

Family-based Association Studies

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Family-based Association Studies: Outline

- Definitions
- Advantages and disadvantages
- Possible study designs
- Computer software
- Summary

Two types of association tests

- There are two types of association tests that are usually performed
 - Population-based: to compare frequencies of sequence variants between cases and controls
 - Family-based: to compare the transmission of sequence variants from parents to affected offspring

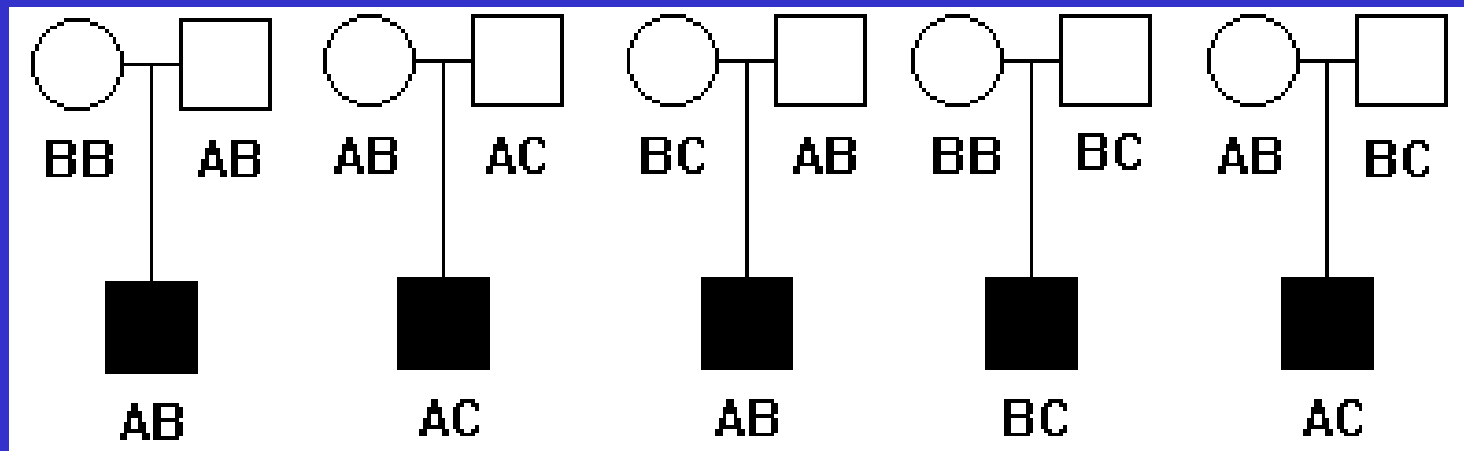
Purpose of an association test

- Candidate genes: whether sequence variants within a gene are associated with a disease, primarily look for a causal mutation
 - Functional SNPs, SNPs with much denser resolution
- Fine mapping: whether sequence variants in a chromosomal region are associated with a disease, primarily looking for LD with a causal mutation
 - SNP with less denser resolution

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Transmission Disequilibrium Test (TDT) in Trios



Allele 'A' is transmitted 4 out of 5 times

Population-based or family-based association studies

Population-based

- Population cases and controls
- Easy to generalize
- More informative
- More heterogeneous

Family-based

- Family members (trios or extended)
- Difficult to generalize?
- Less informative
- Less heterogeneous

Population-based or family-based association studies

Population-based

- Easier to ascertain
- Subject to population stratification
- Prone to genotyping error

Family-based

- More difficult to ascertain
- NOT subject to population stratification
- Less prone to genotyping error

Advantages of family-based association studies (transmission test)

- Important to demonstrate transmission between generations
- Different source of information than from cases and control studies
- Not susceptible to population stratification
- Family with multiple affected members are more likely to be genetic cases

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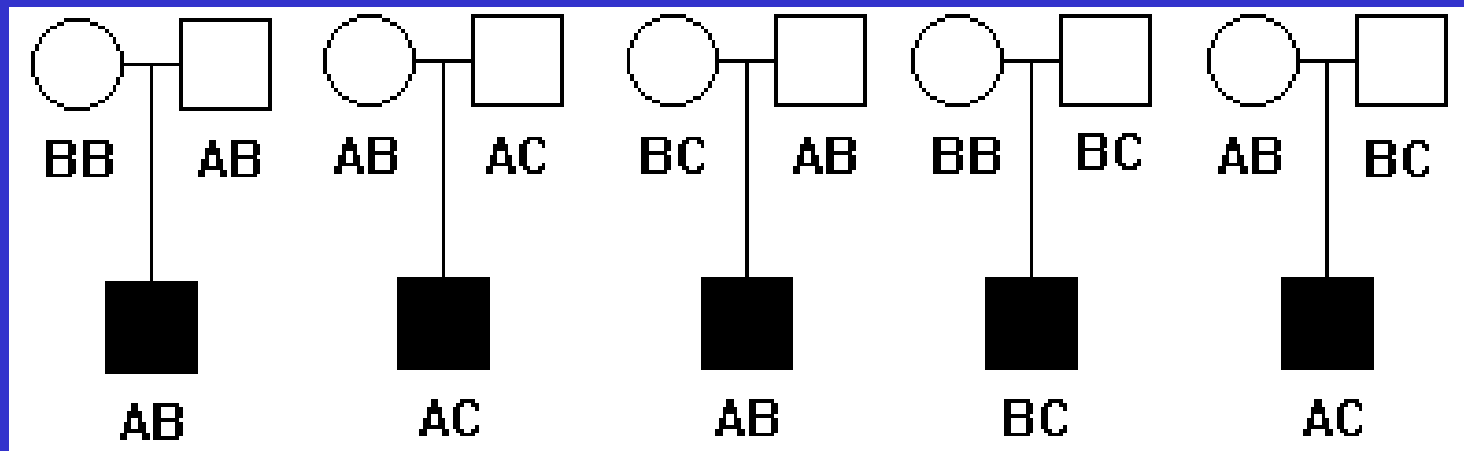
Several types of family-based association studies

- Comparing frequencies among affected and unaffected
 - Probands and spouses (association)
 - Discordant sibs (association)
 - All family members, GEE (linkage and association)

Several types of family-based association studies

- Transmission tests
 - TDT in trios (association)
 - TDT in nuclear and extended families (linkage and association)
 - FBAT in nuclear and extended families (linkage and association)

Transmission Disequilibrium Test (TDT) in Trios



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Commonly available computer programs

- TDT for qualitative variables: Genehunter
- TDT for quantitative variables: QTDT
- Family-based association test: FBAT
- Family-based association test: TRANSMIT

TDT for qualitative variables: Genehunter

- Perform TDT for affection status
- For typical trios (association) and nuclear/extended families (linkage and association)
- Families with or without parental genotypes
- Can perform two-locus, three-locus, four-locus analysis
- Can perform permutation test for determining TDT significance
- Easy to run
- <http://www.fhcrc.org/labs/kruglyak/Downloads/index.html>

TDT for quantitative variables: QTDT

- Perform TDT for quantitative and qualitative variables
- For typical trios (association) and nuclear/extended families (linkage and association)
- Families with or without parental genotypes
- Can perform permutation test for determining TDT significance
- Easy to run
- <http://www.sph.umich.edu/csg/abecasis/QTDT/>

Family-based association test: FBAT

- For qualitative trait (affection status)
- Perform haplotype analysis based on several closely linked markers
- Uses data from nuclear families and extended families
- Parental genotype and/or haplotype phase may be missing
- Allele/haplotype specific or global tests
- <http://www-gene.cimr.cam.ac.uk/clayton/software/>

PBAT (C Lange)

- PBAT: Tools for Family Based Association Tests (FBAT)
- <http://www.biostat.harvard.edu/~clange/default.htm>
- Haplotype and single SNP analysis
- Nuclear families and extended pedigrees
- Discrete and quantitative traits

PBAT (Cont)

- Adjustment for covariates
- <http://www.biostat.harvard.edu/~clange/default.htm>
- Screening tools to handle the issue of multiple comparisons in genome wide association studies
- Review: Laird and Lange: Family-based designs in the age of large-scale gene- association studies, Nature Genetics Review, May 2006

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Issues to consider

- Choice of population
 - Enrichment of genetic cases?
 - Sources of heterogeneity (attempt to increase frequency of a specific mutation)

Take home lessons: Issues to consider

- Study design – case-control or family-based
 - Ideal versus practical
- Source of information (due to linkage or association)

Take home lessons: Issues to consider

- Phenotype of cases
 - Definition of disease
 - Testing to be performed

- Controls
 - Comparable, any phenotype testing?

Example: Real life

- Case-control study (probands and spouses)
 - p value = 0.016
- TDT: p value = 0.06
- FBAT: p value = 0.09
- Looks good, however..

Example: Real life

- Looks good, however..
- Case-control study: significance due to increased frequency of '22' in cases versus control
- Family based: Allele 1 is over-transmitted!
- Inconsistent results