



Genetic Etiology of

Mental Health Disorders

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5 Mental Health Disorders Found Share Genetic Etiology

1. Autism
2. ADHD
3. Schizophrenia
4. Bipolar Disorder
5. Major Depressive Disorder

Hong, L.S., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goodard, M.E., Witte, J.S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O.A., Anjoriin, A., Anney, R., Anttila, V., Arking, D.E. & Asherson, P. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics* 45(9), 984-994.

2013 Study by Hong et al-What did they study?

First what's SNPs?

- ▶ Hong et al, used SNPs to see if there was a common genetic link for the five psychiatric conditions
- ▶ Single nucleotide polymorphisms, frequently called SNPs (pronounced “snips”), are the most common type of genetic variation among people
- ▶ SNPs occur normally throughout a person's DNA
- ▶ They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome
- ▶ Most commonly, these variations are found in the DNA between genes
- ▶ They can act as biological markers, helping scientists locate genes that are associated with disease
- ▶ When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene's function
- ▶ SNPs can also be used to track the inheritance of disease genes within families

2013 Study by Hong et al-What did they study?

Five psychiatric disorders

- ▶ Most **psychiatric disorders** are moderately to highly heritable, but the degree to which **genetic variation** is unique to individual **disorders** or shared across **disorders** is unclear
- ▶ They examined shared **genetic etiology**, by using genome-wide genotype data from the **Psychiatric Genomics Consortium (PGC)** for cases and controls in schizophrenia, bipolar **disorder**, major depressive **disorder**, autism spectrum **disorders (ASD)** and attention-deficit/hyperactivity **disorder (ADHD)**

2013 Study by Hong et al

What did they find?

Genetic correlation calculated using common SNPs was

- ▶ High **between** schizophrenia and bipolar disorder (0.68 ± 0.04 s.e.),
- ▶ Moderate **between** schizophrenia and major depressive disorder (0.43 ± 0.06 s.e.), bipolar disorder and major depressive disorder (0.47 ± 0.06 s.e.), and ADHD and major depressive disorder (0.32 ± 0.07 s.e.)
- ▶ Low **between** schizophrenia and Autism Spectrum Disorder (ASD) (0.16 ± 0.06 s.e.)
- ▶ Non-significant for other pairs of **disorders** as well as **between psychiatric disorders** and the negative control of Crohn's disease
- ▶ They concluded: This empirical evidence of shared **genetic etiology** for **psychiatric disorders** can inform nosology (classification of diseases) & encourages the investigation of common pathophysiologies for related **disorders**

At the Beginning of the 21st Century there was acceptance of Genetic Etiology of Mental Illness

Hyman (2000) concluded that:

It was well established that the risk of mental illness runs in families. Family, twin and adoption studies had shown that for:

- ▶ Schizophrenia
- ▶ Autism
- ▶ Bipolar Disorder
- ▶ Major Depression
- ▶ Attention Deficit Hyperactivity Disorder (ADHD)
- ▶ Panic Disorder
- ▶ Other mental illnesses,
- ▶ the transmission of risk is due to heredity

Hyman, S.E. (2000). The genetics of mental illness: Implications for practice. *Bulletin of the World Health Organization*, 78(4), 455-463.

What was the thinking at the Beginning of this Century

In 2001, some examples of genes thought to be associated with different disorders or traits

Gene	Alleles	Associated Disorder or Trait
Dopamine D4 receptor (DRD4)	Long	ADHD
Serotonin transporter (5-HTT)	Short	Neuroticism Bipolar Disorder
Serotonin 2a receptor (5-HT2a)	C polymorphism	Schizophrenia

Link to Chromosome 18?

Kamnasaren (2003) found that linkage, association and chromosome aberration studies have suggested that intervals on both the short arm (p) and long arm (q) of chromosome 18 may contain genes for psychiatric disorders:

- ▶ Autism
- ▶ Schizophrenia
- ▶ Affective disorders

Kamnasaran, D. (2003). 2003 Genetic analysis of psychiatric disorders associated with human chromosome 18. *Clinical & Investigative Medicine*, 26(6), 285-302.

Impact of Family, Twin & Adoption Studies by 2004

Shih et al (2004) concluded that:

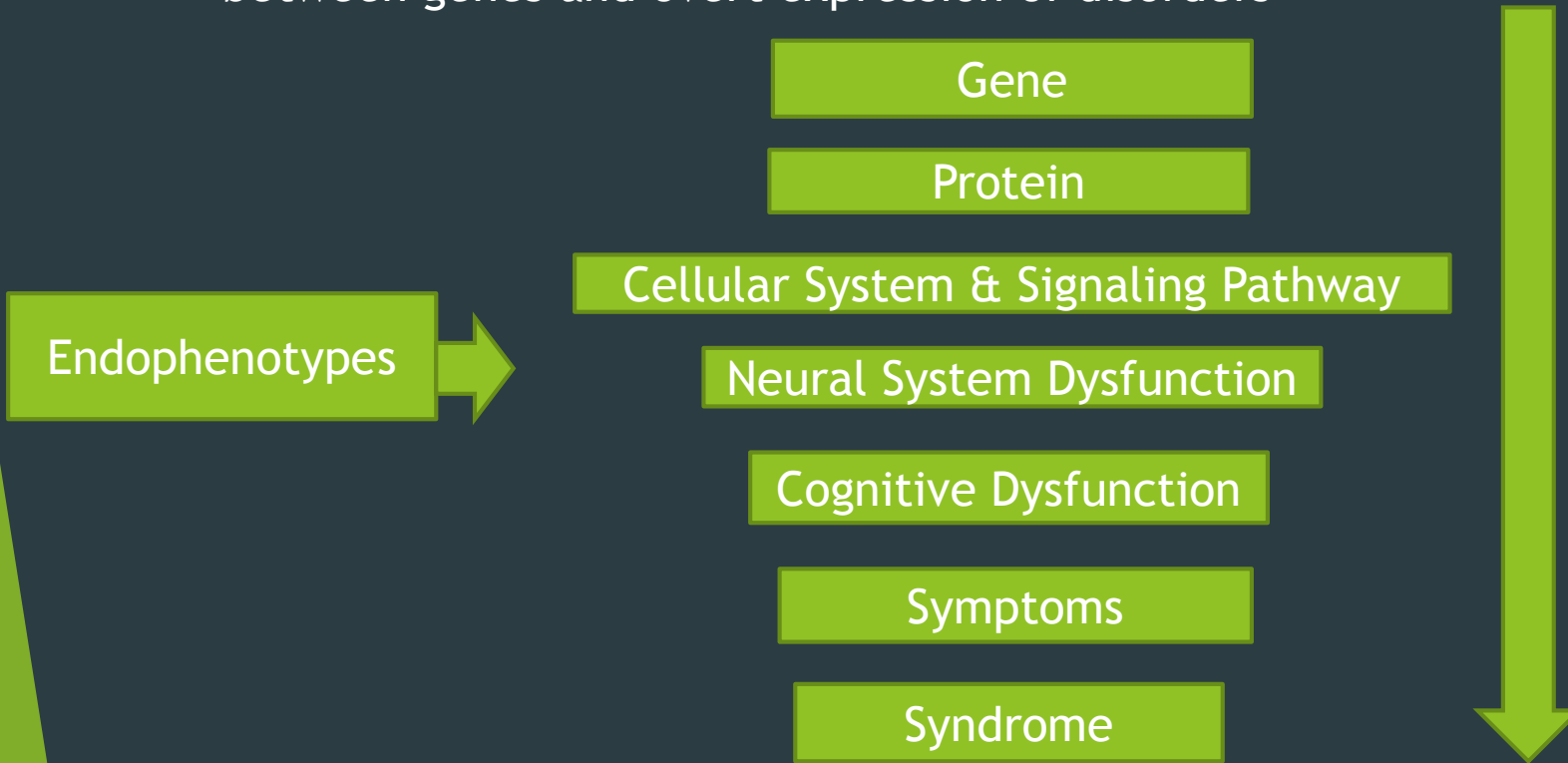
Family, twin and adoption studies provided major evidence for the role of genetics in numerous psychiatric disorders including:

- ▶ obsessive-compulsive disorder
- ▶ panic disorder
- ▶ major depressive disorder
- ▶ bipolar disorder
- ▶ schizophrenia
- ▶ Alzheimer's disease.

Shih, R. A., Belmonte, P. L., & Zandi, P. P. (2004). A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International Review Of Psychiatry*, 16(4), 260-283.
doi:10.1080/09540260400014401

Cannon and Keller (2006) Used Endophenotypes to Analyze Genetic Etiology

- ▶ Endophenotypes—intermediate phenotypes that form the causal links between genes and overt expression of disorders



Cannon, T.D. & Keller, M.C. (2006). Endophenotypes in the genetic analyses of mental disorders. *Annual Review of Clinical Psychology*, 2, 267-290. doi: 10.1146/annurev.clinpsy.2.022305.095232

2008 Call for Use of other Factors in getting to Genetic Etiology of Disorders

Researches stated that several psychiatric disorders – such as bipolar disorder, schizophrenia and autism – are highly heritable, yet identifying their genetic basis has been challenging, with most discoveries failing to be replicated

However, inroads have been made by the incorporation of:

1. Intermediate traits (endophenotypes)
2. Environmental factors into genetic analyses
3. Through the identification of rare inherited variants and novel structural mutations

Burmeister, M., McInnis, M. G., & Zöllner, S. (2008). Psychiatric genetics: progress amid controversy. *Nature Reviews Genetics*, 9(7), 527-540. doi:10.1038/nrg2381

Co-morbidity of Bipolar, Alcohol Use Disorder and other conditions

Carmioli et al (2014) looked into Bipolar disorder and alcohol use disorder (AUD) due to their high rate of comorbidity, more than 50% of individuals with bipolar disorder also receive a diagnosis of AUD in their lifetimes

Although both disorders are heritable, it is unclear if the same genetic factors mediate risk for bipolar disorder and AUD

They examined 733 Costa Rican individuals from 61 bipolar pedigrees. Based on a best estimate process,

- ▶ 32% of the sample met criteria for bipolar disorder
- ▶ 17% had a lifetime AUD diagnosis
- ▶ 32% met criteria for lifetime nicotine dependence
- ▶ 21% had an anxiety disorder
- ▶ AUD, nicotine dependence and anxiety disorders were relatively more common among individuals with bipolar disorder than in their non-bipolar relatives
- ▶ All illnesses were shown to be heritable and bipolar disorder was genetically correlated with AUD, nicotine dependence and anxiety disorders
- ▶ The genetic correlation between bipolar and AUD remained when controlling for anxiety, suggesting that unique genetic factors influence the risk for comorbid bipolar and AUD independent of anxiety

Their findings provide evidence for shared genetic effects on bipolar disorder and AUD risk. Demonstrating that common genetic factors influence these independent diagnostic constructs could help to refine our diagnostic nosology.

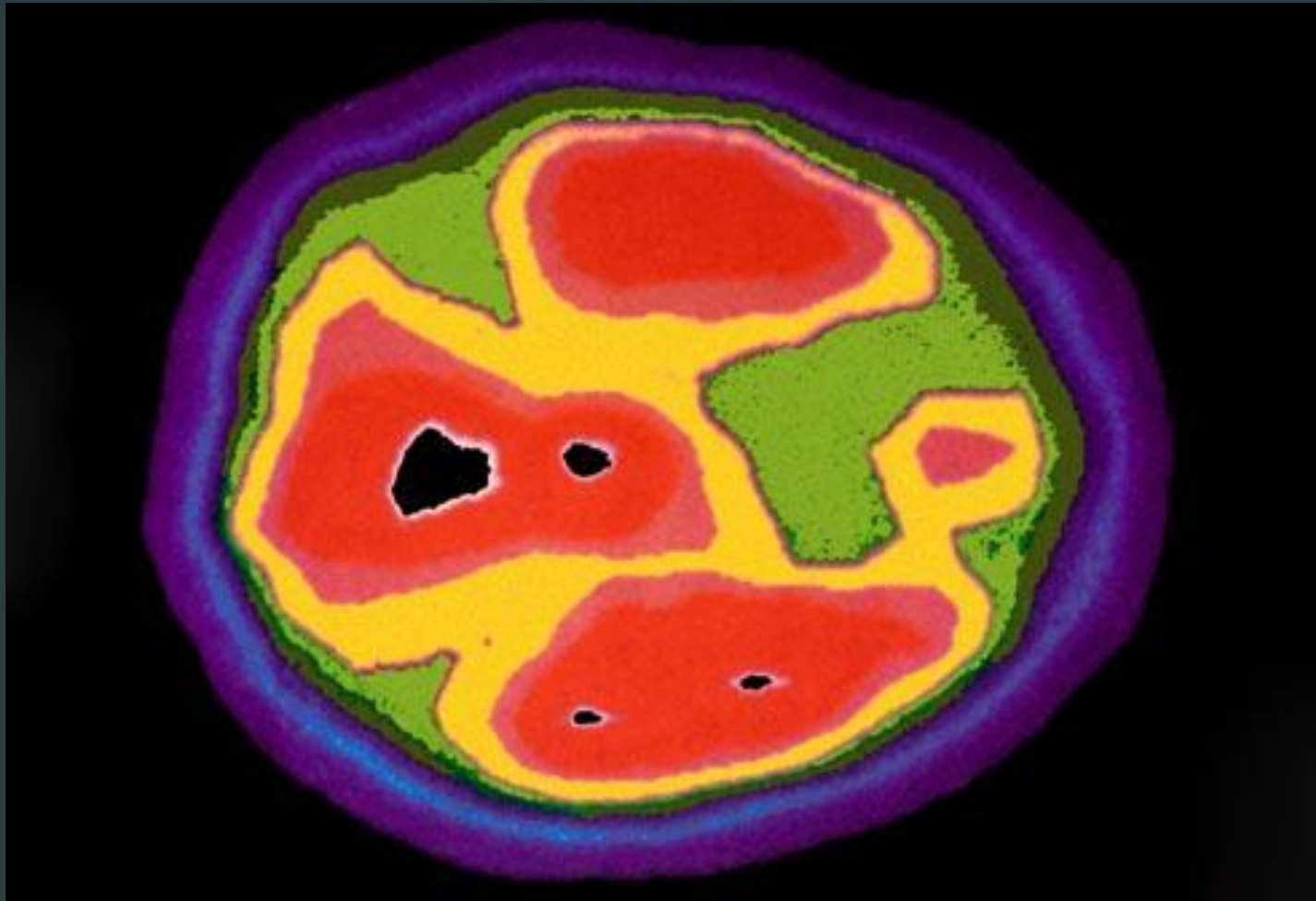
Carmioli, N. N., Peralta, J. M., Almasy, L. L., Contreras, J. J., Pacheco, A. A., Escamilla, M. A., & ... Glahn, D. C. (2014). Shared genetic factors influence risk for bipolar disorder and alcohol use disorders. *European Psychiatry*, 29(5), 282-287. doi:10.1016/j.eurpsy.2013.10.001

Specific Studies on Specific Mental Health Disorders



What Is Autism?

Autism is a brain disorder that limits a person's ability to communicate and relate to other people. It first appears in young children, who fall along a spectrum from mild to severe. Some people can navigate their world, some have exceptional abilities, while others struggle to speak. Autism spectrum disorders (ASDs) affect about one child in 68, striking nearly five times as many boys as girls.



How Does Autism Affect the Brain?

Autism affects parts of the brain that control emotions, communication, and body movements. By the toddler years, some children with ASDs have unusually large heads and brains -- which may be because of problems with brain growth. Abnormal genes, passed down through a family, have been linked to poor functions in some parts of the brain. Researchers hope to find a way to diagnose autism through brain scans.

Autism Study (1) Chromosome 15

In 1999, researchers examined a series of 127 children diagnosed with autistic disorder the karyotypes of 8, on whom data were available, showed the following chromosomal abnormalities:

- ▶ breakage
- ▶ a 47 XY pattern: 47 XY +der (15) (pter q15: p11 pter), 47 XXY and 46 XY, inv (2) (p11:q13pat, 3q+)
- ▶ trisomy 13
- ▶ inversion-duplication of chromosome 15

Compared to those who were not karyotyped or had normal karyotypes, the children with abnormalities, although cognitively more delayed, were not rated as more severely autistic

Facial dysmorphias and minor physical anomalies tended to be more frequent in the chromosomally deviant subgroup

No differences in demographic characteristics or parental ages were evident

Results were consistent with the view of variability of expression of marker chromosome deviations and a greater severity of retardation and symptoms of autism in those affected

Konstantareas, M., & Homatidis, S. S. (1999). Chromosomal abnormalities in a series of children with autistic disorder. *Journal Of Autism & Developmental Disorders*, 29(4), 275.

Autism Study (2) Chromosome 7

In 2001, Gutknecht found that:

Although his findings must be considered with caution because LOD scores (Method of Estimating Linkage Distances) values did not reach the threshold for significant linkage:

- ▶ a region of approximately 50 cM on the long arm of chromosome 7 appears to play a role in the etiology of autistic disorder.

Gutknecht, L. (2001). Full-Genome scans with autistic disorder: A review. *Behavior Genetics*, 31(1), 113-123.

Autism Study (3) Chromosomes 2, 7, 15, X

In 2001 after reviewing the research on the genetics of Autism, Folstein & Rosen-Sheidley found that on the basis of decades of research, genetic factors have clearly emerged as the most significant etiology for autism spectrum disorders

Although there are numerous case reports of cytogenetic abnormalities and associations with specific Mendelian disorders, most cases are idiopathic and apparently due to complex inheritance patterns

This had made the identification of susceptibility genes difficult

Nevertheless, considerable progress has been made in identifying chromosomal regions of interest for some of the genes involved, particularly on chromosomes:

- ▶ 2
- ▶ 7
- ▶ 15
- ▶ X

Folstein, S. E., & Rosen-Sheidley, B. (2001). Genetics of autism: Complex aetiology for a heterogeneous disorder. *Nature Reviews Genetics*, 2(12), 943-955. doi:10.1038/35103559

Autism Study (4) X-linked genes

Researchers in 2003 concluded that after examining cases with mutations in two X-linked genes encoding neuroligins NLGN3 and NLGN4 in siblings with autism-spectrum disorders. These mutations affect cell-adhesion molecules localized at the synapse and suggest that a defect of synaptogenesis may predispose to autism

Jamain, S., Quach, H., Betancur, C., Rastam, M., Colineaux, C., Gillberg, I., & ... Philippe, A. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature Genetics*, 34(1), 27.

Autism Study (5) Family Relatedness

Yirmiya & Shadek (2005) did a meta-analysis of 17 studies in which the psychiatric difficulties of parents of individuals with autism were compared to the psychiatric difficulties of other groups of parents.

The overall group comparison revealed a significant difference of low magnitude. They explored six potential moderator variables. A notable contribution of the current meta-analysis comprises its identification of the moderator variable of 'type of comparison group', which highlights the importance of the comparison group to which researchers compare parents of individuals with autism.

Parents of individuals with autism demonstrated more psychiatric difficulties than did three other parent groups:

1. parents of typically developing individuals
2. parents of individuals with Down Syndrome
3. parents of individuals with Mental Retardation of unknown etiology

Parents of individuals with autism actually revealed significantly fewer psychiatric difficulties compared to parents of individuals with Learning Disabilities, and compared to parents of children with psychiatric disorders

Yirmiya, N., & Shaked, M. (2005). Psychiatric disorders in parents of children with autism: a meta-analysis. *Journal Of Child Psychology & Psychiatry*, 46(1), 69-83. doi:10.1111/j.1469-7610.2004.00334.x

Autism Study (6) Family Relatedness

Also in 2005, Lauritsen et al found that the highest risk of autism was found in families with a history of autism, or Asperger's syndrome and other Pervasive Developmental Delays (PDDs) in siblings, supporting the commonly accepted knowledge that genetic factors are involved in the etiology of autism

Lauritsen, M., Pedersen, C., & Mortensen, P. (2005). Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. *Journal Of Child Psychology & Psychiatry*, 46(9), 963-971.
doi:10.1111/j.1469-7610.2004.00391.x

Autism Study (7) Genomic Imprinting

Badcock & Crespi in 2006 proposed hypothesis of imbalanced genomic imprinting as supported by:

1. strong genomic-imprinting component to the genetic and developmental mechanisms of autism, Angelman syndrome, Rett syndrome and Turner syndrome
2. core behavioral features of autism, such as self-focused behavior, altered social interactions and language, and enhanced spatial and mechanistic cognition abilities
3. degree to which relevant brain functions and structures are altered in autism and related disorders

The imprinted brain theory of autism has important implications for understanding the genetic, epigenetic, neurological and cognitive bases of autism, as ultimately due to imbalances in the outcomes of intragenomic conflict between effects of maternally vs. paternally expressed genes

Badcock, C. C., & Crespi, B. B. (2006). Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism. *Journal Of Evolutionary Biology*, 19(4), 1007-1032. doi:10.1111/j.1420-9101.2006.01091.x

Autism Study (8) Family Relatedness

In 2007 Familial history risk factors in relation to autism were examined in a cohort of 164 autistic children referred to The Autism Center at New Jersey Medical School—University of Medicine and Dentistry of New Jersey, Newark, over a 2-year period (2001-2003).

Information related to familial history was obtained from each family and reviewed by a clinician.

It is shown that

1. these families carry a higher overall burden of **psychiatric** and developmental illnesses compared to reported national levels
2. These families also carry a relatively high incidence of medical **disorders**, independently of developmental and **psychiatric disorders**
3. This work supported the underlying presence of **genetic** factors in the **etiology** of autism

Brimacombe, M., Xue, M., & Parikh, A. (2007). Familial Risk Factors in Autism. *Journal Of Child Neurology*, 22(5), 593-597.

Autism Study (9) DRD3 Gene

In 2009, researcher concluded that the DRD3 gene is related to stereotyped behavior, liability to side effects of antipsychotic medication, and movement disorders and may therefore have important clinical implications for Autism Spectrum Disorder

de Krom, M., Staal, W. G., Ophoff, R. A., Hendriks, J., Buitelaar, J., Franke, B., & ... van Ree, J. M. (2009). A common variant in DRD3 receptor is associated with autism spectrum disorder. *Biological Psychiatry*, 65(7), 625-630.
doi:10.1016/j.biopsych.2008.09.035

Autism Study (10)

Chromosomes 7 (AUTS 1) & 2 (AUTS 5)

In 2010, Researchers performed a high-density association analysis in AUTS1 and AUTS5, testing more than 3000 single nucleotide polymorphisms (SNPs) in all known genes in each region, as well as SNPs in non-genic highly conserved sequences.

SNP genotype data were also used to investigate copy number variation within these regions.

Researchers looked at a study sample which consisted of 127 and 126 families, showing linkage to the AUTS1 and AUTS5 regions, respectively, and 188 gender-matched controls

Further investigation of the strongest association results was conducted in an independent European family sample containing 390 affected individuals.

Association and copy number variant analysis highlighted several genes that warrant further investigation, including *IMMP2L* and *DOCK4* on chromosome 7

Maestrini, E. E., Pagnamenta, A. T., Lamb, J. A., Bacchelli, E. E., Sykes, N. H., Sousa, I. I., & ... Minderaa, R. B. (2010). High-density SNP association study and copy number variation analysis of the AUTS1 and AUTS5 loci implicate the *IMMP2L-DOCK4* gene region in autism susceptibility. *Molecular Psychiatry*, 15(9), 954-968.
doi:10.1038/mp.2009.34

Autism Study (11) PHF8 and WNK3 Genes

In 2011 Baniaga discovered findings that suggest a number of genes involved in neurodevelopment as well as craniofacial and systemic features that may account for the observed phenotypes in the nine affected patients with Autism. Among the candidate genes found

1. *CYFIP1* gene, which is involved in maturation and maintenance of dendrites
2. Gamma acid receptor family (*GABA*) which exhibit linkage disequilibrium with autistic disorders
3. *PHF8* and *WNK3* genes, which have been shown to be associated with X-linked mental retardation (XLMR), present the most interesting findings as they may account for most of the neurodevelopmental pathogenesis observed in the affected patients

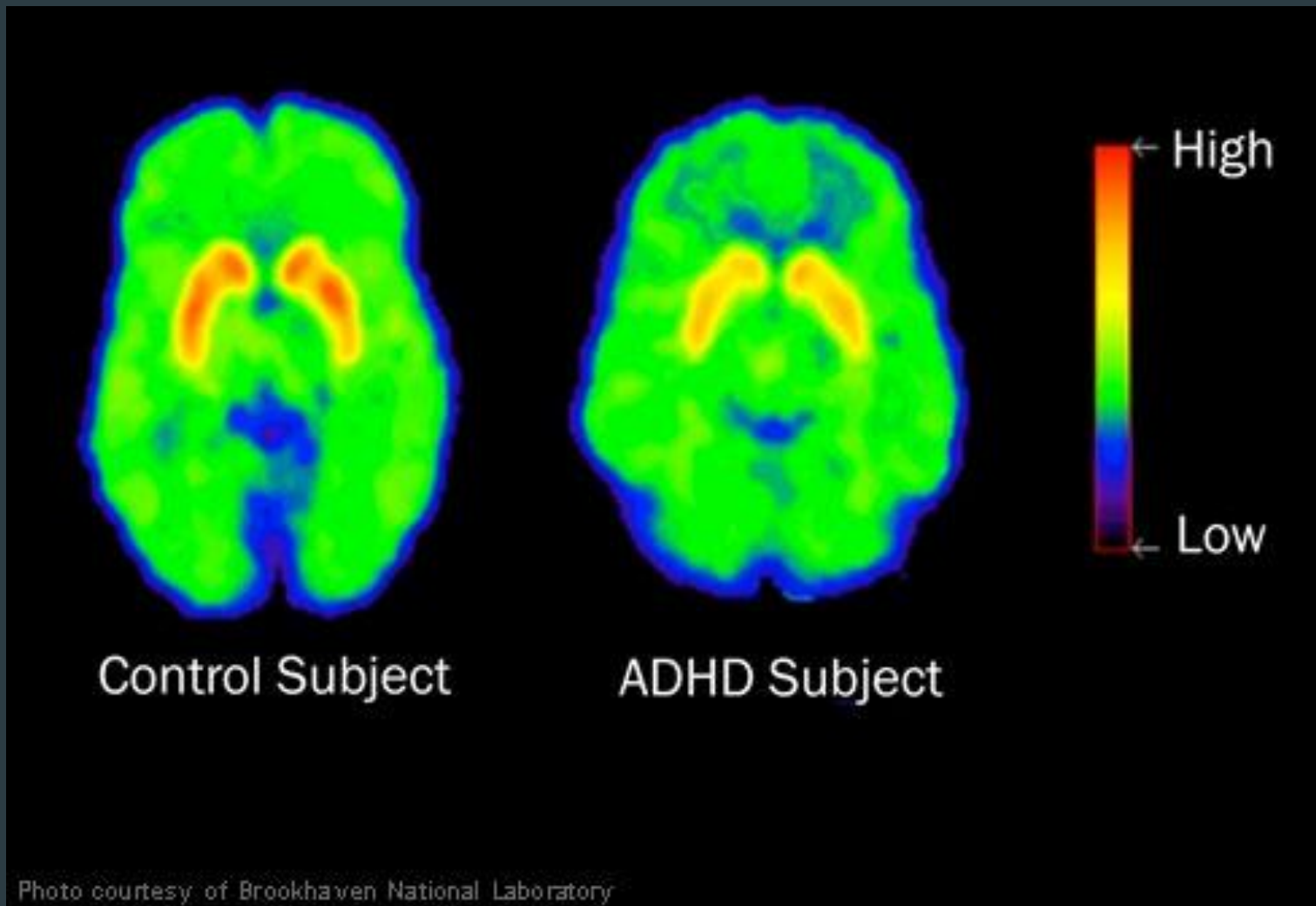
Future studies need to be conducted in order to precisely determine the networks these genes participate in and how they are regulated to gain a deeper understanding in the roles they play in the clinical presentations of affected individuals with ASDs.

Baniaga, A. (2011). Pathogenic copy number variants (pCNVs) in individuals diagnosed on the autism spectrum disorder (ASD): A closer look at candidate genes. *McGill Science Undergraduate Research Journal*, 6(1), 15-22.



ADHD: What Is It?

Attention deficit hyperactivity disorder (ADHD) is a condition that robs children of their ability to focus and pay attention. Kids with ADHD are fidgety and easily distracted. This makes it difficult to stay "on task," whether it's listening to a teacher or finishing a chore. A recent national study reported by the CDC noted that 11% of school aged children are being diagnosed with ADHD. The National Institute of Mental Health estimates 3% to 5% of kids have ADHD, but some experts believe that figure could be as high as 10%.



Children with ADHD have less activity in areas of the brain that control attention. They may also have imbalances in brain chemicals called neurotransmitters. It's unclear what causes these irregularities, but ADHD runs in families, so many experts believe genetics play a role

ADHD Study (1) DRD4

Evidence from twin, adoption, and family studies provide support for a genetic contribution to the etiology of ADHD

Several gene studies have identified an association between a 7-repeat variant in exon 3 of the dopamine 4 receptor gene (DRD4) and ADHD

In 2000, McCracken et al study's Results showed a significant preferential transmission of the 240-bp (long) allele with ADHD. Exploratory analyses of the Inattentive phenotypic subtype of ADHD strengthened the evidence for linkage.

This data added further support for the role of DRD4 variants conferring increased risk for ADHD

McCracken, J. T., Smalley, S. L., McGough, J. J., Crawford, L. L., Del'Homme, M. M., Cantor, R. M., & ... Nelson, S. F. (2000). Evidence for linkage of a tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4) with attention deficit hyperactivity disorder (ADHD). *Molecular Psychiatry*, 5(5), 531.

ADHD Study (2) SNAP-25

Mills et al in 2004 investigated the evidence suggesting a role for SNAP-25 (synaptosomal-associated protein of 25 kDa) in the genetic etiology of ADHD and found:

- ▶ Analyses of transmission by parental sex suggested that the association of SNAP-25 with ADHD is largely due to transmission of alleles from paternal chromosomes to affected probands, suggesting that this locus may be subject to genomic imprinting
- ▶ Overall our data provide some evidence for a role of this gene in ADHD

Mill, J. J., Richards, S. S., Knight, J. J., Curran, S. S., Taylor, E. E., & Asherson, P. P. (2004). Haplotype analysis of SNAP-25 suggests a role in the aetiology of ADHD. *Molecular Psychiatry*, 9(8), 801-810. doi:10.1038/sj.mp.4001482

ADHD Study (3) Multiple Gene Pool

Yeh et al in 2004 identified current targets for etiology of ADHD:

- ▶ Dopamine receptor D4
- ▶ Solute carrier family 6, member 3
- ▶ Dopamine receptor D5
- ▶ Multigenic and genome scan approaches (the association between ADHD and 20 genes, including those from dopamine, serotonin, and adrenergic pathways)

Yeh, M., Morley, K. I., & Hall, W. D. (2004). The policy and ethical implications of genetic research on attention deficit hyperactivity disorder. *Australian & New Zealand Journal Of Psychiatry*, 38(1/2), 10-19. doi:10.1111/j.1440-1614.2004.01292.x

ADHD Study (4) Use of Phenotypic Correlations

In 2011, Grevan et al, identified that heritabilities were high, around 70% for ADHD symptoms and 45-65% for the reading measures

- ▶ Some of the same genes affected combined ADHD and reading with a genetic correlation of $-.31$
- ▶ Most notable finding was that the genetic correlation with reading was significantly greater for inattentiveness ($-.31$) than for hyperactivity-impulsivity ($-.16$), suggesting that genetic overlap between combined ADHD and reading is largely driven by inattentiveness
- ▶ Results showed that it is word decoding rather than reading comprehension that is differentially related to the ADHD dimensions (lower genetic correlation to hyperactivity-impulsivity than to inattentiveness)

Conclusion: Genetic overlap between ADHD and reading is largely driven by inattentiveness rather than hyperactivity-impulsivity.

Grevan, C. U., Harlaar, N., Dale, P. S., & Plomin, R. (2011). Genetic overlap between ADHD symptoms and reading is largely driven by inattentiveness rather than hyperactivity-impulsivity. *Journal Of The Canadian Academy Of Child & Adolescent Psychiatry*, 20(1), 6-14.

ADHD Study (5) Gβ5-RGS Complexes

- ▶ Xie et al in 2012 researched the disruption of monoamine neurotransmitter signaling through G protein-coupled receptors (GPCR) is considered to be a major contributing factor to the etiology of the ADHD
- ▶ They concluded that: Genetic association evidence and functional data suggest that regulators of G protein signaling proteins of the R7 family (R7 RGS) that form obligatory complexes with type 5 G protein beta subunit (Gβ5) and negatively regulate signaling downstream from monoamine GPCRs may play a role in controlling hyperactivity.

Xie, K., Ge, S., Collins, V., Haynes, C., Renner, K., Meisel, R., & ... Martemyanov, K. (2012). Gβ5-RGS complexes are gatekeepers of hyperactivity involved in control of multiple neurotransmitter systems. *Psychopharmacology*, 219(3), 823-834. doi:10.1007/s00213-011-2409-y

ADHD Study (6) 14 Noradrenergic Genes

Hawi et al reported in 2013 that haplotype analyses demonstrated a significant association between ADHD and a SLC6A2 haplotype comprising the markers rs36009, rs1800887, rs8049681, rs2242447 and rs9930182 ($\chi^2=209.39$, p -corrected=0.019, OR=1.51)

A rare ADRA1B haplotype made of six SNPs (rs2030373, rs6884105, rs756275, rs6892282, rs6888306 and rs13162302) was also associated ($\chi^2=207.79$, p -corrected=0.042 OR=2.74) with the disorder

These findings provide evidence of a contribution of the noradrenaline system to the genetic etiology of ADHD

The observed haplotype association signals may be driven by as yet unidentified functional risk variants in or around the associated regions. Functional genomic analysis is warranted to determine the biological mechanism of the observed association.

Hawi, Z., Matthews, N., Barry, E., Kirley, A., Wagner, J., Wallace, R., & ... Bellgrove, M. (2013). A high density linkage disequilibrium mapping in 14 noradrenergic genes: Evidence of association between SLC6A2, ADRA1B and ADHD. *Psychopharmacology*, 225(4), 895-902. doi:10.1007/s00213-012-2875-x

ADHD Study (7) Twin Research

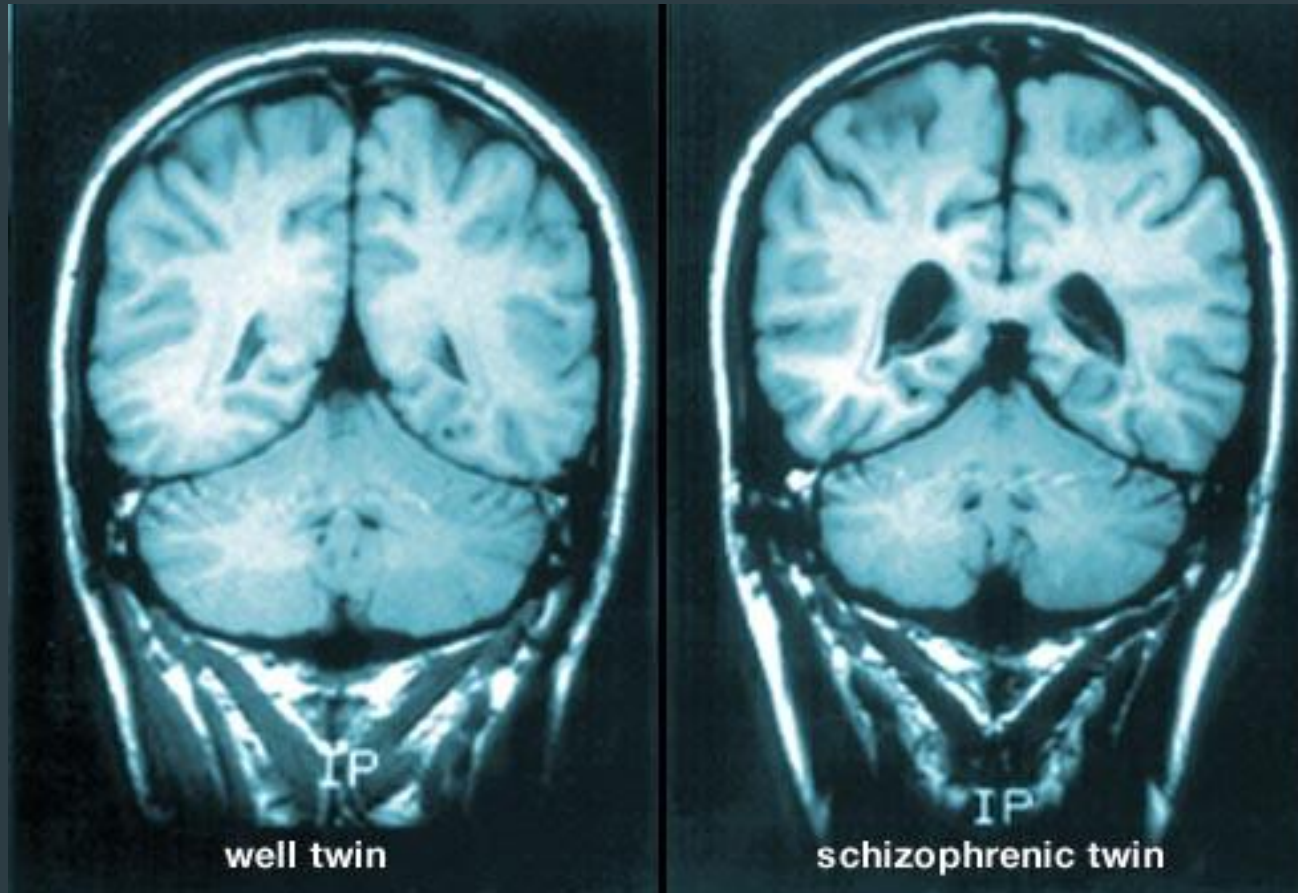
- ▶ Langer et al study in 2013 clearly reproduced the well-known strong genetic component in the etiology of ADHD
- ▶ ADHD cases were identified by hospital or ambulatory ICD-10 diagnoses (F90.0 or F90.1) and prescriptions. We estimated tetrachoric correlations, percentage of concordant pairs, concordance rates, and heritability. Weighted estimates for the indirect assessment of mono- and dizygotic pairs were derived

Langner, I., Garbe, E., Banaschewski, T., & Mikolajczyk, R. T. (2013). Twin and sibling studies using health insurance data: The example of Attention Deficit/Hyperactivity Disorder (ADHD). *Plos ONE*, 8(4), 1-8.
doi:10.1371/journal.pone.0062177



What Is Schizophrenia?

Schizophrenia is a chronic, disabling brain disorder that affects about 1% of Americans. It may cause people to hear voices, see imaginary sights, or believe other people are controlling their thoughts. These sensations can be frightening and often lead to erratic behavior. There is no cure, but treatment can usually control the most serious symptoms.



What Causes Schizophrenia?

The exact cause is not known, but scientists suspect genes and environment both play a role. Inside the brain, levels of the chemical messengers dopamine and glutamate may be out of balance. And brain structures may be abnormal, too. For example, brain scans of identical twins show that the fluid-filled "ventricles" can be larger in a twin with schizophrenia, compared with a twin who does not have the illness. Activity levels can also be higher or lower than normal in some areas of the schizophrenic brain.

Schizophrenia Study (1) 8 Genes

In 2000, Lichtenman et al was able to extend the spectrum concept to include neuropsychologically, neurophysiologically and neuroradiologically measurable familial traits as subclinical endophenotypes of schizophrenia that may be more fundamental to the development of the disease than overt psychopathology.

Replicable linkage findings have emerged from genome scans that imply at least seven chromosomal regions to harbor schizophrenia susceptibility genes.

They strengthen the conviction that schizophrenia is indeed a genetically complex disorder, based on a larger number of susceptibility genes with risk-increasing alleles that are common in the population and exert a limited effect on the individual level.

They mentioned several schizophrenia susceptibility genes: 1q, 5q, 6p, 8p, 10p, 13q, 18p, 22q

Lichtermann, D., Karbe, E., & Maier, W. (2000). The genetic epidemiology of schizophrenia and of schizophrenia spectrum disorders. *European Archives Of Psychiatry & Clinical Neuroscience*, 250(6), 304.

Schizophrenia Study (2) Biological Markers

- ▶ In 2004, Joseph detailed that biological markers in psychiatry (also known as "endophenotypes," "subclinical traits," "intermediate phenotypes," and "vulnerability markers") have been defined as "any neurobiological measure related to the underlying molecular genetics of the illness, including biochemical, endocrinological, neurophysiological, neuroanatomical, or neuropsychological markers “

Characteristics researchers require for a biological marker are

1. that it can be reliably measured
2. that it be manifest among all people with a susceptibility locus (independent of state)
3. that it is specific to the disorder under study
4. that it is inherited

Joseph, J. (2004). The fruitless search for schizophrenia genes. *Ethical Human Psychology and Psychiatry*, 6(3), 167-181.

Schizophrenia Study (3) Reelen Gene risk for Women only

In 2008, Shifman et al performed a genome-wide association scan for schizophrenia in an Ashkenazi Jewish population using DNA pooling.

They found a female-specific association with rs7341475, a SNP in the fourth intron of the reelin (RELN) gene ($p = 2.9 \times 10^{-5}$ in women), with a significant gene-sex effect ($p = 1.8 \times 10^{-4}$).

They also studied rs7341475 in four additional populations, totaling 2,274 cases and 4,401 controls. A significant effect was observed only in women, replicating the initial result ($p = 2.13 \times 10^{-3}$ in women; $p = 4.23 \times 10^{-3}$ for gene-sex interaction).

Based on all populations the estimated relative risk of women carrying the common genotype is 1.58 ($p = 8.8 \times 10^{-7}$; $p = 1.6 \times 10^{-5}$ for gene-sex interaction).

They concluded that the female specific association between RELN and schizophrenia is one of the few examples of a replicated sex-specific genetic association in any disease.

Shifman, S., Johannesson, M., Bronstein, M., Chen, S. X., Collier, D. A., Craddock, N. J., & ... Darvasi, A. (2008). Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women. *Plos Genetics*, 4(2), 1-7. doi:10.1371/journal.pgen.0040028

Schizophrenia Study (4) ERBB3

Li et al (2009) stated that: Schizophrenia is a common psychiatric disorder with a complex genetic aetiology.

Their evidence shows that the oligodendrocyte and myelin-related genes including ERBB3 are closely related to schizophrenia.

They presented findings of the first association study between ERBB3 and schizophrenia in the Caucasian population

Li, D., Feng, G. & He, L. (2009) Case-control study of association between the functional candidate gene ERBB3 and schizophrenia in Caucasian population. *World Journal Of Biological Psychiatry*, 10(4_2), 595-598.
doi:10.1080/15622970903304442.

Schizophrenia Study (5) Results of Studies

- ▶ In 2011, Haraldsson et al reviewed current literature on schizophrenia genetics with special emphasis on new developments such as genome-wide association studies (GWAS), associations of copy number variations (CNVs) with schizophrenia and the role of endophenotypes in genetic research
- ▶ They reported that the first GWAS of schizophrenia had identified new putative candidate risk genes and opened avenues for investigating how multiple genes may act in functional biological pathways forming the genetic basis of schizophrenia and other complex diseases. There is growing evidence that rare *de novo* CNVs as well as some inherited CNVs contribute to the susceptibility to several neuropsychiatric disorders including schizophrenia.
- ▶ They concluded that Schizophrenia endophenotypes which possibly better represent biological phenomena than the complex clinical phenotype, are turning out to be helpful for investigating neurobiological pathways of putative risk genes

Haraldsson, H., Ettinger, U., & Sigurdsson, E. (2011). Developments in schizophrenia genetics: From linkage to microchips, deletions and duplications. *Nordic Journal Of Psychiatry*, 65(2), 82-88. doi:10.3109/08039488.2011.552734

Schizophrenia Study (6) Impact of SNPs

Lee et al in 2012, estimated that 23% (s.e. = 1%) of variation in liability to schizophrenia is captured by SNPs. Schizophrenia is a complex disorder caused by both genetic and environmental factors. They used 9,087 affected individuals, 12,171 controls and 915,354 imputed SNPs from the Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (PGC-SCZ).

They showed that a substantial proportion of this variation must be the result of common causal variants, that the variance explained by each chromosome is linearly related to:

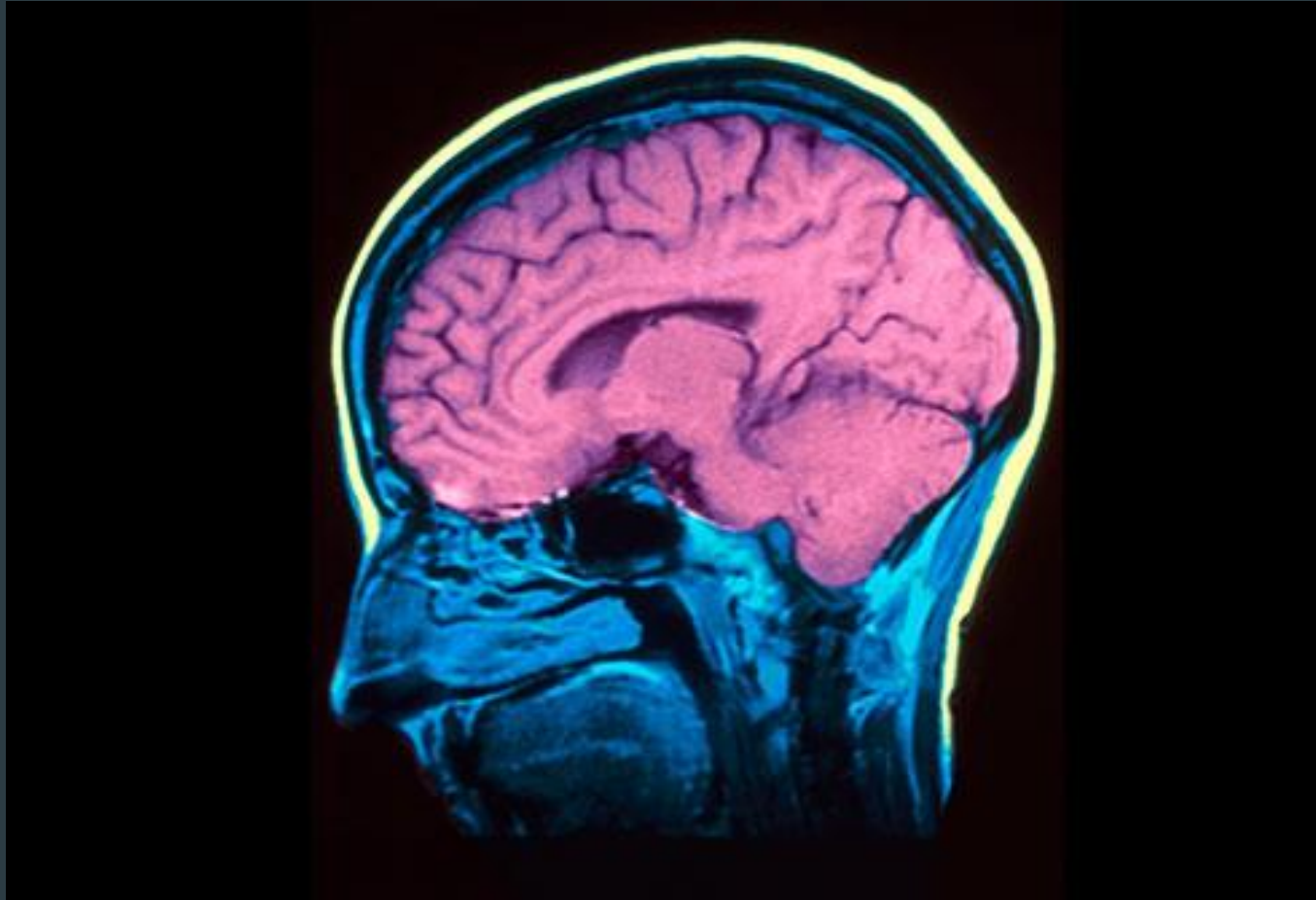
- ▶ its length ($r = 0.89$, $P = 2.6 \times 10^{-8}$)
- ▶ that the genetic basis of schizophrenia is the same in males and females
- ▶ that a disproportionate proportion of variation is attributable to a set of 2,725 genes expressed in the central nervous system (CNS; $P = 7.6 \times 10^{-8}$)
- ▶ These results are consistent with a polygenic genetic architecture and imply more individual SNP associations will be detected for this disease as sample size increases.

Lee, S., DeCandia, T., Ripke, S., Yang, J., Sullivan, P., Goddard, M., & ... Wray, N. (2012). Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nature Genetics*, 44(3), 247-250. doi:10.1038/ng.1108

Bipolar Disorder: What Is It?



Bipolar disorder, sometimes called manic depression, is a disorienting condition that causes extreme shifts in mood. Like riding a slow-motion roller coaster, patients may spend weeks feeling like they're on top of the world before plunging into a relentless depression. The length of each high and low varies greatly from person to person. In any given year, bipolar disorder affects more than 2% of American adults.



Causes of Bipolar Disorder

Doctors aren't exactly sure what causes bipolar disorder. A leading theory is that brain chemicals fluctuate abnormally. When levels of certain chemicals become too high, the patient develops mania. When levels drop too low, depression may result.

Bipolar Disorder Study (1) 2 SNPs

Sklar et al in 2002 found that Two SNPs were closely related to Bipolar Disorder they are:

1. Brain-Derived Neurotropic Factor (BDNF)
2. Alpha subunit of the voltage-dependent calcium channel

BUT

Only BDNF in further study was the most potential risk for Bipolar disorder

Sklar, P. P., Gabriel, S. B., McInnis, M. G., Bennet, P. P., Lim, Y. M., Tsan, G. G., & ... Lander, E. S. (2002). Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. *Molecular Psychiatry*, 7(6), 579.

Bipolar Disorder Study (2) Markers & LOD Scores

Lambert et al in 2005 using a broad diagnostic model, found two markers gave LOD scores (Method of Estimating Linkage Distances) exceeding 3 with two-point analysis:

1. D4S392 (LOD $\frac{1}{4}$ 3.30)
2. D10S197 (LOD $\frac{1}{4}$ 3.18)

Multipoint analysis demonstrated suggestive evidence of linkage between Bipolar Disorder and chromosomal regions

1. 6q16-q21 (MLS $\frac{1}{4}$ 2.61)
2. 4q12-q21 (MLS $\frac{1}{4}$ 2.38).

6q16-q21 was of particular interest because their data, together with those from two recent genome scans, make this the best supported linkage region for Bipolar Disorder

Lambert, D. D., Middle, F. F., Hamshere, M. L., Segurado, R. R., Raybould, R. R., Corvin, A. A., & ... Holmans, P. P. (2005). Stage 2 of the Wellcome Trust UK-Irish bipolar affective disorder sibling-pair genome screen: Evidence for linkage on chromosomes 6q16-q21, 4q12-q21, 9p21, 10p14-p12 and 18q22. *Molecular Psychiatry*, 10(9), 831-841. doi:10.1038/sj.mp.4001684

Bipolar Disorder Study (3) Possible impact of personality traits

In 2006 Savitz & Ramesar reported that: Progress in identifying the genetic basis of bipolar affective disorder was disappointing, most probably because of the genetic and phenotypic heterogeneity of the condition. These setbacks have led to the adoption of alternative strategies such as the use of endophenotypes or intermediate traits to identify those individuals at genetic risk for developing the disorder

They concluded that A review of the literature suggests that certain personality traits or temperaments are associated with the illness in a state independent manner, that personality is at least partly heritable, and that various temperaments aggregate in the non-affected relatives of bipolar probands.

Savitz, J., & Ramesar, R. (2006). Personality: is it a viable endophenotype for genetic studies of bipolar affective disorder?. *Bipolar Disorders*, 8(4), 322-337.
doi:10.1111/j.1399-5618.2006.00309.x

Bipolar Disorder Study (4) DGKH & Other Genes

Baum et al in 2008, in their research found that of 37 SNPs selected for individual genotyping, the strongest association signal was detected at a marker within the first intron of diacylglycerol kinase eta (DGKH; $P = 1.5108$, experiment-wide $P < 0.01$, OR = 1.59).

This gene encodes DGKH, a key protein in the lithium-sensitive phosphatidyl inositol pathway.

This first genome-wide association study of bipolar disorder shows that several genes, each of modest effect, reproducibly influence disease risk.

They concluded that Bipolar disorder may be a polygenic disease

Baum, A. E., Akula, N. N., Cabanero, M. M., Cardona, I. I., Corona, W. W., Klemens, B. B., & ... McMahon, F. J. (2008). A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Molecular Psychiatry*, 13(2), 197-207. doi:10.1038/sj.mp.4002012

Bipolar Disorder Study (6) Co-morbidity with Autism?

Ragunath et al's (2011) systems biology study of Autism Spectrum Disorders (ASD) and Bipolar Disorder (BP) proved to yield important insight on the genetic basis of comorbidity between the two disorders

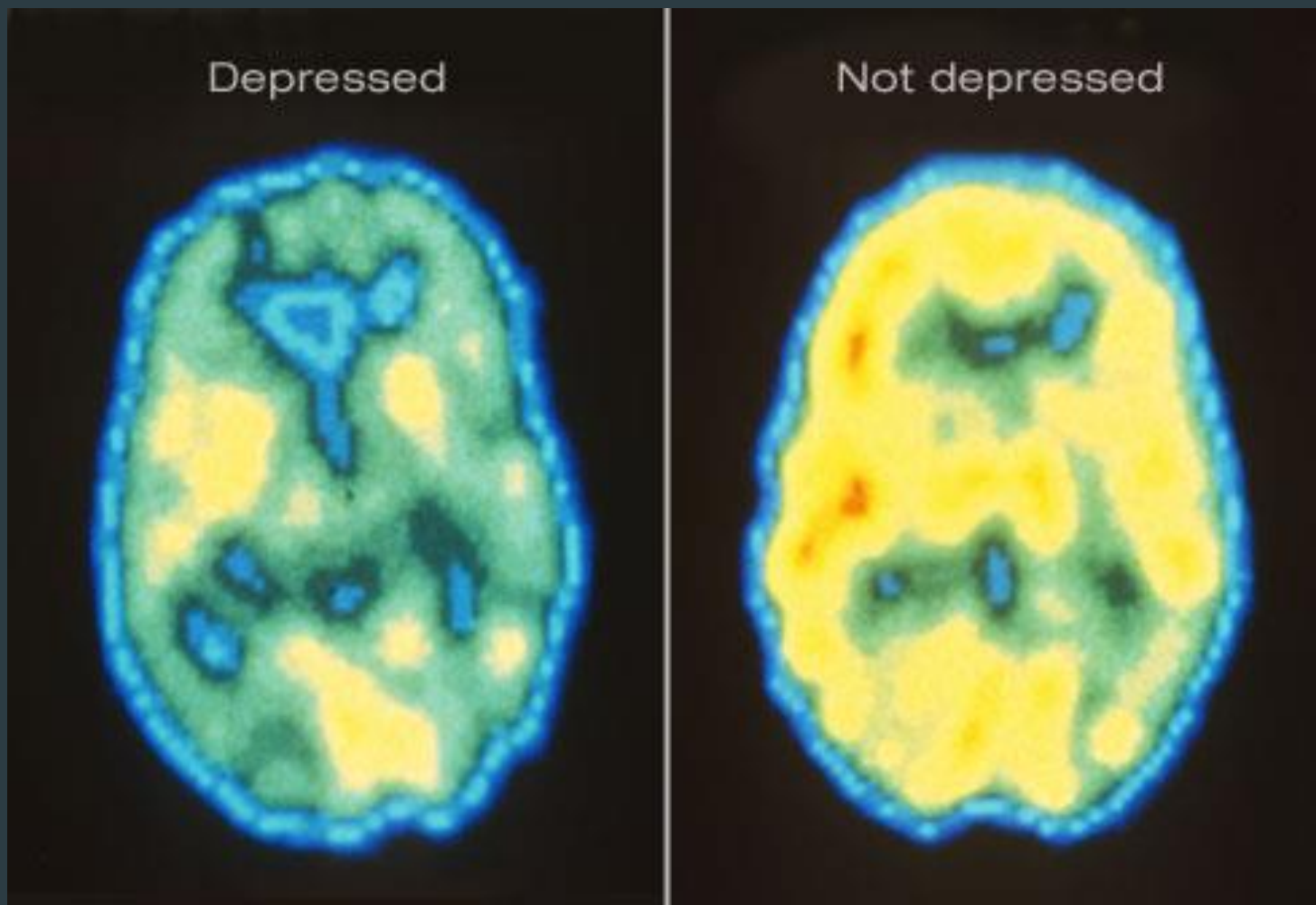
1. The networks constructed for the selected 4 pathways leads to a hypothesis that the comorbidity of ASD and BP can be correlated to the genes involved in the pathways common to the two disorders and a further examination can pave way to the identification of the specific genes that contribute to comorbidity
2. Such knowledge would help in devising a novel management technique or developing therapeutics

Ragunath, P. K., Chitra, R. R., Mohammad, S., & Abhinand, P. A. (2011). A systems biological study on the comorbidity of autism spectrum disorders and bipolar disorder. *Bioinformation*, 7(3), 102-106

Bipolar Disorder Study (7) Cognitive Endophenotype

- ▶ Drysdale et al (2013) found that verbal learning and semantic verbal fluency impairments may represent a cognitive endophenotype for both bipolar disorder & major depression in relatives of bipolar disorder patients, as impairment was also present in high-risk relatives who had not developed any affective disorder symptoms
- ▶ These findings suggest that impairment in semantic organization may be linked to the genetic etiology of bipolar disorder

Drysdale, E., Knight, H., McIntosh, A., & Blackwood, D. (2013). Cognitive endophenotypes in a family with bipolar disorder with a risk locus on chromosome 4. *Bipolar Disorders*, 15(2), 215-222. doi:10.1111/bdi.12040



Depression: What Is It?

It's natural to feel down sometimes, but if that low mood lingers day after day, it could signal depression. Major depression is an episode of sadness or apathy along with other symptoms that lasts at least two consecutive weeks and is severe enough to interrupt daily activities. Depression is not a sign of weakness or a negative personality. It is a major public health problem and a treatable medical condition. Shown here are PET scans of the brain showing different activity levels in a person with depression, compared to a person without depression.



Neurons (nerve cells) in the brain communicating via neurotransmitters

Depression Study (1) Familial Transmission

In 1998 in a formal commentary about research into the familial transmission of depression, Farosone & Biederman stated:

- ▶ Weissman and colleagues found offspring of depressed parents showed greater social impairment and had a three-fold increased risk of depression and phobias as well as a five-fold increased risk of panic disorder and alcohol dependence
- ▶ They went on to say: this finding confirmed a report from the UK that adult mood disorders were found in nearly half of a sample that had been diagnosed as having depression while in childhood
- ▶ They concluded: If symptoms of depression represented normal responses to development transitions, they should have waxed and waned with development.

Farosone, S.V. & Biederman, J. (1998). Depression: A family affair. *Lancet*, 351 (9097). 00995355

Depression Study (2) Serotonergic Genes impact on Amygdala

Dannlowski et al (2007) looked at serotonergic genes implicated in the pathogenesis of depression probably via their influence on neural activity during emotion processing

They used an imaging genomics approach to investigate amygdala activity in major depression as a function of common functional polymorphisms in the serotonin transporter gene (5-HTTLPR) and the serotonin receptor 1A gene (5-HT1A-1019C/G)

In 27 medicated patients with major depression, amygdala responses to happy, sad and angry faces were assessed using functional magnetic resonance imaging at 3 Tesla

Patients were genotyped for the 5-HT1A-1019C/G and the 5-HTTLPR polymorphism, including the newly described 5-HTT-rs25531 single nucleotide polymorphism

Risk allele carriers for either gene showed significantly increased bilateral amygdala activation in response to emotional stimuli, implicating an additive effect of both genotypes

Their data suggest that the genetic susceptibility for major depression might be transported via dysfunctional neural activity in brain regions critical for emotion processing.

Dannlowski, U. U., Ohrmann, P. P., Bauer, J. J., Kugel, H. H., Baune, B. T., Hohoff, C. C., & ... Suslow, T. T. (2007). Serotonergic genes modulate amygdala activity in major depression. *Genes, Brain & Behavior*, 6(7), 672-676. doi:10.1111/j.1601-183X.2006.00297.x

Depression Study (3) Relatedness of LHPP & HTR1A genotype

Neff et al (2009) reported that the HTR1A -1019C>G genotype was associated with major depression in the Utah population.

Linkage analysis on Utah pedigrees with strong family histories of major depression including only cases with the HTR1A -1019G allele revealed a linkage peak on chromosome 10 (maximum HLOD=4.4)

Sequencing of all known genes in the linkage region revealed disease-segregating single-nucleotide polymorphisms (SNPs) in LHPP (phospholysine phosphohistidine inorganic pyrophosphate phosphatase- Gene ID: 64077)

LHPP SNPs were also associated with major depression in both Utah and Ashkenazi populations

Consistent with the linkage evidence, LHPP associations depended on HTR1A genotype

LHPP or a product of a collinear brain-specific transcript, therefore, may interact with HTR1A in the pathogenesis of major depression

Neff, C. D., Abkevich, V. V., Packer, J. L., Chen, Y. Y., Potter, J. J., Riley, R. R., & ... Katz, D. A. (2009). Evidence for HTR1A and LHPP as interacting genetic risk factors in major depression. *Molecular Psychiatry*, 14(6), 621-630. doi:10.1038/mp.2008.8

Depression Study (4) Somatization Impact

Klengel et al (2011) found that thirty SNPs exhibit nominally significant associations with somatization

One SNP (rs9534505) located in intron 2 of the HTR2A gene withstood correction for multiple testing

Clinical data provided further evidence for strong impact of somatization on the presentation of depressive symptoms and description of a patient subgroup with unfavorable clinical outcome

Conclusion: Results demonstrate the influence of a HTR2A polymorphism on aspects of somatization in major depression, which co-occurs with an unfavorable antidepressant treatment outcome. These results confirm and expand previous findings on somatization as a risk factor for treatment outcome in major depression.

Klengel, T. T., Heck, A. A., Pfister, H. H., Brückl, T. T., Hennings, J. M., Menke, A. A., & ... Ising, M. M. (2011). Somatization in major depression - clinical features and genetic associations. *Acta Psychiatrica Scandinavica*, 124(4), 317-328.
doi:10.1111/j.1600-0447.2011.01743.x

Depression Study (5) Multiple Genetic Variants

Wong et al (2012) found that risk-classification tree analysis, using 15 nsSNPs that had a nominal association with Major Depressive Disorder (MDD) diagnosis, identified multiple increased-MDD genotype clusters and significant additive interactions in combinations of genotype variants that were significantly associated with MDD.

The results in the dbGaP for major depression disclosed a multidimensional dependent phenotype constituted of MDD plus significant modifiers (smoking, marriage status, age, alcohol abuse/dependence and gender), which then was used for the association tree analysis.

The reconstructed tree analysis for the dbGaP data showed robust reliability and replicated most of the genes involved in the branching process found in their exploratory analyses.

Pathway analysis using all six major events of branching (PSMD9, HSD3B1, BDNF, GHRHR, PDE6C and PDLIM5) was significant for positive regulation of cellular and biological processes that are relevant to growth and organ development.

Their findings not only provide important insights into the biological pathways underlying innate susceptibility to MDD but also offer a predictive framework based on interactions of multiple functional genetic variants and environmental factors.

Wong, M., Dong, C., Andreev, V., Arcos-Burgos, M., & Licinio, J. (2012). Prediction of susceptibility to major depression by a model of interactions of multiple functional genetic variants and environmental factors. *Molecular Psychiatry*, 17(6), 624-633.
doi:10.1038/mp.2012.13

Depression Study (6) Testing Impact of Socioeconomic Disparity in Depression

Mezuk et al (2013) found consistent with the social causation hypothesis, education (odds ratio [OR] = 0.78; 95% confidence interval [CI] = 0.66, 0.93; $P < .01$) and income (OR = 0.93; 95% CI = 0.89, 0.98; $P < .01$) were significantly related to past-year major depression

Upward social mobility was associated with lower risk of depression

There was no evidence that childhood SES was related to development of major depression (OR = 0.98; 95% CI = 0.89, 1.09; $P > .1$)

Consistent with a common genetic cause, there was a negative correlation between the genetic components of major depression and education ($r^2 = -0.22$)

Co-twin control analyses indicated a protective effect of education and income on major depression even after accounting for genetic liability

Conclusion: This study utilized a genetically informed design to address how social position relates to major depression. Results generally supported the social causation model

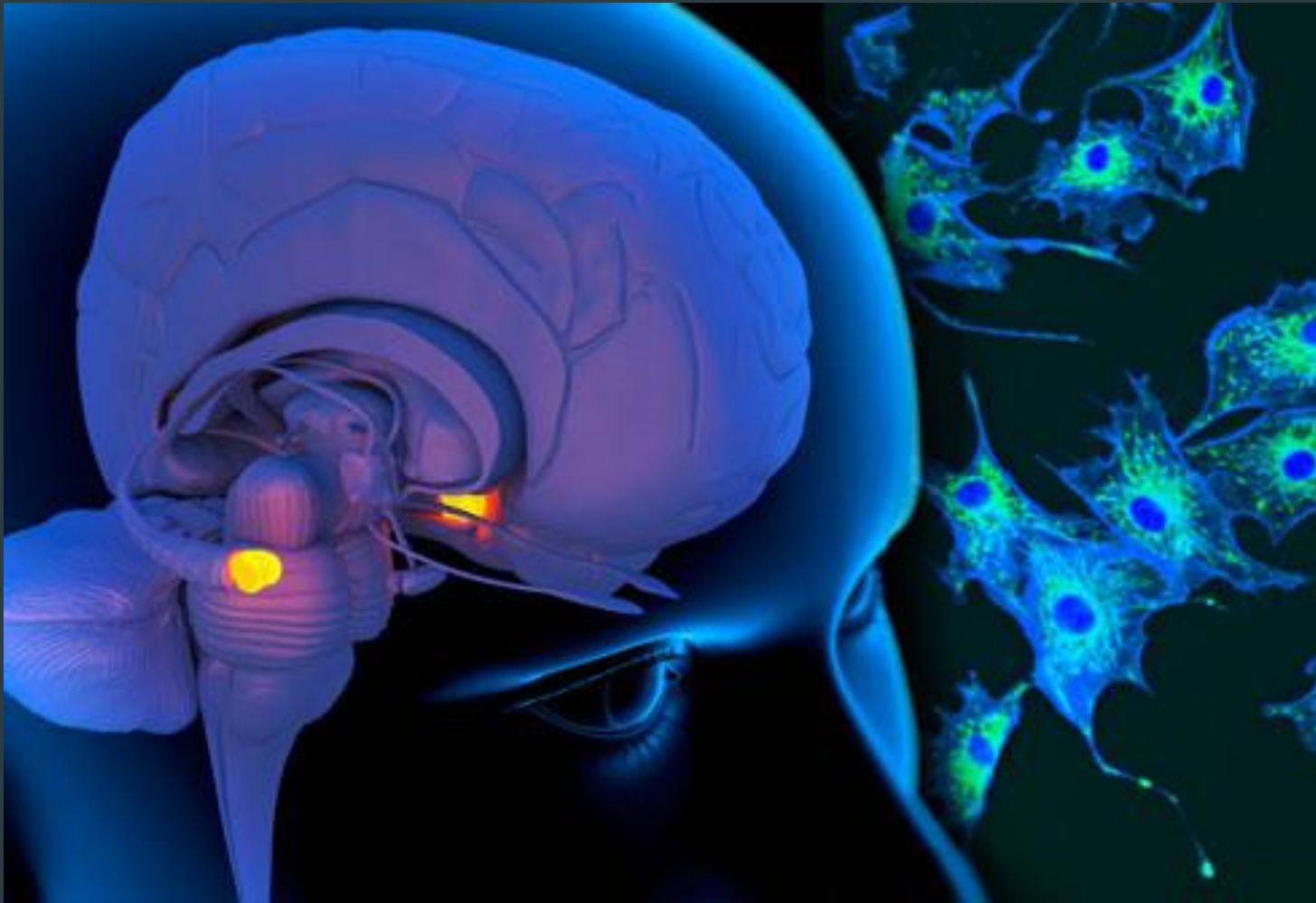
Mezuk, B., Myers, J. M., & Kendler, K. S. (2013). Integrating social science and behavioral genetics: Testing the origin of socioeconomic disparities in depression using a genetically informed design. *American Journal Of Public Health*, 103(S1), S145-S151. doi:10.2105/AJPH.2013.301247

Depression Study(7) CNRI Gene

Mitjans et al (2013) observed a higher frequency of rs806371 G carriers in Major Depression (MD) patients with both presence of melancholia ($p = 0.018$) and psychotic symptoms ($p = 0.007$) than in controls.

- ▶ Haplotype frequency distributions between MD sample and controls showed a significant difference for Block 1 (rs806368-rs1049353-rs806371) ($p = 0.008$).
- ▶ This haplotype finding was consistent when compared controls with MD subsample stratified by melancholia ($p = 0.0009$) and psychotic symptoms ($p = 0.014$)
- ▶ The TT homozygous of the rs806368 and rs806371 presented more risk of no Remission than the C carriers ($p = 0.008$ and 0.012 , respectively)
- ▶ Haplotype frequency distributions according to Remission status showed a significant difference for Block 1 ($p = 0.032$)
- ▶ Also observed were significant effect of time-sex-genotype interaction for the rs806368, showing that the C carrier men presented a better response to antidepressant treatment throughout the follow-up than TT homozygous men and women group ($p = 0.026$)
- ▶ Conclusion: These results suggest an effect of CNR1 gene in the etiology of MD and clinical response to citalopram.

Mitjans, M., Serretti, A., Fabbri, C., Gastó, C., Catalán, R., Fañanás, L., & Arias, B. (2013). Screening genetic variability at the CNR1 gene in both major depression etiology and clinical response to citalopram treatment. *Psychopharmacology*, 227(3), 509-519.
doi:10.1007/s00213-013-2995-y



What Causes Anxiety Disorders

Genes passed down through a family may put some people at higher risk for anxiety, but that's not the whole picture. Scientists think that a mix of DNA, environment, and psychological factors are to blame. Researchers are looking at brain chemicals called neurotransmitters, as well as a pair of structures inside the brain called the amygdalae.

Anxiety Disorder Study (1) Common Genetic Etiology Panic Disorder & Agoraphobia

Mosing et al (2009) in a community sample of 5,440 twin pairs showed that Major Depression, Panic Disorder, Agoraphobia, and Social Phobia strongly coaggregate within families and that common genetic factors explain a moderate-to-high proportion of variance in these four disorders with no evidence for influences of common environment

- ▶ The high genetic correlation (.83) between Panic Disorder and Agoraphobia and the increased odds ratio for Panic Disorder and Agoraphobia in siblings of those with Agoraphobia without Panic Disorder supports the theory of a common genetic etiology for Panic Disorder and Agoraphobia

Mosing, M. A., Gordon, S. D., Medland, S. E., Statham, D. J., Nelson, E. C., Heath, A. C., & ... Wray, N. R. (2009). Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. *Depression & Anxiety (1091-4269)*, 26(11), 1004-1011. doi:10.1002/da.20611

Anxiety Disorders Study (2) Neuroticism

Webb et al (2012) identified that genetic factors underlying trait neuroticism, reflecting a tendency towards negative affective states, may overlap genetic susceptibility for anxiety disorders and help explain the extensive comorbidity amongst internalizing disorders

11 Genome-wide linkage (GWL) studies of either neuroticism (n=8) or anxiety disorders (n=3) were collected, which comprised of 5341 families with 15 529 individuals.

The rank-based genome scan meta-analysis (GSMA) approach was used to analyze each trait separately and combined, and global correlations between results were examined

Using 10 cM intervals, bins nominally significant for both GSMA statistics, PSR and POR, were found on chromosomes 9, 11, 12, and 14 for neuroticism and on chromosomes 1, 5, 15, and 16 for anxiety disorders

Genome-wide, the results for the two phenotypes were significantly correlated, and a combined analysis identified additional nominally significant bins

Although none reached genome-wide significance, an excess of significant PSRP-values were observed, with 12 bins falling under a FDR threshold of 0.50

As demonstrated by the identification of multiple, consistent signals across the genome, meta-analytically combining existing GWL data is a valuable approach to narrowing down regions relevant for anxiety-related phenotypes. This may prove useful for prioritizing emerging genome-wide association data for anxiety disorders

Webb, B., Guo, A., Maher, B., Zhao, Z., van den Oord, E., Kendler, K., & ... Heath, A. (2012). Meta-analyses of genome-wide linkage scans of anxiety-related phenotypes. *European Journal Of Human Genetics*, 20(10), 1078-1084. doi:10.1038/ejhg.2012.47

Anxiety Disorders Study (3) SLC6A4, BDNF & GABRA6

Arias et al (2012) aim of their study was to test the individual association of the serotonin transporter gene (SLC6A4), the brain-derived neurotrophic factor gene (BDNF) and the GABRA6 receptor subunit gene (GABRA6) with anxiety-related traits and to explore putative gene-gene interactions in a Spanish healthy sample

A sample of 937 individuals from the general population completed the Temperament and Character Inventory questionnaire to explore Harm Avoidance (HA) dimension; a subsample of 553 individuals also filled in the Big Five Questionnaire to explore the Neuroticism dimension. The whole sample was genotyped for the 5-HTTLPR polymorphism (SLC6A4 gene), the Val66Met polymorphism (BDNF gene) and the T1521C polymorphism (GABRA6 gene).

Homozygous individuals for the T allele of the T1512C polymorphism presented slightly higher scores for HA than C allele carriers ($F = 2.96$, $P = 0.019$).

There was a significant gene-gene interaction on HA between the 5-HTTLPR and Val66Met polymorphisms ($F = 3.4$, $P = 0.009$)

Conclusion: GABRA6 emerges as a candidate gene involved in the variability of HA. The effect of a significant gene-gene interaction between the SLC6A4 and BDNF genes on HA could explain part of the genetic basis underlying anxiety-related traits

Arias, B. B., Aguilera, M. M., Moya, J. J., Sáiz, P. A., Villa, H. H., Ibáñez, M. I., & ... Fañanás, L. L. (2012). The role of genetic variability in the SLC6A4, BDNF and GABRA6 genes in anxiety-related traits. *Acta Psychiatrica Scandinavica*, 125(3), 194-202.
doi:10.1111/j.1600-0447.2011.01764.x

Anxiety Disorders Study (4) FKBP5

Minelli et al (2013) pointed out that Anxiety disorders exhibit remarkably high rates of comorbidity with major depressive disorder (MDD) and are considered stress-related diseases

Genetic variations in the co-chaperone FK506-binding protein 51, FKBP5, which modulates the function of glucocorticoid receptors, have been associated with an increased risk for the development of posttraumatic stress disorder, but data regarding its role in MDD are controversial

The aims of their study were to clarify the role of the FKBP5 gene in depression and anxiety disorders through a case-control study and an association study with personality traits using the Temperament and Character Inventory (TCI) in healthy subjects

Six hundred fifty-seven MDD patients, with or without an anxiety disorder in comorbidity, and 462 healthy volunteers were enrolled in the study. Two hundred fifty-six controls agreed to fill out the TCI.

The results showed that the T allele of rs1360780 was more frequent among the patients affected by MDD with a comorbidity of anxiety disorders, compared to those without ($P < .001$)

Among the controls, they found that the T allele more often exhibited personality traits associated with an increased vulnerability to anxiety

Conclusions Their results support the hypothesis that allelic variants of FKBP5 are a risk factor for anxiety disorders.

Minelli, A., Maffioletti, E., Cloninger, C., Magri, C., Sartori, R., Bortolomasi, M., & ... Gennarelli, M. (2013). Role of allelic variants of FK506-binding protein 51 (FKBP5) in the development of anxiety disorders. *Depression & Anxiety* (1091-4269), 30(12), 1170-1176. doi:10.1002/da.22158

Anxiety Disorders Study (5) Anxiety Sensitivity

Zavos et al (2012) looked into how anxiety sensitivity is associated with both anxiety and depression and has been shown to be heritable

They explored role of genetic influence on continuity and change of symptoms over time

Their aim was to examine the stability of anxiety sensitivity during adolescence

They used a genetically sensitive design and were also able to investigate the extent to which genetic and environmental factors influence anxiety sensitivity over time

Self-reports of anxiety sensitivity were obtained for over 1,300 twin and sibling pairs at 3 time points

Data were analyzed using multivariate genetic models

Anxiety sensitivity was moderately heritable at all time points with substantial nonshared environmental contributions

Time 1 genetic factors accounted for continuity of symptoms at Times 2 and 3

New genetic factors at Time 2 also influenced Time 3 symptoms

New nonshared environmental influences emerged at each time point

Analysis of a latent factor of trait anxiety sensitivity revealed some stable nonshared environmental influences

Genetic effects were generally stable over time, with new genetic influences emerging in late adolescence

Environmental influences on anxiety sensitivity were, on the whole, more time specific; however, some stable environmental influences were also found

Zavos, H. S., Eley, T. C., & Gregory, A. M. (2012). Longitudinal genetic analysis of anxiety sensitivity. *Developmental Psychology*, 48(1), 204-212. doi:10.1037/00024996

Anxiety Disorders Study(6) Genome Wide Association Study

Trzaskowski et al (2013) used together Genome Wide Association Studies (GWAS) and Genome-wide Complex Trait Analysis (GCTA) and their results suggest that anxiety - similar to height, weight and intelligence - is affected by many genetic variants of small effect, but unlike these other prototypical polygenic traits, genetic influence on anxiety is not well tagged by common SNPs

Trzaskowski, M., Eley, T. C., Davis, O. P., Doherty, S. J., Hanscombe, K. B., Meaburn, E. L., & ... Plomin, R. (2013). First genome-wide association study on anxiety-related Behaviours in childhood. *Plos ONE*, 8(4), 1-7.
doi:10.1371/journal.pone.0058676

In Conclusion

We have explored the Genetic Etiology of the Following Mental Health Disorders:

1. Autism Spectrum Disorder
2. ADHD
3. Schizophrenia
4. Bipolar Disorder
5. Major Depressive Disorder
6. Anxiety Disorders

We found that since the Genome Study Report of 2004, there have been great advances in the identification of the genetic etiology of mental health disorders and it is important for us as mental health professionals to always do a thorough psychosocial assessment which includes the mental health and substance use disorder background of our client's families going back at least three generations to pick up if there is a heritable trait in the family for the presenting condition