MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychiatric Genetics in the Direct-to-Consumer Era

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Equities (<1%) in Pfizer, Merck, Abbvie

Learning objectives

- To review genetic measures that have been introduced into clinical psychiatry, or may be in the near-term
- To understand implications of direct-to-consumer genetic testing on routine care
- To anticipate patient questions on genetic testing, and be able to answer them based on the latest scientific evidence

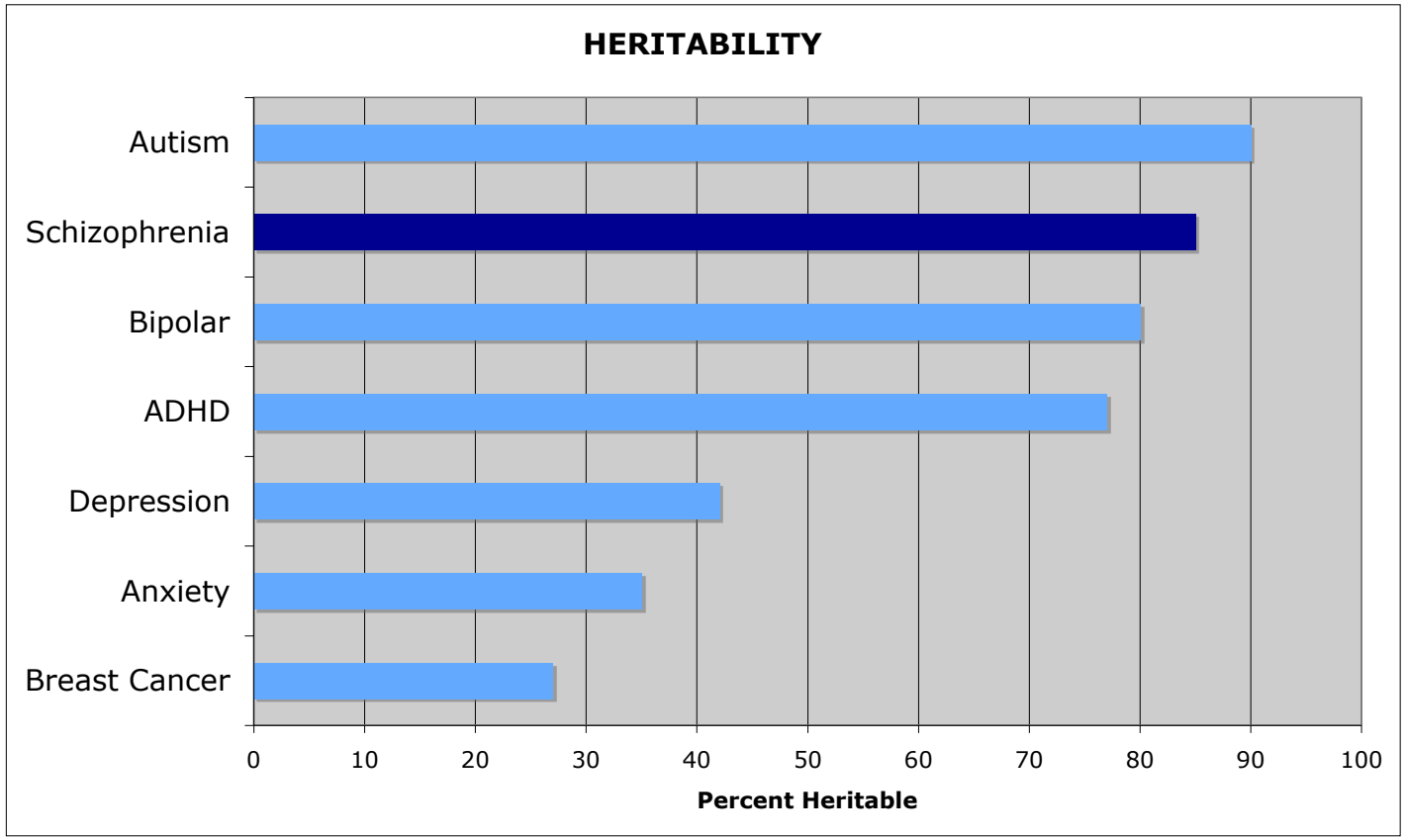
Case study

Your new patient is a 23 year old man with a diagnosis of schizophrenia, and who has persistent negative symptoms. He is accompanied by his parents, who have brought with them a report on their son's genetic profile from 23andMe®.

His parents are concerned that he is an "MTHFR double heterozygote" and want to know what this means for his long-term prognosis and treatment options.

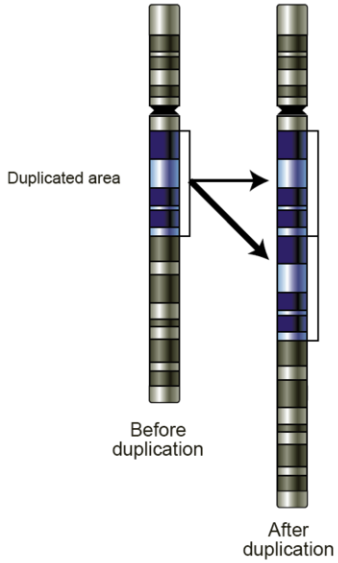
They have gone online and found several "MTHFR support groups," and based on what they have found are wondering if he should take a special form of folic acid called methylfolate.

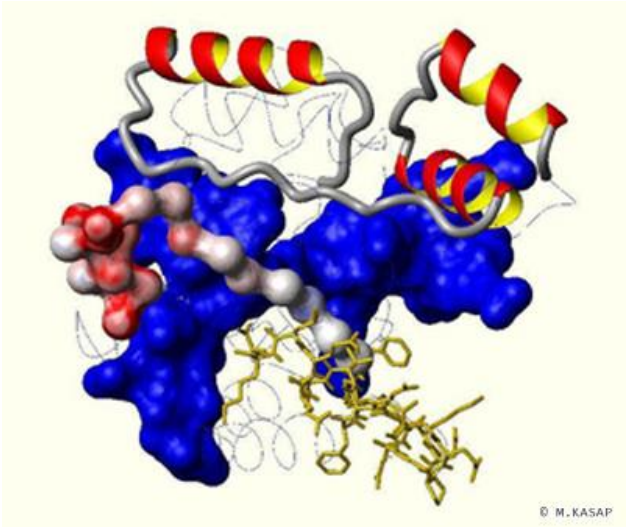
Why are genetics important?



Some basic terminology…

Copy Number Variant (CNV)





Possible consequences of CNV change:

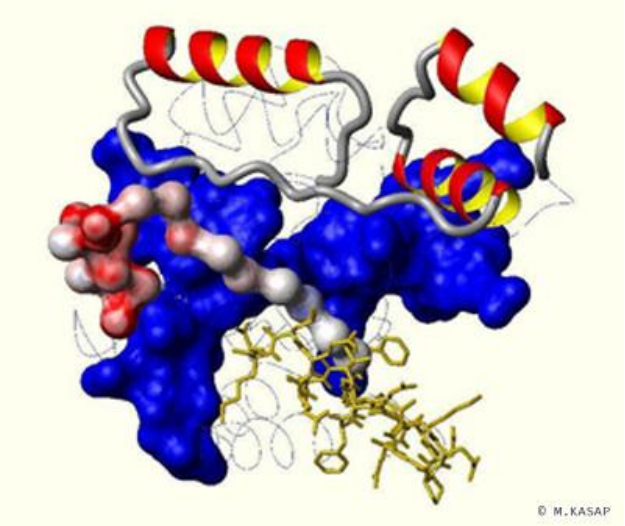
- Genes duplicated, deleted, or disrupted
- Amount and/or function of protein changes

Some basic terminology…

Single Nucleotide Polymorphism (SNP)

…A G C G T A A G A T C G T G A A C G T A G A C C…

…A G C G T A A C A T C G T G A A C G T A G A C C…

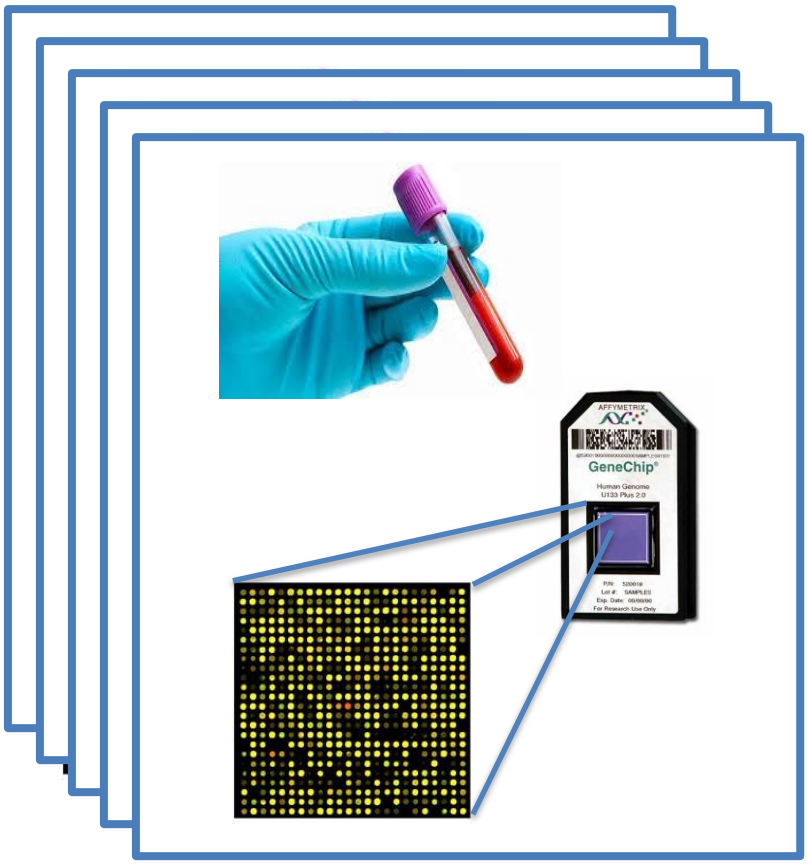


Possible consequences of G to C change:

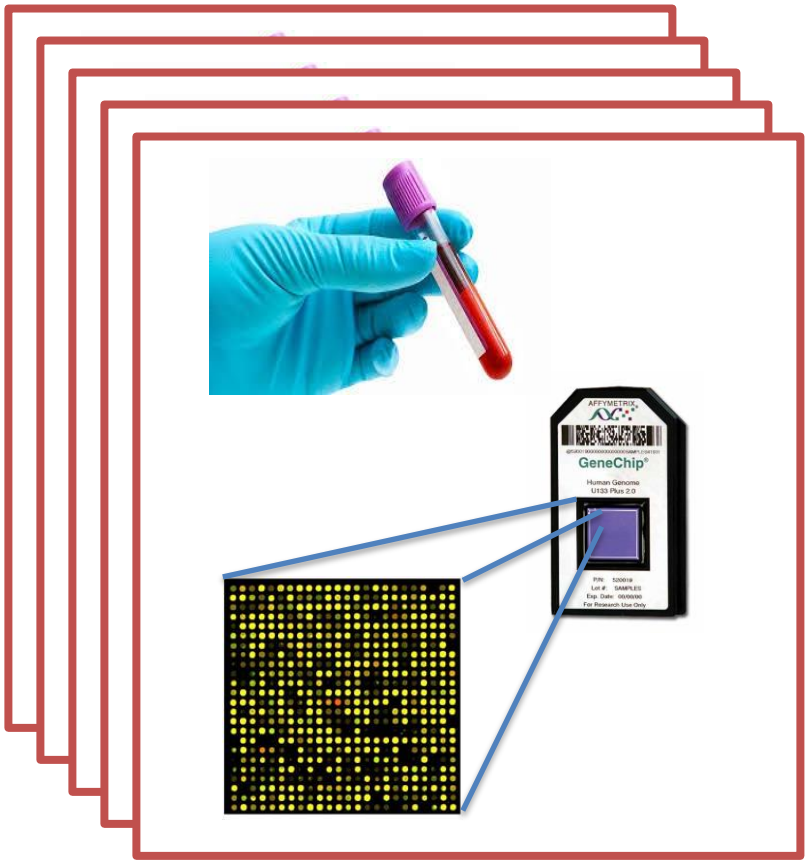
- Silent or unknown
- Change in protein structure
- Change in amount of protein that is made

Some basic terminology…

Genome Wide Association Study (GWAS)



x 1000's of healthy individuals

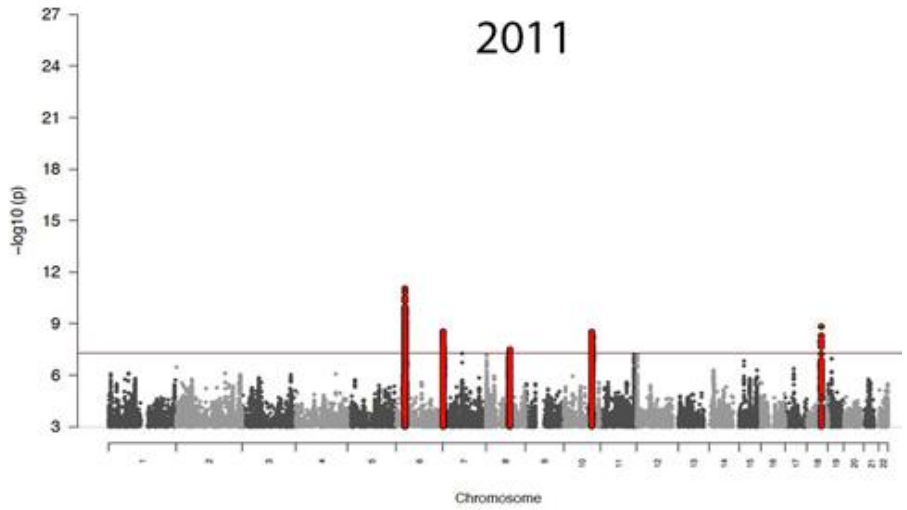


x 1000's of individuals with schizophrenia

Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)

Nat Genet 2011, Nature 2014



21,856 participants

5 loci

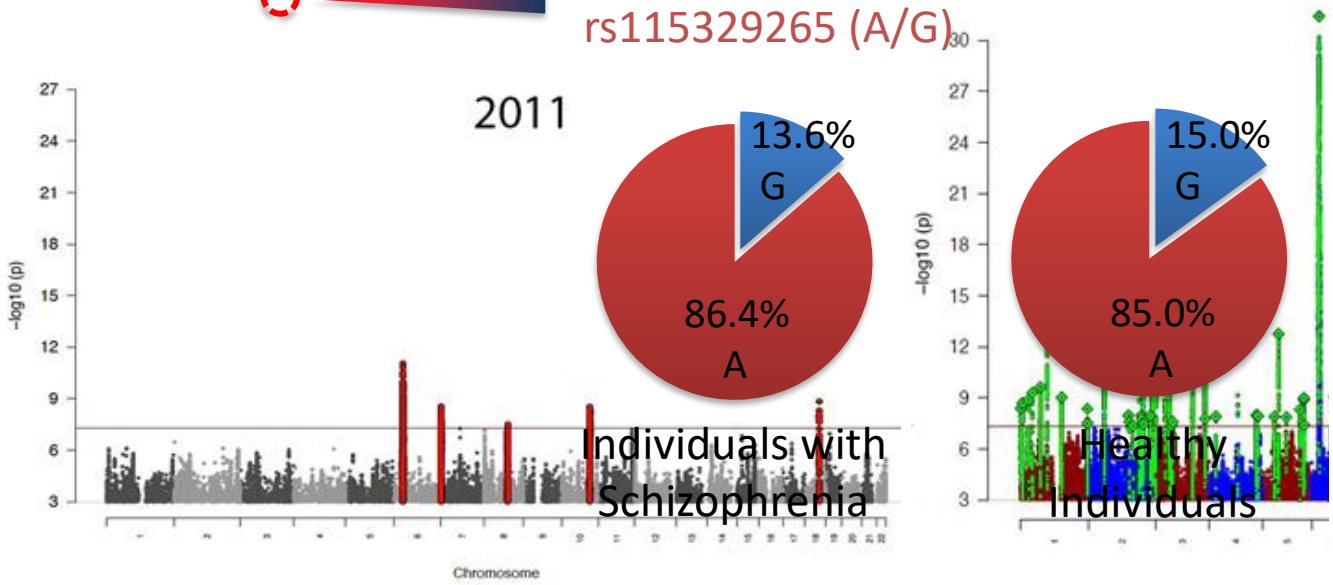
Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)

Nat Genet 2011, Nature 2014

Major Histocompatibility Complex (MHC)

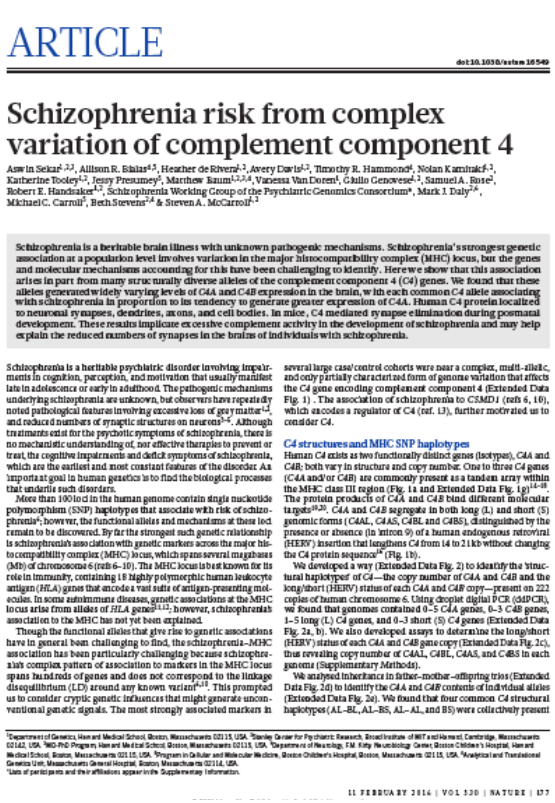
rs115329265 (A/G)



21,856 participants

5 loci

150



ARTICLE

doi:10.1038/nature16549

Schizophrenia risk from complex variation of complement component 4

Aswin Sekar[1,2,3], Allison R. Bialas[1,3], Heather de Rivera[1,3], Avery Davis[1,2], Timothy R. Hammond[4], Nolan Kamitaki[1,3], Katherine Tooley[1,2], Jessy Presumey[1], Matthew Baum[1,2,3,4], Vanessa Van Doren[1], Giulio Genovese[1,3], Samuel A. Rose[1], Robert E. Handsaker[1,3], Schizophrenia Working Group of the Psychiatric Genomics Consortium*, Mark J. Daly[3,5], Michael C. Carroll[1], Beth Stevens[1,4] & Steven A. McCarroll[1,3]

Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Here we show that this association arises in part from many structurally diverse alleles of the complement component 4 (*C4*) genes. We found that these alleles generate widely varying levels of *C4A* and *C4B* expression in the brain, with each common *C4* allele associating with schizophrenia in proportion to its tendency to generate greater expression of C4A. Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

Schizophrenia is a heritable psychiatric disorder involving impairments in cognition, perception, and motivation that usually manifest late in adolescence or early in adulthood. The pathogenic mechanisms underlying schizophrenia are unknown, but observers have repeatedly noted pathological features involving excessive loss of grey matter[1,2] and reduced numbers of synaptic structures on neurons[3–6]. Although treatments exist for the psychotic symptoms of schizophrenia, there is no mechanistic understanding of, nor effective therapies to prevent or treat, the cognitive impairments and deficit symptoms of schizophrenia, which are the earliest and most constant features of the disorder. An important goal in human genetics is to find the biological processes that underlie such disorders.

More than 100 loci in the human genome contain single nucleotide polymorphism (SNP) haplotypes that associate with risk of schizophrenia[7]; however, the functional alleles and mechanisms at these loci remain to be discovered. By far the strongest such genetic relationship is schizophrenia's association with genetic markers across the major histocompatibility complex (MHC) locus, which spans several megabases (Mb) of chromosome 6 (refs 6–10). The MHC locus is best known for its role in immunity, containing 18 highly polymorphic human leukocyte antigen (*HLA*) genes that encode a vast suite of antigen-presenting molecules. In some autoimmune diseases, genetic associations at the MHC locus arise from alleles of *HLA* genes[11,12]; however, schizophrenia's association to the MHC has not yet been explained.

Though the functional alleles that give rise to genetic associations have in general been challenging to find, the schizophrenia–MHC association has been particularly challenging because schizophrenia's complex pattern of association to markers in the MHC locus spans hundreds of genes and does not correspond to the linkage disequilibrium (LD) around any known variant[6,13]. This prompted us to consider cryptic genetic influences that might generate unconventional genetic signals. The most strongly associated markers in several large case/control cohorts were near a complex, multi-allelic, and only partially characterized form of genome variation that affects the *C4* gene encoding complement component 4 (Extended Data Fig. 1). The association of schizophrenia to *CSMD1* (refs 6, 10), which encodes a regulator of C4 (ref. 13), further motivated us to consider *C4*.

C4 structures and MHC SNP haplotypes

Human *C4* exists as two functionally distinct genes (isotypes), *C4A* and *C4B*; both vary in structure and copy number. One to three *C4* genes (*C4A* and/or *C4B*) are commonly present as a tandem array within the MHC class III region (Fig. 1a and Extended Data Fig. 1g)[14–18]. The protein products of *C4A* and *C4B* bind different molecular targets[19,20]. *C4A* and *C4B* segregate in both long (L) and short (S) genomic forms (*C4AL*, *C4AS*, *C4BL* and *C4BS*), distinguished by the presence or absence (in intron 9) of a human-endogenous retroviral (HERV) insertion that lengthens *C4* from 14 to 21 kb without changing the C4 protein sequence[16] (Fig. 1b).

We developed a way (Extended Data Fig. 2) to identify the structural haplotypes of *C4*—the copy number of *C4A* and *C4B* and the long/short (HERV) status of each *C4A* and *C4B* copy—present on 222 copies of human chromosome 6. Using droplet digital PCR (ddPCR), we found that genomes contained 0–5 *C4A* genes, 0–3 *C4B* genes, 1–5 long (L) *C4* genes, and 0–3 short (S) *C4* genes (Extended Data Fig. 2a, b). We also developed assays to determine the long/short (HERV) status of each *C4A* and *C4B* gene copy (Extended Data Fig. 2c), thus revealing copy number of *C4AL*, *C4BL*, *C4AS*, and *C4BS* in each genome (Supplementary Methods).

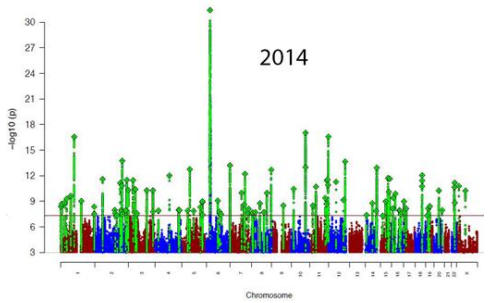
We analysed inheritance in father–mother–offspring trios (Extended Data Fig. 2d) to identify the *C4A* and *C4B* contents of individual alleles (Extended Data Fig. 2e). We found that four common *C4* structural haplotypes (AL–BL, AL–BS, AL–AL, and BS) were collectively present

[1]Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA. [2]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142, USA. [3]MD-PhD Program, Harvard Medical School, Boston, Massachusetts 02115, USA. [4]Department of Neurology, F.M. Kirby Neurobiology Center, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA. [5]Program in Cellular and Molecular Medicine, Boston Children's Hospital, Boston, Massachusetts 02115, USA. [6]Analytical and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
*Lists of participants and their affiliations appear in the Supplementary Information.

Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)

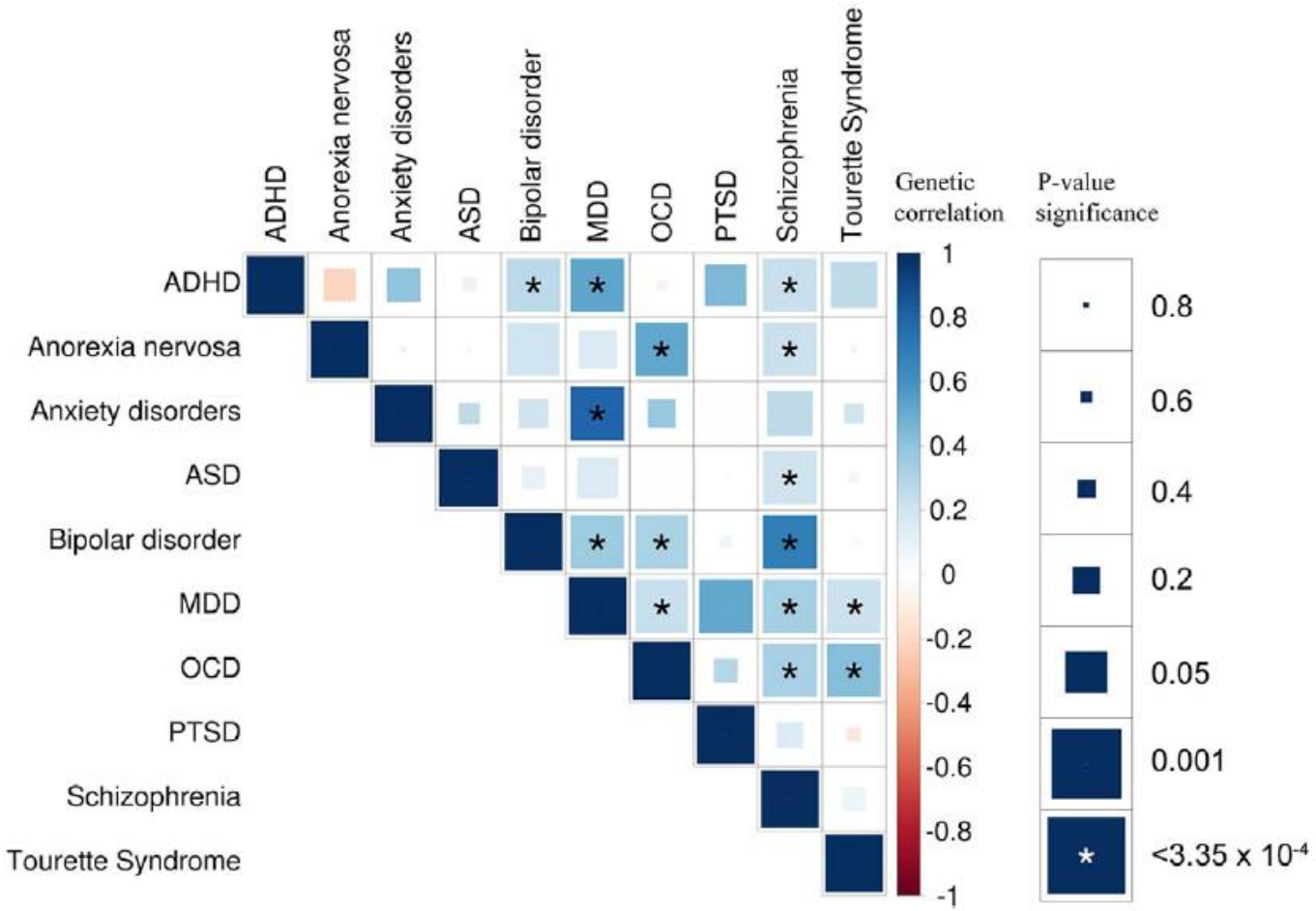
Nat Genet 2011, Nature 2014



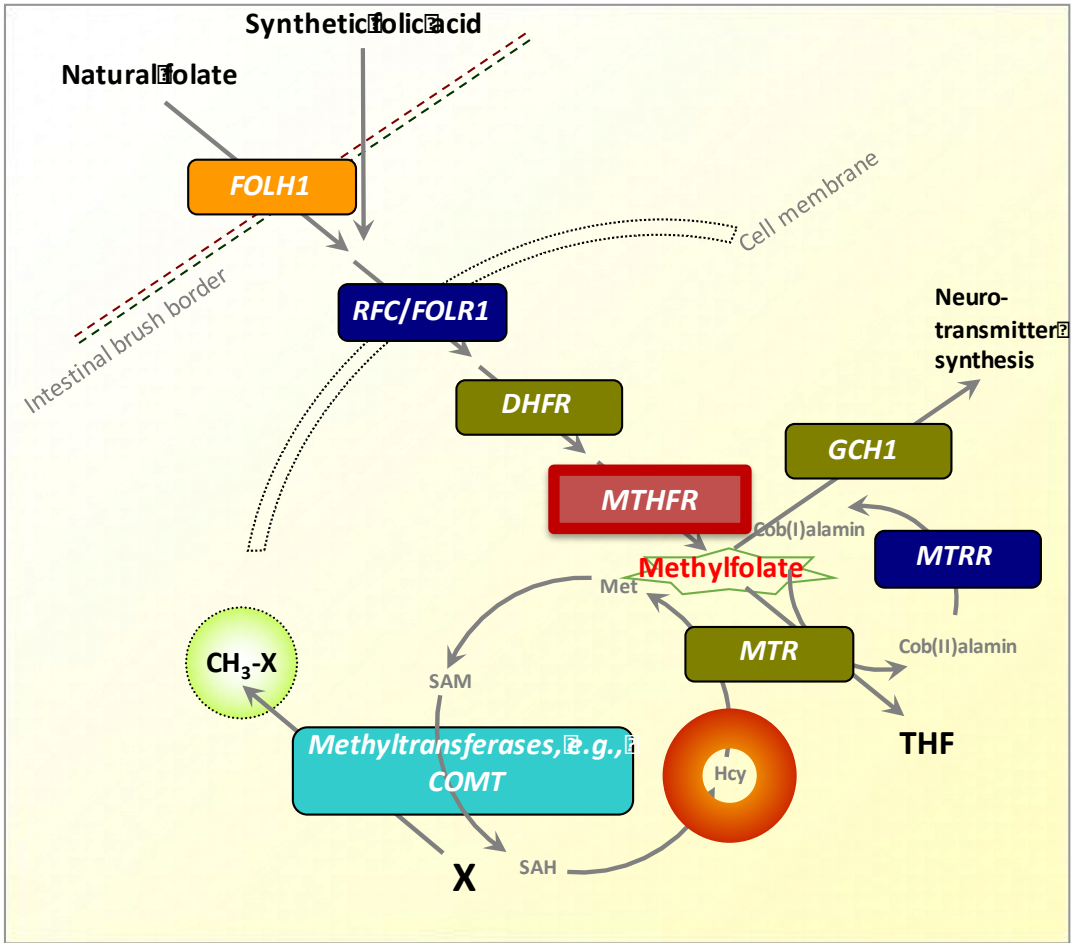
>18% of genetic risk explained by common genetic variants

Polygenic risk

Brainstorm Consortium, Science 2018



MTHFR

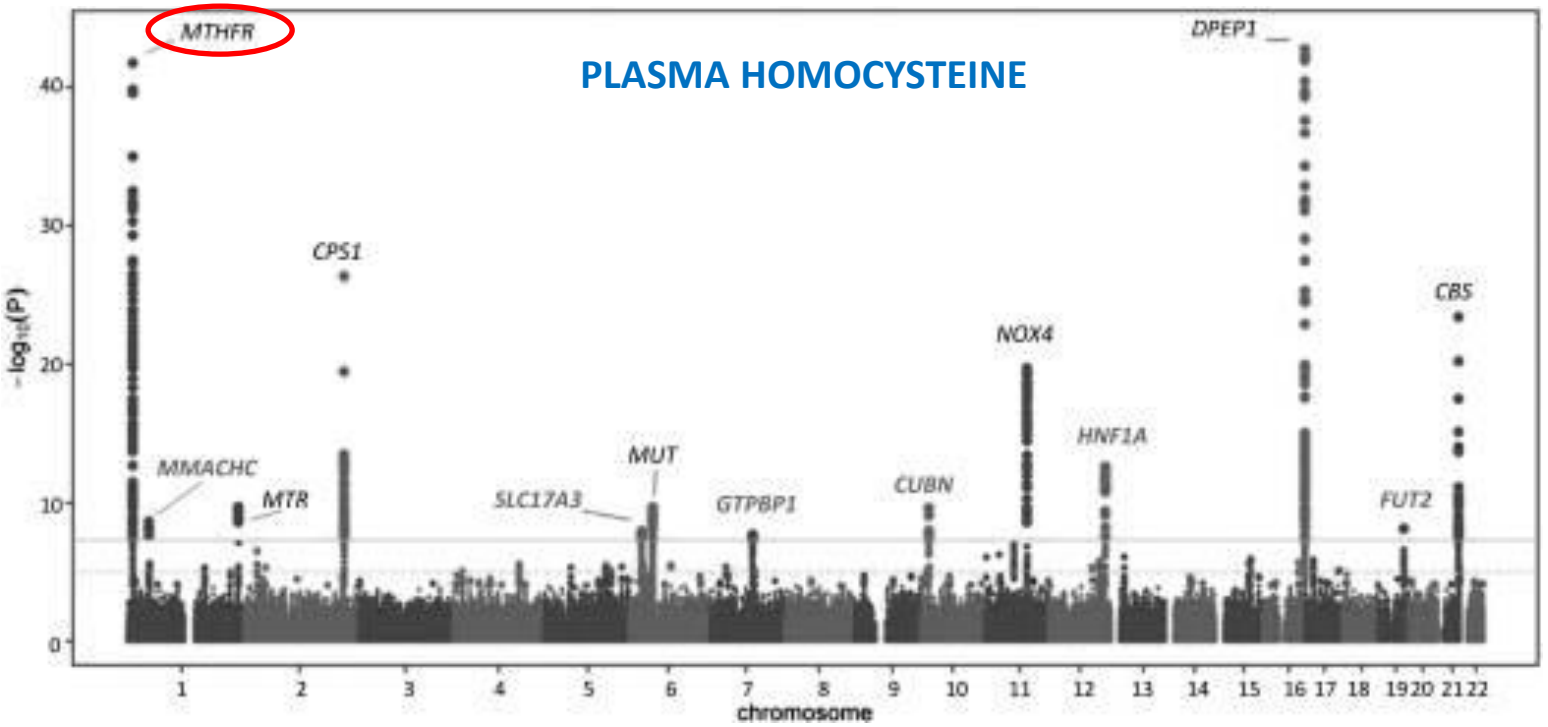


Common variants:

rs1801133
677C>T
222Ala>Val

rs1801131
1298A>C
429Glu>Ala

MTHFR



van Meurs et al., Am J Med Nutr 2013

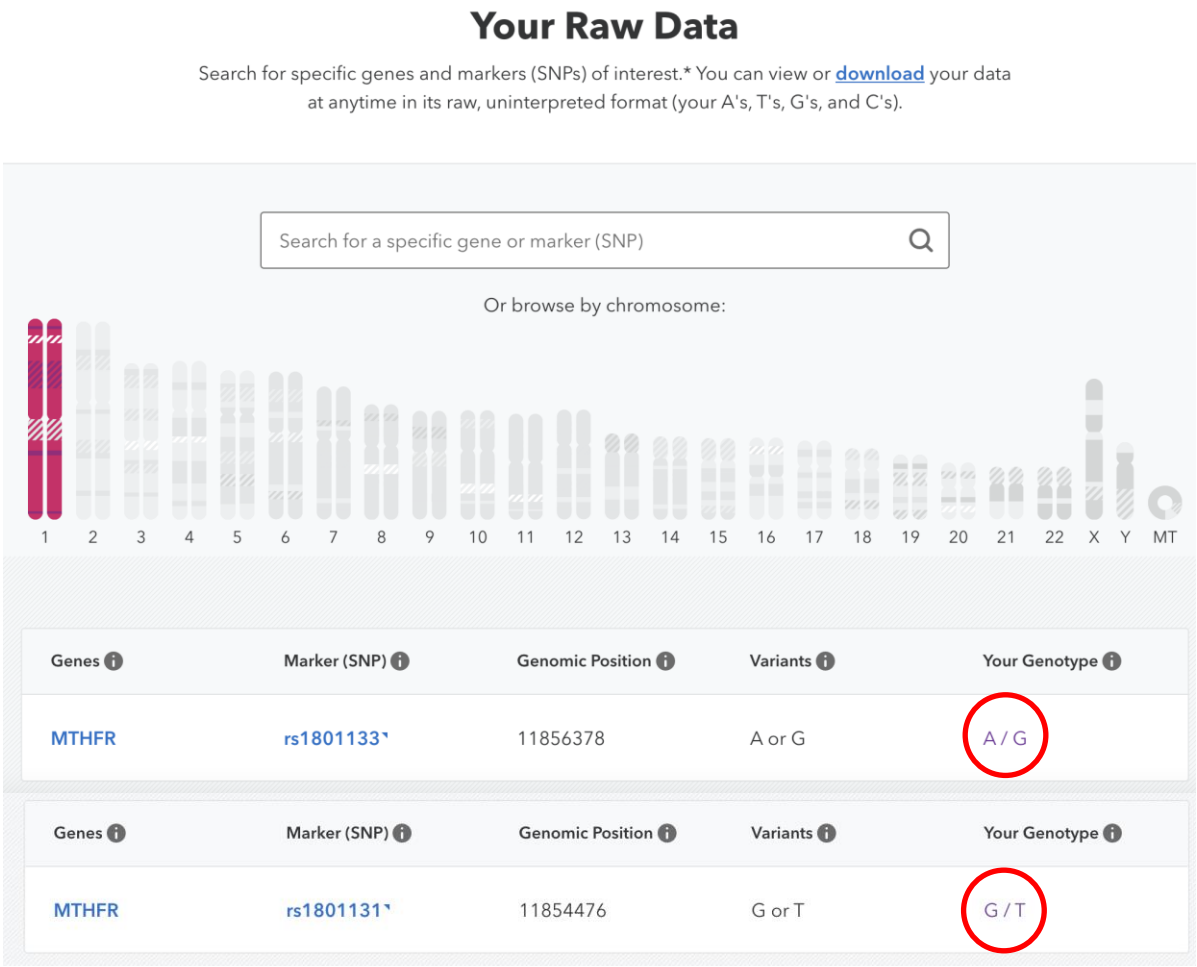
MTHFR “double heterozygote”

rs1801133
Copy 1: 677C
Copy 2: 677T

rs1801131
Copy 1: 1298A
Copy 2: 1298C

…~40% of the U.S. population are double heterozygotes

MTHFR “double heterozygote”



MTHFR genotype: clinical value

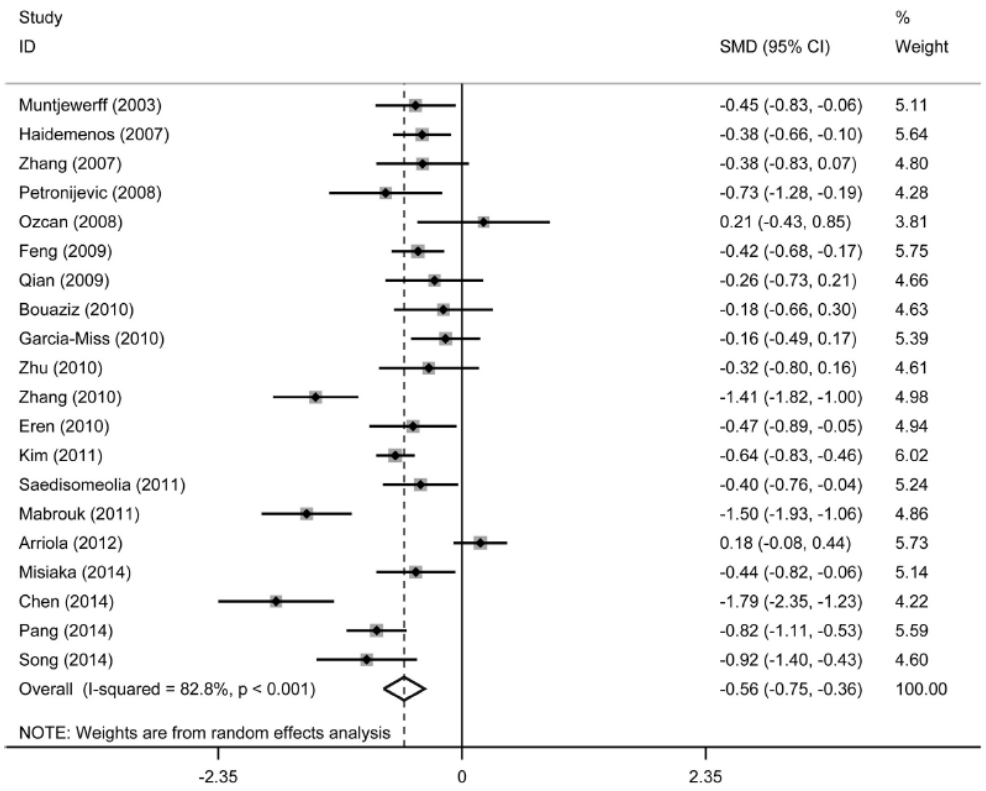
- Does being a double heterozygote increase risk for schizophrenia?

  …No

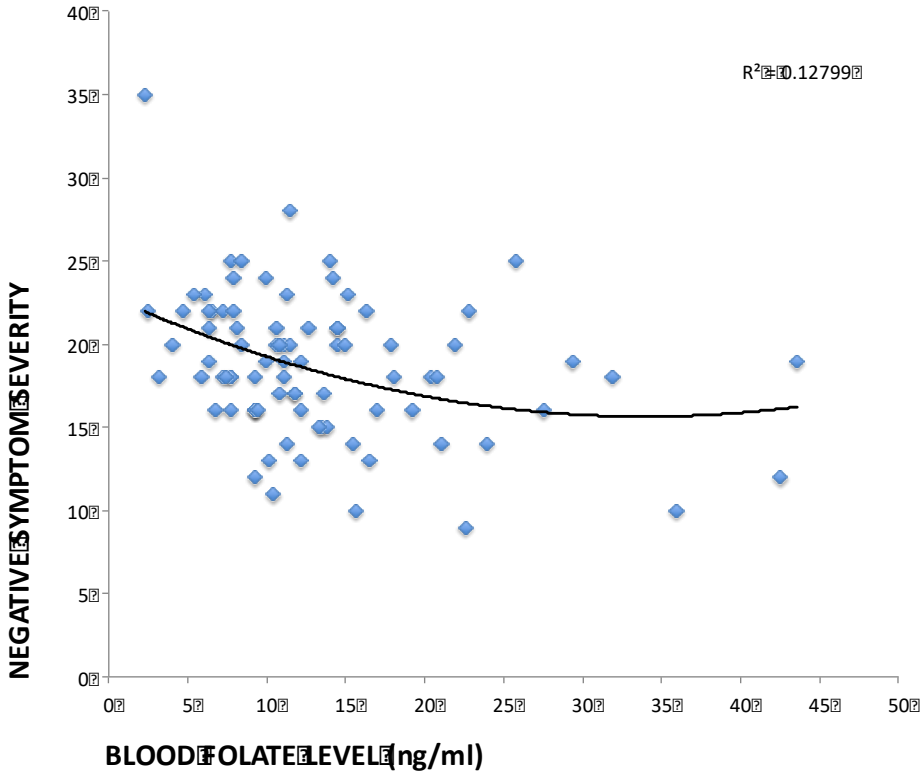
- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?

  …Maybe

Folate and negative symptoms

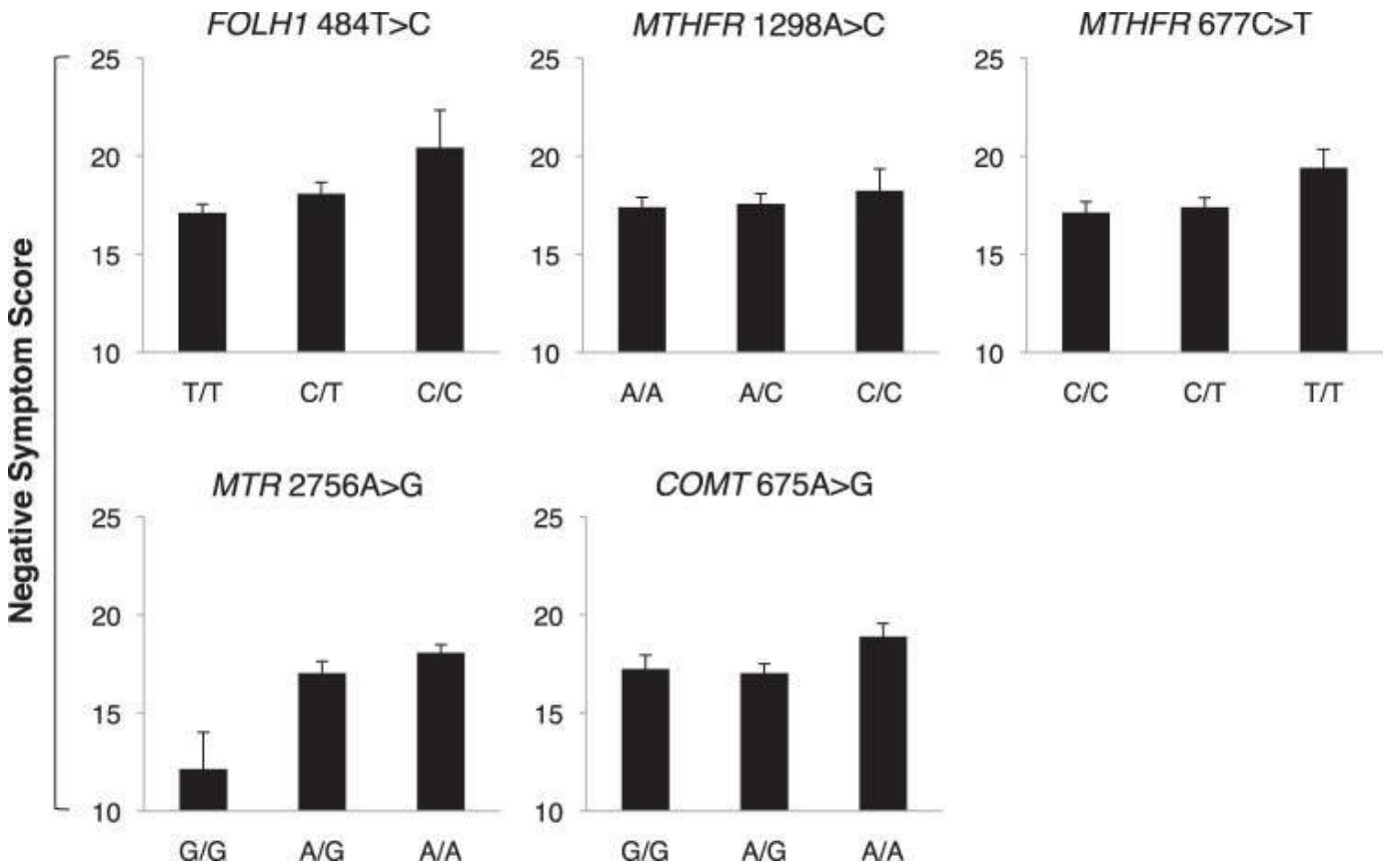


Cao et al., Psychiatry Res 2016



Goff et al, Am J Psychiatry 2004

MTHFR and negative symptoms



Roffman et al., Schiz Bull 2013

MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia?

  …No

- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?

  …Maybe

- Does taking folic acid help?

  …Maybe

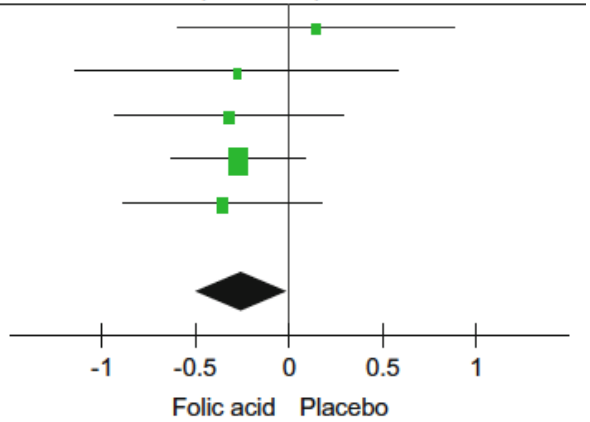
Folic acid for negative symptoms

	N	*n*	I^2 (%)	SMD	WMD	95% CI	*p* value
Total symptoms[a]	7	340	0	−0.20		−0.41 to 0.02	0.08
Negative symptoms	5	281	0	−0.25		−0.49 to −0.01	0.04
PANSS positive subscale score	4	260	21		−0.07	−0.69 to 0.55	0.83
PANSS general subscale score	2	97	0		−1.57	−3.62 to 0.48	0.13
CDSS score	5	281	28		0.18	−0.45 to 0.81	0.58

	Folic acid			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Hill 2011	-8.5	7.6	14	-9.7	8.5	14	10.6%	0.14 [-0.60, 0.89]
ISRCTN32434568	19.6	5.2	10	21.4	6.9	11	7.8%	-0.28 [-1.14, 0.58]
Levine 2006	-1.7	3.13049517	20	-0.8	2.34520788	22	15.6%	-0.32 [-0.93, 0.29]
Roffman 2013	-0.19	0.77012091	89	0.02	0.76128194	46	45.5%	-0.27 [-0.63, 0.09]
Roffman 2017	-0.5	8.2425992	29	2.4	7.8046217	26	20.4%	-0.36 [-0.89, 0.18]
Total (95% CI)			**162**			**119**	**100.0%**	**-0.25 [-0.49, -0.01]**

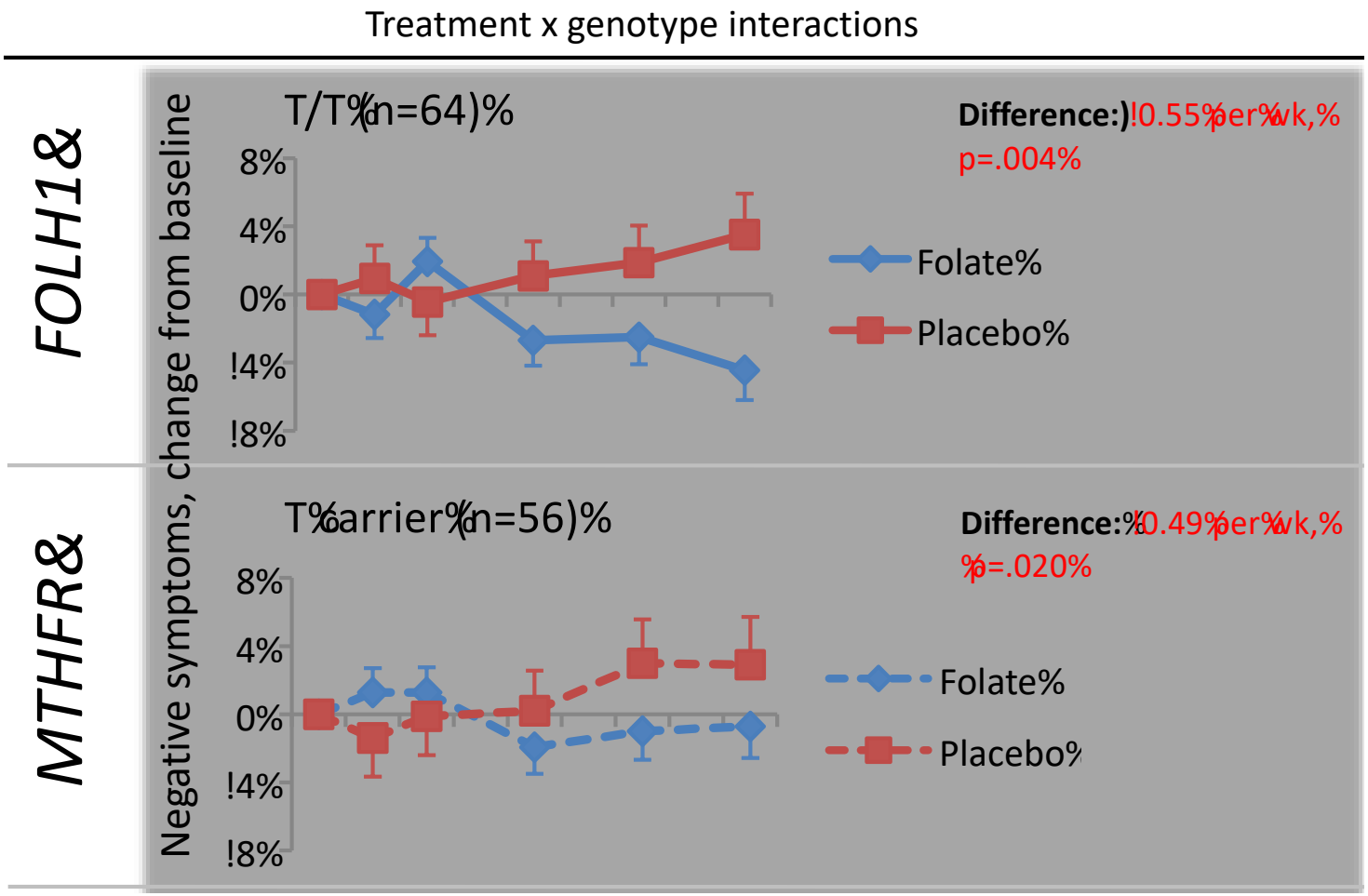
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 4 (P = 0.86); I² = 0%

Test for overall effect: Z = 2.06 (P = 0.04)



Sakuma et al., Psychopharmacology, 2018

Folic acid for negative symptoms



Roffman et al., JAMA Psychiatry, 2013

MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia?

  …No

- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?

  …Maybe

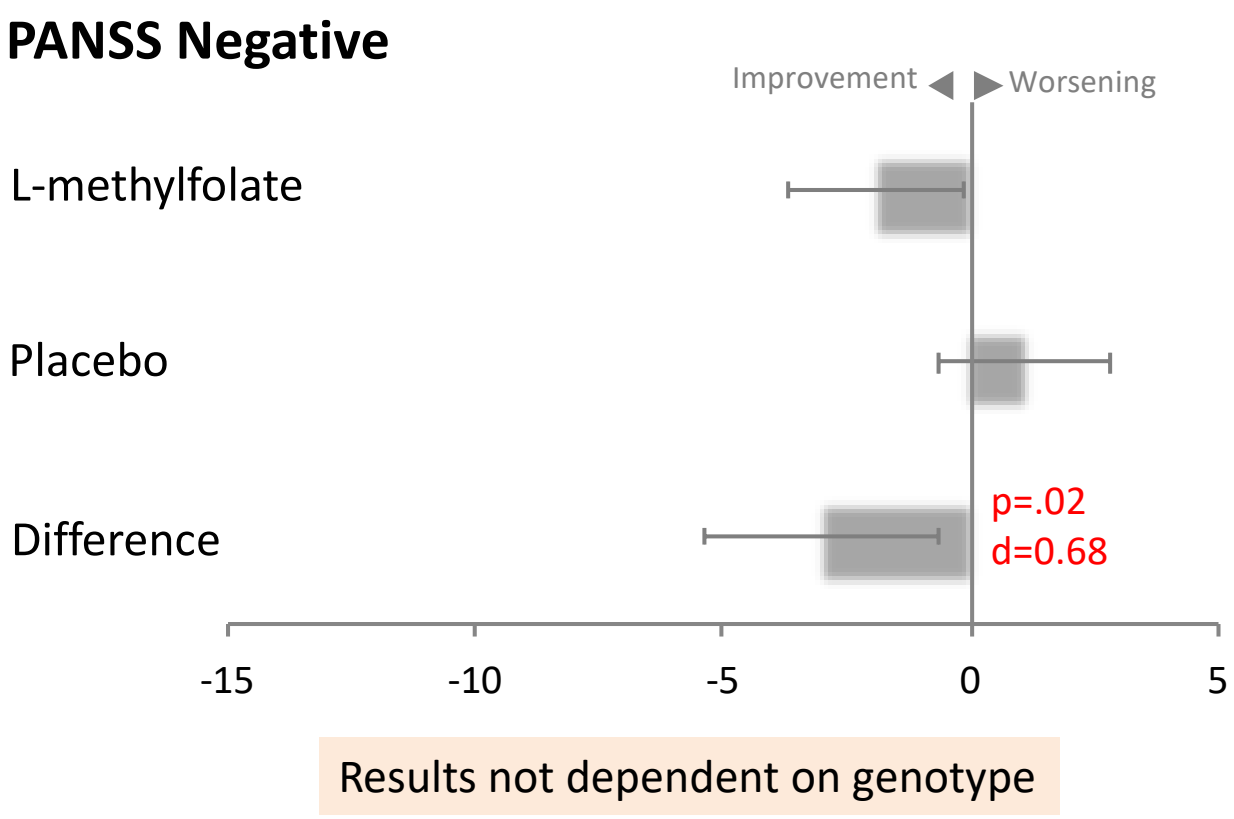
- Does taking folic acid help?

  …Maybe

- Should methylfolate be taken instead of folic acid?

  …Maybe

Methylfolate for negative symptoms



Results not dependent on genotype

Roffman et al., Mol Psychiatry, 2017

Does MTHFR genotype add value?

- Worried about low serum folate?

  …Check it. No need to genotype, at 10x the cost, and questionable utility.

- Does your patient have negative symptoms?

  …No good reason not to treat empirically with folic acid first.

- But could MTHFR genotype help get to methylfolate more quickly?

  …Insufficient evidence to say, either from cost effectiveness or efficacy perspective.

Even 23andMe® agrees…

23andMeBlog

HOME CATEGORIES ALL POSTS

Our Take On The MTHFR Gene

January 5, 2017 By 23andMe under Health and Traits

The *methylenetetrahydrofolate reductase gene*, more commonly known as MTHFR, is the most asked-about gene by 23andMe customers.

Some websites and products have made bold claims that common genetic variants in MTHFR can cause a wide array of health conditions, ranging from blood clots and cancer to autism and migraines. So we decided to dig deeper into the published scientific literature to evaluate the evidence.

Our conclusion?

Despite lots of research – and lots of buzz – the existing scientific data doesn't support the vast majority of claims that common MTHFR variants impact human health.

Most Discussed Variants in the MTHFR Gene

…but the genie is out of the bottle

First came the home DNA kits. Now come the support groups

23 and Me is one of the companies offering home DNA tests. (Nathan Siemers/Creative Commons)

By Beth Teitell | GLOBE STAFF FEBRUARY 24, 2019

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Genetics company 23andMe is rolling out a huge initiative for people with ADHD and depression — but psychologists are worried

Erin Brodwin Apr. 30, 2018, 11:42 AM

Hollis Johnson

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TECH

23andMe Is Terrifying, but Not for the Reasons the FDA Thinks

The genetic-testing company's real goal is to hoard your personal data

By Charles Seife on November 27, 2013

When *is* genetic testing indicated?

- **FDA guidance:**

HLA-B*1502 prior to carbamazepine in patients of Asian descent (boxed warning)
Other pharmacogenomic panels (PGx):

CYP2D6	Clomipramine	Imipramine	Thioridazine
	Clozapine	Modafinil	Trimipramine
Amitriptyline	Desipramine	Nefazodone	Venlafaxine
Amoxapine	Desvenlafaxine	Nortriptyline	Vortioxetine
Amphetamine	Doxepin	Paliperidone	
Arapiprazole	Duloxetine	Paroxetine	CYP2C19
Atomoxetine	Escitalopram	Perphenazine	
Brexpiprazole	Fluoxetine	Pimozide	Citalopram
Carprazine	Fluvoxamine	Protriptyline	Doxepin
Citalopram	Iloperidone	Risperidone	Escitalopram

Consensus is that they are of limited value in routine clinical use – e.g., among Caucasians, 7-10% are poor metabolizers and <1% are ultrarapid metabolizers

- **Autism spectrum disorder with intellectual disability** (Copy number variants)
- **Updated recommendations:** https://ispg.net/genetic-testing-statement/

Conclusions and recommendations

- At present, there is no high-quality evidence to support use of direct-to-consumer genetic testing to guide clinical decision-making
- More broadly, despite significant research advances on genetic origins of psychiatric illness, genetic testing is unlikely to be of routine benefit in the clinic in the near term
- Watch this space though…

Proof-of-concept…

RISK STRATIFICATION

Table 4. Coronary Artery Calcification Burden, by Polygenic Risk Score Quintile in CARDIA (Coronary Artery Risk Development in Young Adults)

Polygenic Risk Score Quintile	CAC>1%, %	CAC >0*	
		OR (95% CI)	*P* Value
1	8.7	1	
2	12.1	2.08 (0.89–4.83)	0.09
3	10.9	2.08 (0.87–4.98)	0.10
4	14.3	3.02 (1.31–7.00)	0.01
5 (High)	15.6	2.51 (1.08–5.85)	0.04

Natarajan et al., Circulation 2017

Thank you!

PREVENTION

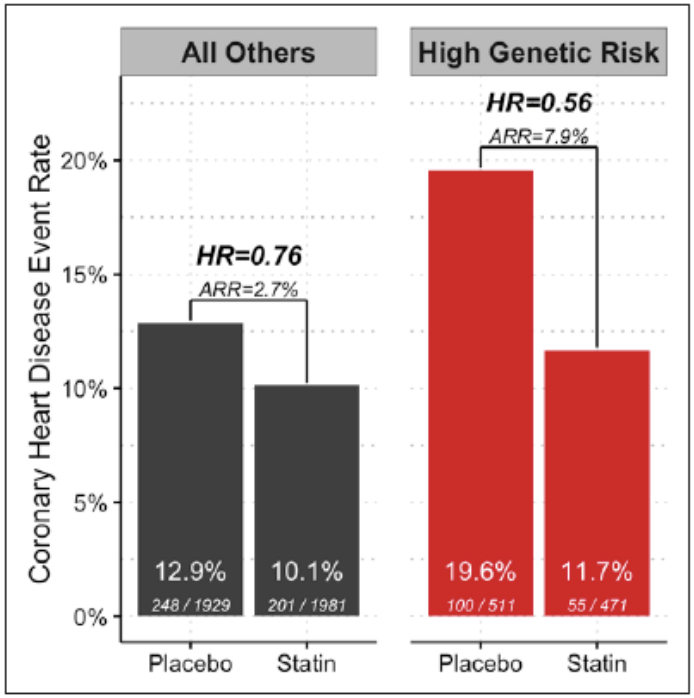

Figure 1. Incident coronary heart disease events by statin therapy and genetic risk group in WOSCOPS (West of Scotland Coronary Prevention Study).