Genetics of Mood Disorders

Introduction

- Mood disorders run in families is a common observation of patients and clinicians.
- Genes contribute to predisposition that must interact with the environmental factors to cause disease.
- Recent molecular techniques have helped to identify specific genes involved.
- The study of how genes influence medication response is also making progress (pharamcogenetics)

Genetic epidemiology

The following questions can be addressed:

Are mood disorders familial? Are they genetic?

What portion of the etiology is genetic?

How are the genes for mood disorder transmitted?

How do different forms of mood disorder differ in their genetic transmission?

How are different forms of mood disorder related to each other?

Family studies

- Is the rate of illness in the family members of someone with the disorder greater than that of the general population?
- The rates of illness are then compared to either the rates in the general population or the rates in first-degree relatives of control subjects.
- Rates of illness are typically adjusted for age to indicate the morbid risk.

Family studies

- The studies indicate a morbid risk of bipolar disorder in first-degree relatives of 3-8%.
- The ratio of risk to family members divided by the population rate of illness is a genetic parameter typically notated as λ.
- Compared to a rate of 1% in the general population, bipolar disorder has a λ value of approximately 7, indicating a strong familial risk.
- Studies of families of unipolar probands reveal morbid risks for unipolar disorder among first-degree relatives that are elevated 2-3x over those of the general population.

Family studies

- Unipolar disorder is typically the most common form of mood disorder in families of bipolar probands.
- However, the rate of bipolar disorder is only slightly elevated in the families of unipolar probands.
- This familial overlap suggests some degree of common genetic underpinnings between these two forms of mood disorder.

Twin studies

- Twin studies provide the most powerful approach to **separating genetic from environmental factors, or "nature" from "nurture."**
- The **proportion of twin pairs in which both twins are affected is determined. This is termed the concordance rate.**
- 2-4x increase in concordance rate for mood disorder in the MZ twins compared to those in the DZ twins.
- Concordance rate for MZ twins is not 100%.
- MZ to DZ concordance ratio for bipolar–bipolar pairs is higher than that for unipolar–unipolar pairs.

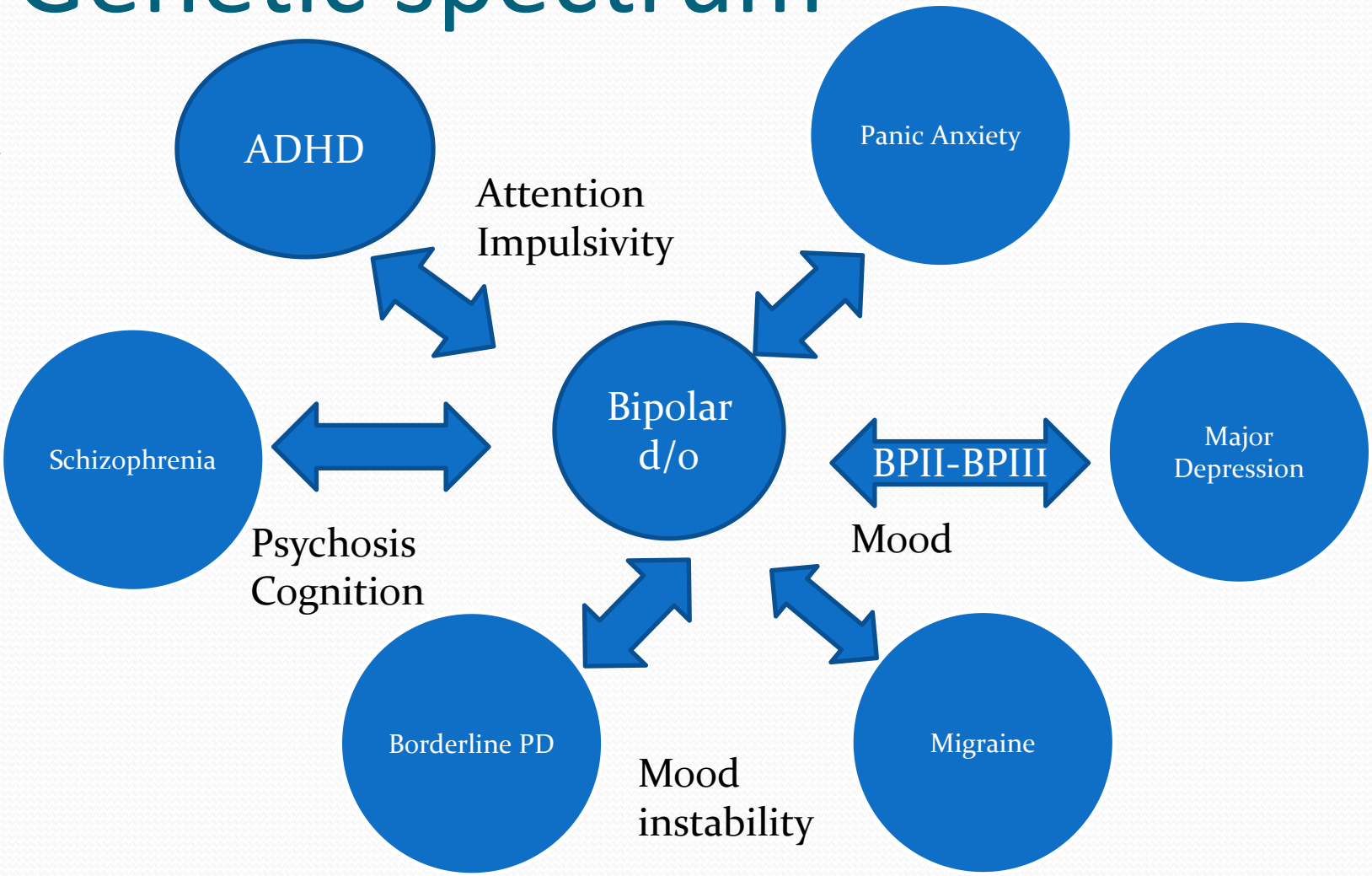
Adoption studies

- The probands are identified who have a mood disorder and were adopted at birth. Through this event, nature is separated from nurture.
- The rates of psychiatric illness are then determined in both the biological and adoptive parents.
- 3x increase in the rate of bipolar disorder and a 2x increase in unipolar disorder in the biological relatives of bipolar proband.
- 3x increase in the rate of unipolar disorder and a 6x increase in the rate of completed suicide in the biological relatives of affectively ill probands were reported.

Mode of transmission

- **Segregation analysis** help to predict the patterns of several different models of transmission.
- Results of such analyses have been mixed.
- X-linkage has also been argued based on the observation that female relatives of bipolar probands have a 2x higher risk for unipolar disorder.
- **Mood disorders are transmitted in a hetrogenous fashion.**

Genetic spectrum



Forms of Mood Disorder That Are Partially Genetically Distinct or More Heritability

Bipolar Disorder

Psychosis
Early age at onset
Comorbid alcoholism
Suicidality
Comorbid migraine
Comorbid panic or anxiety
Bipolar II
Lithium responsive

Unipolar Disorder

Early age at onset
Recurrent
Comorbid alcoholism
Psychosis

Linkage studies

- **Numerous linkage studies of bipolar disorder have implicated many different chromosomal regions**.
- **Linkage to Chr 18q to preferentially occur in families in which affective illness was transmitted through the mother, suggesting a possible parent-of-origin effect**.
- Chromosome 12q was first suspected based on the identification of a Welsh family in which bipolar disorder cosegregated with a rare skin disease, Darier's disease.

Linkage studies

- Chr 22q11 deletion syndrome called velocardiofacial syndrome.
- A specific gene, G protein receptor kinase 3 (GRK3) has been reported as a gene for bipolar disorder within one of these 22q linkage peaks.
- One study identified 13q and 22q as the two reasons with strongest evidence to bipolar disorder.

Candidate genes

Gene symbol	Gene name or function	Bipolar assc.	Unipolar association
HTTLPR	Serotonin transporter	+	+
BDNF	Brain-derived neurotrophic factor	+	+
CREBT	Cyclic AMP response element binding protein	+	+
FKBP5	Glucocorticoid receptor chaperone protein	+	+
P2RX7	ATP receptor	+	+
COMT	Catechol O methyl transferase	+	+
TPH2	Tryptophan hydroxylase 2	+	+
GRK3	G Protein receptor kinase 3	+	
NTRK3	Neurotrphin receptor tyrosine kinase 3		+
DAT1	Dopamine transporter	+	
DRD4	D4 dopamine receptor	+	
GRIK4	Kainic acid type glutamate receptor	+	+
HTR2A	Serotonin receptor 2 A	+	
NRG1	Neuregulin	+	+
DISC1	Disrupted in schizophrenia	+	+
DAOA (G72)	D- Amino acid oxidase activator	+	+

Pharmacogenetics

- Genetic variation in the cytochrome P450 system influences the degradation of a number of drugs.
- A drug may work in one patient with depression and not another because the two patients have illnesses that are biochemically distinct.
- A G protein subunit gene (GNB3) has been reported to predict response to antidepressants and lithium.
- BDNF and the gene for its receptor,NTRK2, have been associated with lithium response.
- The serotonin transporter has also been reported to predict antidepressant-induced mania and antidepressant response to sleep deprivation.

Genetic counselling

- The twins studies argue strongly that only **50-70% of etiology mood disorders is genetic.**
- If **one parent** has a mood disorder, then a child will have a risk for mood disorder of between **10 and 25 percent.**
- If both parents are affected, then this risk roughly doubles.
- The more members of the family that are affected, the greater the risk to a child.

Genetic counselling

- The risk is greater if the affected family members are first-degree relatives rather than more distant relatives.
- The presence of more severe illness in the family also likely conveys a greater risk.
- It is **important to emphasize that their child carries a risk or predisposition to illness rather than a certainty of illness.**
- It is also **useful to emphasize the range of illness, from mild to severe,** that could result and the availability and efficacy of treatment

Genetic counselling

- For existing children, it is important **to educate parents about the typical age of onset, presenting symptoms, and the importance of early recognition and treatment.**
- This must be balanced with the goal of not labeling the child or being overly protective.

Conclusion

- Genetic studies promise a new era of understanding and treatment of mood disorders.
- Pharmacogenetics promises better avenues of treatment
- Genetic counselling assumes great clinical significance in mood disorder.

Thank you