Genetic Factors in Serious Mental Illness

Alexander S. Nord, PhD, Assistant Professor, Department of Psychiatry and Behavioral Sciences, University of California, Davis, School of Medicine, Sacramento

Basic science: field entering new era of genetic testing for mental illness

DNA: changes in 4 bases termed polymorphisms or mutations depending on frequency in population; each cell contains ~3 billion base pairs of DNA; only 1% to 2% of genome encodes genes (information for making proteins); remaining genetic material mix of evolutionary detritus and regulatory information that controls when and where genes expressed

Epigenetics: refers to structure and packaging of DNA that affects function of genome; epigenetic factors translated across cells during development and across generations through inheritance

Mutations: emphasis in psychiatry currently on how mutations cause disorders; common mutations are switch of one base for another (substitution) or short loss (insertion or deletion); changes in position or orientation may involve few base pairs or entire chromosome (eg, aneuploidy and trisomy); mutation may interrupt triplicate code of DNA and thereby change single amino acid or entire structure of protein, possibly rendering protein nonfunctional; microdeletions, microduplications, and chromosomal mutations involve gains or losses of thousands or millions of base pairs; large mutations associated with schizophrenia

Mutations vs polymorphisms: mutations often inherited and relatively rare; in contrast, polymorphisms common across population; inherited mutations and common polymorphisms can underlie familial disorders; de novo mutations not inherited but arise during gametogenesis or meiosis; developmental disorders may arise from de novo mutations

Psychiatric disorders: most psychiatric disorders can be inherited, but precise causes hard to identify; at present, genetic diagnosis not possible; heritable disorders include schizophrenia (probably 80% heritable), bipolar illness (75%), autism (80% to 90%), attention-deficit/hyperactivity disorder (75%), and depression (estimates of heritability lower); diagnosis and prediction with genetic studies not yet feasible

Transmission of mutations: new mutation may be transmitted and reshuffled through recombination; continued transmission of de novo polymorphism changes its frequency in population

Genome-wide association (GWA) studies: genetic causes of disease studied using map of genome and knowledge of population-level variation in polymorphisms; however, GWA studies have led to few changes in clinical care; biologic discoveries exciting; GWA studies provide new insights into development of brain but cannot be used clinically to predict, diagnose, or choose treatment

Whole genome sequencing: coming in 5 to 15 yr; unclear whether it will alter management; goal to provide precision approaches based on genetic background; for example, pharmacogenomics deals with metabolism and effects of drugs

Types of studies: family studies assess contribution of genetics to disease; approach not fruitful for studying autism, schizophrenia, or other psychiatric disorders; in most cases, specific causal mutations not identified in families with high burden of disease, indicating that autism and schizophrenia do not follow rules of Mendelian inheritance; assessment of individual genomes provides some insight; on population level, these studies can explain 10% to 40% of causal mutations associated with severe autism; statistical inference used to understand genetic causes; large chromosomal mutations may strongly predispose toward psychiatric disorders, autism, and schizophrenia; current efforts focusing on large chromosomal mutations, smaller mutations across genome, and full genome analysis

Genetic risk: relationship between mutation and genetic risk reveals level of causality of mutation; assessed by plotting frequency of mutation against its penetrance; mutation may contribute to or cause disorder; rare low-risk variants difficult to find and contribute weakly to disorder; common high-risk alleles usually not identified (one exception apolipoprotein e4 allele associated with Alzheimer disease); common alleles with high penetrance rare in human disease and not found in autism or schizophrenia; classic causal mutations that behave in Mendelian fashion not identified for psychiatric disorders; many mutations not causal but do increase risk; mutations common in population typically contribute little to risk and therefore not useful for diagnosis

Rare variants: studies of de novo mutations have revealed some causal mutations; penetrance not 100%, but most individuals who carry these mutations have phenotype of interest

Neurodevelopmental disorders: few disorders behave in Mendelian fashion; single mutation or gene causes disease in Rett syndrome, fragile X syndrome, and tuberous sclerosis

Rare variants: highly penetrant rare variants and common variants provide useful information about autism and schizophrenia; rare variants associated with autism, and common variants associated with schizophrenia; mutations that cause autism tend to be more severe, cause changes to development of brain, and present early; in contrast, common polymorphisms might require interaction with environment (eg, stress, illness) to produce schizophrenia

Educational Objectives

The goals of this program are to improve understanding of the genetics of mental illnesses and to improve the diagnosis and management of treatment-resistant depression. After hearing and assimilating this program, the clinician will be better able to:
1. Explain how genetic risk is evaluated.
2. Describe the implications of overlapping biologic processes in patients with various psychiatric disorders.
3. Diagnose treatment-resistant depression.
4. Discuss the role of atypical antipsychotics for patients with treatment-resistant depression.
5. Manage a patient with treatment-resistant depression.

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22q11.1 deletion syndrome: numerous genes removed from chromosome 22; carriers have 1 mutant and 1 normal chromosome; also called DiGeorge syndrome or velocardiofacial syndrome; 2 deletions described (involving 3 million base pairs or 1.5 million base pairs); many patients exhibit psychiatric illness (most commonly schizophrenia, occurring in ≈25%); patients may have heart defects, dysmorphic features, immunodeficiency, intellectual disability, and behavioral problems; molecular diagnosis defines risk for individual and permits changes to care and monitoring; better understanding of pathophysiology shows why carriers have certain phenotypes

Other large deletion or duplication syndromes: these include 1q21.1 and 3q29; deletions or duplications individually rare, but they make up growing proportion of patients with neurodevelopmental disorders; genetics has led to advances in clinical care

Schizophrenia: large genetic study (≈40,000 cases and ≈115,000 controls) examined common variants; study identified 108 loci that contribute to schizophrenia; associated genes unknown for most loci; many variants change how DNA is used or made by cell but do not alter protein itself; immune genes involved in synaptic pruning during development of brain; variant causes one gene to prune more actively during development, altering communication among cells in brain; rare variants (including chromosomal mutations) may contribute

Significance of these contributions: instrumental for understanding neurobiology; investigators discovering key genes and periods during development when these genes may be important; findings beginning to explain pathophysiology, lead to targeted treatments, and reveal risk factors; biotechnology and pharmaceutical companies using new information to design treatments

Autism: common variants associated with autism well known; contributions of rare variants being studied; investigators seeking chromosomal mutations or other large mutations; knowledge of etiology not likely to translate into changes in care soon; identifying genomic mutations may reduce number of tests required to evaluate patients

Overlap: strong overlap found in biologic processes implicated in these disorders; suggests that common events during development of brain might lead to different presentations and phenotypes

Environment: environmental risk factors interact with genetic background to contribute to disease; stress or cortisol signaling may change gene expression; combination of common polymorphisms and environment might cause epigenetic changes

Current implications for clinical practice: advances in genetics still do not allow clinician to predict risk within family or for individual child

Suggested Readings


Psychopharmacologic Management of Refractory Depression

Teresa Pigott, MD, Professor, Department of Psychiatry and Behavioral Sciences, and Chief of Psychopharmacology, University of Texas-Harris County Psychiatric Center McGovern Medical School, Houston

Major depressive disorder: affects 18 million Americans and 340 million people worldwide; lifetime prevalence of depression 16%; two-thirds of patients with depression female; 25% to 40% of patients have recurrence within 2 yr of index episode; 85% of those who recover have another episode within 15 y; in 3 people with depression develops chronic depression

Antidepressants: many drugs available, and drugs similarly effective; selective serotonin reuptake inhibitors (SSRIs) include fluoxetine (Prozac, Sarafem), sertraline (Zoloft), escitalopram (Lexapro), citalopram (Cedia), paroxetine (Brisdelle, Paxil, Pexeva), and fluvoxamine (Luvox); serotonin-norepinephrine reuptake inhibitors (SNRIs) include venlafaxine (Effexor), desvenlafaxine (Khedezla, Pristiq), and duloxetine (Cymbalta); other drugs include bupropion (dopamine-norepinephrine reuptake inhibitor) and α2-blocker mirtazapine (Remeron); vilazodone (Viibryd) combines activity of SSRI with that of buspirone (Buspar); vortioxetine (Brintellix, Tintellix) acts on serotonin receptors and combines activities of SSRI, buspirone, and ondansetron (Zofran, Zuplenz)

Efficacy: meta-analysis of 46 randomized trials concluded that no second-generation antidepressant clearly superior; SSRIs as effective as other agents and have more acceptable side effect profile; patients unlikely to overdose on SSRIs

Selecting antidepressants: anxiety—patients with comorbid anxiety may benefit from SSRI or SNRI; bipolar depression—treated with lurasidone (Latuda), quetiapine (Seroquel), or lamotrigine (Lamictal); pain—SNRI such as duloxetine or venlafaxine better agent than SSRI for depressed patient with chronic pain; psychotic features—require use of antipsychotic plus antidepressant, or electroconvulsive therapy (ECT); seasonal component—managed with light and bupropion; atypical features—patients in whom depression characterized by excessive sleeping and eating may benefit from monoamine oxidase inhibitors (MAOIs)

If patient does not improve on first agent: clinician should first ensure that patient taking medication and consider possibilities of misdiagnosis, medical comorbidity, undertreatment, or inadequate trial of drug; current treatment should be maximized to avoid polypharmacy; ECT indicated in some cases; meta-analysis of 4 randomized trials in 1500 patients considered management after failure of SSRI; outcomes similar whether patient switched to another SSRI, mirtazapine, bupropion, or SNRI; if first SSRI ineffective, reasonable to try second one; however, if 2 SSRIs do not help, third SSRI should not be used; instead, SNRI, bupropion, or mirtazapine may be used; TCA or MOAIs appropriate but rarely used

Assessing efficacy: data suggest that if patient not improved by ≥20% after 2 wk, likelihood of full response by 6 wk only 20%; “treatment refractory”—no universally accepted definition; often defined as failure of 2 drugs at adequate doses for ≥6 wk; about one-third of patients do not respond to 2 antidepressants

If patient does not improve on second agent: clinician should reassess whether he or she has missed something (eg, bipolar depression or psychotic symptoms); psychotic symptoms in context of depression may be subtle; clinician should ask about auditory and other hallucinations and consider possibility of undertreatment; patients with severe depression more likely to relapse or have inadequate response; clinician should ask again whether patient taking medication and look for occult substance abuse, medical conditions, and anxiety

Risk factors for resistance: include severity of depression, longer duration of illness, early onset of illness (history of...
Managing treatment-resistant depression: agents that do not work include buspirone, folate, lamotrigine, and pindolol; if other agents fail, pramipexole (Mirapex) worth trying; other agents include mephaphenidate (Daytrana, Focalin, Ritalin), S-adenosylhomocysteine (SAM); derivative of folate) and ω-3 fatty acids; quetiapine or lurasidone may be used as monotherapy; pramipexole — selective D2/D3 agonist; single trial demonstrated significant response when pramipexole added; monotherapy trials have also been done; evidence for other dopamine agonists weak; stimulants — strong evidence supports adding methylphenidate, but most studies done in geriatric population; data do not support using stimulants in younger patients; SAM — available over the counter; one trial demonstrated efficacy after SSRI failed; ω-3 fatty acids — one study demonstrated effectiveness.

Suggested Readings


Acknowledgments

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Depression in childhood, anxiety, panic symptoms, substance abuse, early trauma, and poor social support

Treatment-resistant depression: clinician may either switch to different agent or add second agent; after lack of response to first SSRI, speaker tries second SSRI or SNRI; if 2 SSRIs tried, SNRI or bupropion used next; if patient initially failed SNRI, SSRI used; augmenting treatment preferred over switching; second-generation (atypical) antipsychotic should be considered; most-studied agents areripiprazole (Abilify), quetiapine (Seroquel), risperidone (Risperdal), and olanzapine (Zyprexa); if this treatment ineffective, clinician should try lithium, followed by triiodothyronine (T3)

Atypical augmentation: in addition to above atypicals, ziprasidone (Geodon) also effective; patients twice as likely to respond if augmentation used; no differences in efficacy demonstrated among individual atypicals, but these drugs associated with higher rates of discontinuation; metabolic syndrome and weight gain concerning, especially with olanzapine; 30% of patients respond if atypical antipsychotic added (vs 15% if placebo added); dose should be lower than for patient with schizophrenia or psychotic depression (patients with affective disorders more sensitive to side effects); atypical agent given for ≥6 wk; if not helpful, second atypical may be tried

Lithium and T3: if second atypical does not work, third atypical should not be used; instead, patient should take lithium or T3; lithium — helps suicidal patients, but some patients do not tolerate drug; T3 — studied in combination with SSRIs and SNRIs; dose 25 to 50 μg; thyroid levels should be followed; T3 contraindicated in patients with hyperthyroidism

Combining antidepressants: few data support this approach, which produces more side effects; changing drug or using augmentation strategy better than adding second antidepressant; some evidence shows that combining antidepressants (eg, mirtazapine plus venlafaxine) in first line may produce more rapid response, but practice uncommon.
1. Epigenetics refers to the study of:
   (A) Structure and function of proteins  (C) Structure and packaging of DNA
   (B) Penetrance  (D) Frequency of mutations in the population

2. Genetic risk is evaluated by:
   (A) Performing whole genome sequencing
   (B) Plotting the frequency of a mutation against its penetrance
   (C) Assessing the frequency of high-risk alleles in the population
   (D) Studying the phenotypes associated with de novo mutations

3. Genetic studies show that ________ variants are associated with autism and ________ variants are associated with schizophrenia.
   (A) Rare; common  (C) Rare; rare
   (B) Common; rare  (D) Common; common

4. Velocardiofacial syndrome (DiGeorge syndrome) is caused by a:
   (A) Polymorphism  (B) Microduplication  (C) Deletion  (D) Trisomy

5. The strong overlap in biologic processes that is observed across many psychiatric disorders suggests that:
   (A) The role of environment is stronger than previously suspected
   (B) Common events during development of the brain may lead to different presentations and phenotypes
   (C) Advances in genetics are unlikely to permit precise diagnosis of these disorders or predict risk
   (D) Rare undetected variants are probably important contributors to psychiatric disorders

6. The majority of patients with depression:
   (A) Experience a recurrence within 2 yr
   (B) Develop chronic depression
   (C) Are female

7. In a meta-analysis of 46 randomized trials, which of the following second-generation antidepressants was shown to be superior?
   (A) Selective serotonin reuptake inhibitors  (C) Bupropion
   (B) Serotonin-norepinephrine reuptake inhibitors  (D) None of the agents was clearly superior to the others

8. A 40-yr-old woman presents with moderate to severe depression that has been unresponsive to an adequate trial of a selective serotonin reuptake inhibitor. She has no anxiety or atypical or psychotic features. At this point, which of the following options IS NOT a recommended treatment?
   (A) Atypical antipsychotic  (C) Serotonin-norepinephrine reuptake inhibitor
   (B) Different selective serotonin reuptake inhibitor  (D) Mirtazapine

9. The patient described in Question 8 also does not respond to second-line therapy with a serotonin-norepinephrine reuptake inhibitor or to bupropion. She is considered to have treatment-resistant depression. Which of the following agents is now the most appropriate to try?
   (A) Tricyclic antidepressant  (C) Atypical antipsychotic
   (B) Lithium  (D) Triiodothyronine

10. Which of the following agents has been shown effective for treatment-resistant depression in one study?
    (A) Buspirone  (B) Pramipexole  (C) Lamotrigine  (D) Pindolol

Answers to Audio Digest Psychiatry Volume 46, Issue 03: 1-D, 2-B, 3-D, 4-C, 5-A, 6-C, 7-B, 8-A, 9-C, 10-A