

39 - A. Causal models

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© SPMM Course memory defects, information processing defects such as prepulse inhibition, smooth pursuit defects, glial cell changes and certain other putative neurocognitive markers are termed as probable endophenotypes for schizophrenia. To be an endophenotype, a character must be observable independent of clinical state and must be measurable in relatives at a higher degree than the general population. In spite of their simplicity, there are some important problems that need to be overcome while studying endophenotypes. □ The endophenotypic expression could be well under the influence of the developmental environment. □ An endophenotype can be differentially expressed in different brain regions. □ Often patients have multiple endophenotypic deficits with significant interaction among these. □ In spite of hard toil, researchers are unable to narrow down genetic linkages of suspected endophenotypes to achieve better than modest LOD (log of odds) scores.

13. Psychiatric genetics A. Causal models Several notable features regarding psychiatric genetics are listed here (excerpted from Craddock et al., BJPsych, 2007:190;3)
14. Families with clear Mendelian inheritance patterns are rare: There are no clear demonstrations of Mendelian pattern of inheritance of schizophrenia or other psychiatric disorders in families.
15. Single genes of major effect have not been found: Even in extended pedigrees with multiple cases of psychiatric illnesses, intensive molecular genetic studies have not demonstrated mutations of major effect (LOD scores are meager). The odds ratio in most psychiatric genetic association studies are in the order of 1 to 2; median being 1.3. This is insufficient to prove a genetic cause for most disorders. These findings are suggestive of multiple risk alleles of modest effect.
16. Mathematical modelling of familial risk is inconsistent with single genes of large effect: According to Craddock et al., “for both schizophrenia and bipolar disorder there is a very rapid, non-linear decrease of risk when moving from a genetically identical individual (i.e. monozygotic co-twin where the risk is 50– 60%), to an individual who shares half the genes (e.g. sibling, parent, dizygotic co-twin where risk is around 10%)”. This rapid, non-linear decrease of risk is compatible with multiple interacting risk factors, albeit of unknown frequency, that individually have modest effects.
17. The causal pathway from an identified genetic abnormality to actual disease expression is too complex and not fully explored in any known genetic markers of psychiatric diseases. For example it is unclear how mutant dysbindin gene that is implicated in schizophrenia can lead to a belief that aliens are invading earth. The association between genes and diseases are very non-specific and weak with respect to psychiatric diseases.

© SPMM Course 5. Contingent models of association: Non-contingent gene-disorder association refers to the fact that the relationship is not influenced by other factors such as environment or presence of other genes i.e. not polygenic or multifactorial. But most psychiatric disorders do not follow non-contingent association models. 6. Practical difficulties in conducting genetic enquiries in psychiatry: a. Wide ethnic, geographical variations are seen in psychiatric disorders. b. Ascertainment method. The spectrum of clinical features (symptoms, severity, functioning, illness course, etc.) of individuals recruited depends upon the mode of ascertainment. These variations can reduce or increase the modest effect sizes noted. c. Unknown phenotypic model. Reliance on DSM-IV or ICD-10 categories is a huge challenge for psychiatric genetics. These are arbitrary classifications, and it is possible that we have been missing many etiological factors due to these empirical categories. For example, the distinct DSM-based categories of affective disorders may not breed true as strong overlap exists between the genetic risk of unipolar and bipolar disorders. Two views exist concerning the causal modeling of genetic factors in psychiatric disorders (Craddock et al., 2007):

1. Common disease-rare variant model: Rarely occurring mutations cause diseases such as schizophrenia. There are various different mutations that can explain the disease (locus and allelic heterogeneity). But each mutation is sufficient but not necessary to cause the disease. Each family inherits one such mutation explaining higher risk in the relatives. These mutations are rare, but when present they commonly cause the disease.
 2. Common disease-common variant model: Here a disease such as schizophrenia is thought to be a result of the co-action of multiple (ranging in principle from a few to many thousand) common variants ('polymorphisms'), each of which has a small effect on illness susceptibility – see table below. When an individual inherits several, or many, susceptibility variants together, they have a sizable influence on disease risk. Hence, the mutations or polymorphisms are not sufficient by themselves to cause disease, but they occur very commonly so they can interact in combinations and produce the disease. This model is more popular currently and forms the basis of association and linkage studies being carried out widely.
- | Characteristics | Mendelian disorders | Most psychiatric disorders |
|-------------------------|---|----------------------------|
| Diagnostic boundaries | Clear | Vague |
| Phenocopies | Absent | Multiple |
| Penetrance | Usually complete/ predictable | Incomplete / unpredictable |
| Association | Non-contingent models | Contingent models |
| Modelling familial risk | Linear change in risk | Non-linear changes in risk |
| MZ concordance | Nearly 100% | 30-70% only |
| Locus heterogeneity | Never within families; often absent across families too | Likely |

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