting SSRI dosage using CYP2D6 and CYP2C19 genotypes after summarizing evidence from the published literature. Updates can be found at www.pharmgkb.org.

MacNeil RR, Müller DJ. (2016) Genetics of common antipsychotic-induced adverse effects. *Mol Neuropsychiatry* 2(2):61-78. Review.

This article reviewed the literature on the pharmacogenetics of common antipsychotic-induced adverse effects including metabolic dysregulation, extrapyramidal symptoms (EPS), and Tardive dyskinesia (TD) from 2010 to 2015. The authors concluded that

HTR2C, MC4R, and OGFR1 are strong candidates with potential clinical utility for metabolic dysregulation, CYP2D6 metabolizer status has accumulated evidence for EPS and TD, and HSPG2 and DPP6 are potentials for predicting TD.

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The paper discussed the promise of personalized medicine in neuropsychiatric disorders.

Pisanu C, Melis C, Squassina A. (2016) Lithium pharmacogenetics: where do we stand? *Drug Dev Res* 77(7):368-73. Review.

The authors have written a comprehensive review on lithium pharmacogenomics. The large international collaborative effort published a recent paper, reporting a significant association for two long non-coding RNAs in lithium response.

Spina E, de Leon J. (2015) Clinical applications of CYP genotyping in psychiatry. *J Neural Transm (Vienna)* 122(1):5-28.

This article summarizes the evidence of cytochrome P450 genes that affects psychotropic medication response and side effects.

Lerer B (ed). (2002) *Pharmacogenetics of Psychotropic Drugs*. Cambridge University Press: New York.

This book provides an overview of psychiatric pharmacogenetics with 21 chapters written by leading neuroscientists. The introduction described the practical and theoretical foundations that organize the field of pharmacogenetics and the contents of this book.

Mrazek DA. (2012) *Psychiatric Pharmacogenomics*. Oxford University Press: New York.

This book provides a teaching guide for clinicians to order and use pharmacogenomics testing, and interpret the results to best choose pharmacotherapy for their patients.

Ethical and Social Issues Related to Genetics – Aaron Besterman, Dorothy Grice and John Nurnberger

Kevles DK, *In the name of eugenics*. Cambridge: Harvard U Press, 1995 (2nd edition).

This is a classic history of the abuse of genetic concepts for social and political reasons.

What research ethics should learn from genomics and society research: lessons from the ELSI Congress of 2011. Henderson GE, Juengst ET, King NM, Kuczynski K, Michie M. *J Law Med Ethics*. 2012 Winter;40(4):1008-24.

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Ethics and neuropsychiatric genetics: a review of major issues - Steven K. Hoge and Paul S. Appelbaum.

Principles of Genetic Counseling – Jehannine Austin

Smoller JW, Sheidley BR, and Tsuang MT (eds), *Psychiatric Genetics: Applications in Clinical Practice*. Arlington, VA: American Psychiatric Publishing, 2008.
Good chapters on clinical application, especially discussion of risk in chapter 3.

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Reviews clinical applicability of CNV data; applies concepts of population attributable risk and exposed attributable risk.

Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJ, Nurnberger JI Jr, and Hallmayer JF, Autism genetics: opportunities and challenges for clinical Translation. *Nature Reviews Genetics*, published online 3/17: <http://www.nature.com/nrg/journal/vaop/ncurrent/full/nrg.2017.4.html>.
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How to talk about etiology, genetics and environment as it relates to psychiatric illness.

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Leach E, Morris E, White H, Lehman A, Austin J. How do physicians decide to refer their patients for psychiatric genetic counseling? A qualitative study of physicians' practice. *Journal of Genetic Counseling* 2016 25(6):1235-1242.
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When to refer to clinical genetics services.

Family Studies and Heritability of Psychiatric Disorders – Lynn DeLisi

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Farmer A, Elkin A, McGuffin P. The genetics of bipolar affective disorder. *Curr Opin Psychiatry*. 2007 Jan;20(1):8-12. *This paper is an excellent review of the genetic epidemiology and family studies of bipolar disorder by a group of pioneers in this field.*

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Kety SS. Schizophrenic illness in the families of schizophrenic adoptees: findings from the Danish national sample. *Schizophr Bull*. 1988;14(2):217-22. PMID: 3201179. *This paper reviews the series of adoption studies led by Kety and Rosenthal in the 1970-80's.*

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familial environment. These studies changed the direction of the field and was of monumental importance.

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Rare Variants in Psychiatry – Daniel Moreno De Luca

General Psychiatry

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Autism Spectrum Disorders

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