

# **Transmission Tests for Linkage and Association**

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# Linkage v. Association (Candidate Gene Study for Type 1 Diabetes)

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- Association study
    - Significant evidence FOR determinant near insulin gene (INS)
  - Linkage study (ASP – 100 affected sib pairs)
    - NO evidence for determinant near INS – lod  $\approx 0$
  - Which shall we believe?
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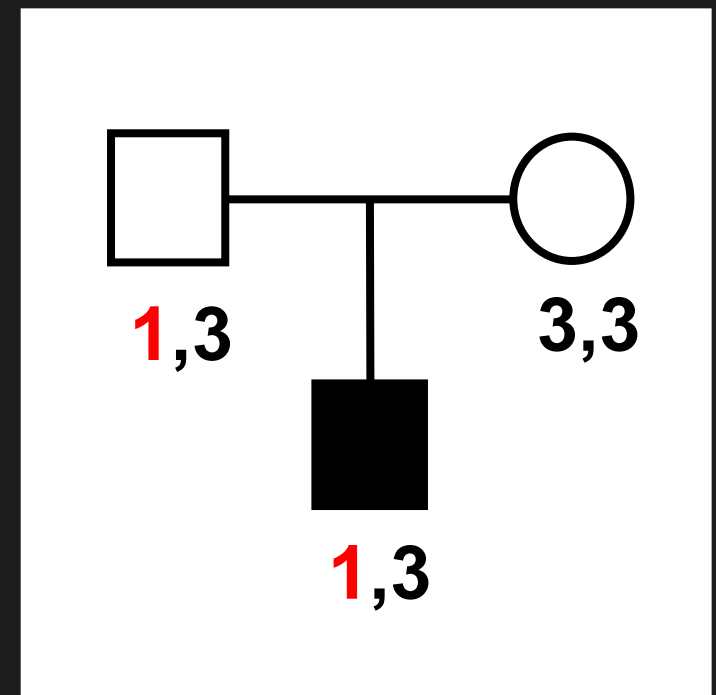
# TDT

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- **Test for simultaneous presence of linkage and association**
    - (i.e., Linkage disequilibrium - LD)
    - **Transmission/disequilibrium test (TDT)**  
**With R. McGinnis, W. Ewens – 1993**
    - **Original idea (Ott); similar concept Ott and Terwilliger**
  
  - **Many further developments since**
    - **“Genomic control”**
    - **Structured population analysis**
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# Transmission/disequilibrium test (TDT)

- Family-based test for linkage and allelic association
- Count transmissions of a **particular marker allele** from heterozygous parents to all affected offspring.
- Observe more (or less) than 50% transmissions if linkage and association present.
- Test significance by  $\chi^2$



1 transmission of allele 1

# TDT Analysis in Practice

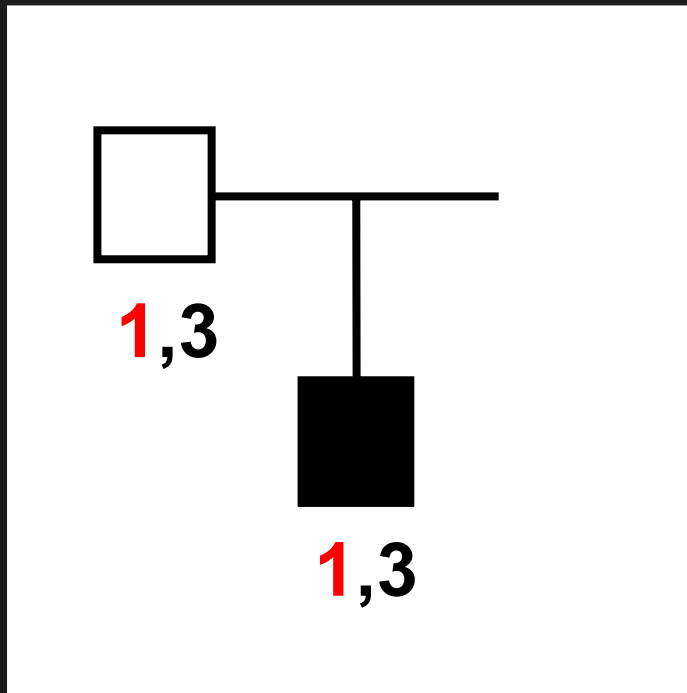
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**Assemble large number of parent-child “Trios”**

- **Determine marker allele transmitted from heterozygous parent(s) in each trio**
  - **Departure from equal transmission is evidence for both linkage and association, i.e., LD**
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# How Does it Work?

$\frac{D \ 1}{d \ 3}$  or  $\frac{D \ 3}{d \ 1}$



**No Linkage: independent assortment**

**No Association: Two “arrangements” equally frequent**

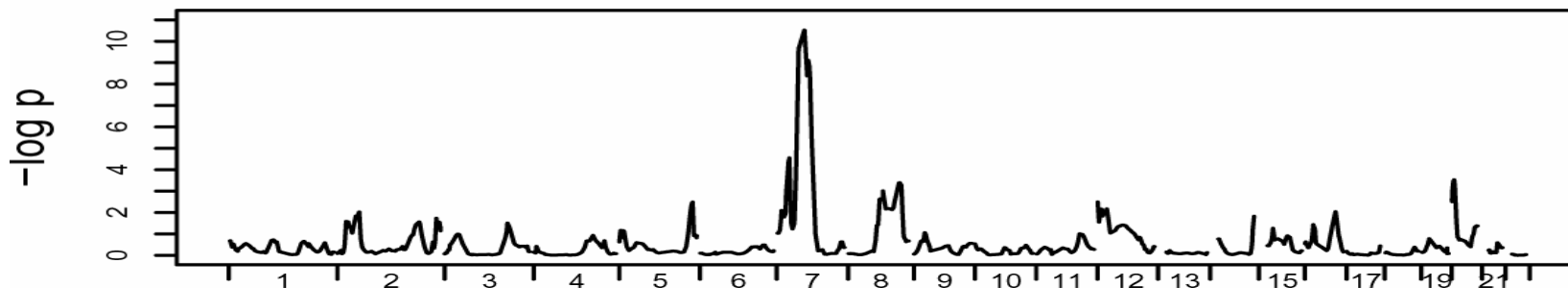
**Association (D with 1): 1 “overtransmitted” to affected**

# Association Also Gives Valid Answers!

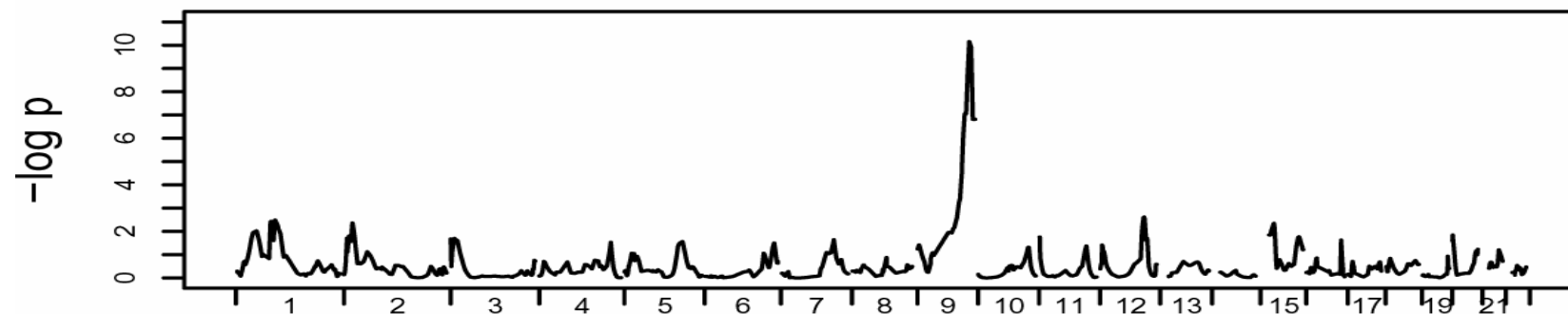
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- Recall genome scans from yesterday
    - Confirmed by association – SNP with expression level
  - Whole-genome association (AMD, Schadt, others)
  - Conclusion: Case-control can give right answer (and of course TDT can give false positive)
  - No “algorithm” for the truth
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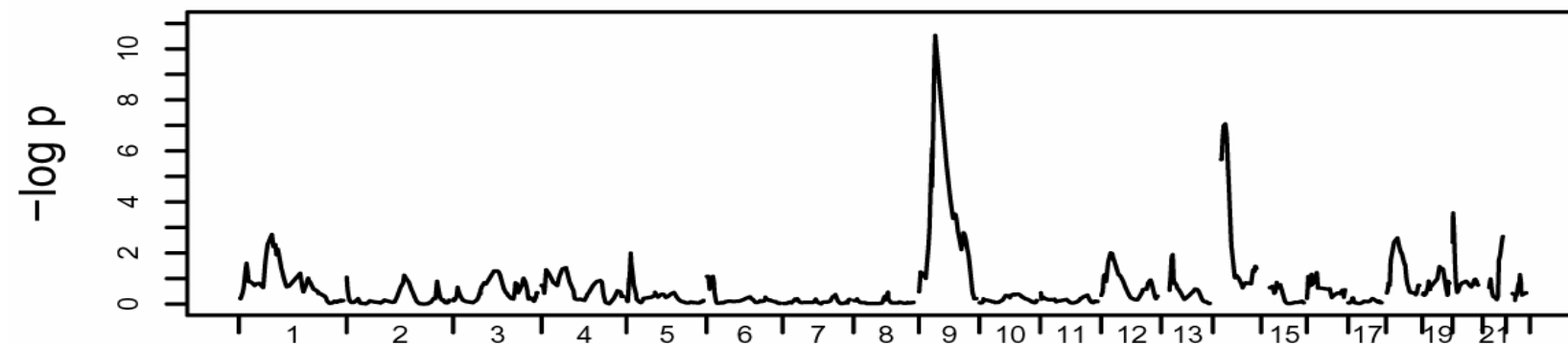
***PSPHL* (Chr 7) cis**



***HOMER1* (Chr 5) trans**



***DSCR2* (Chr 21) multiple**



# ASSOCIATION ANALYSIS

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## Goals:

- Validate the linkage results
- Narrow the candidate regulatory regions

## International HapMap Project:

- genotypes for ~ 1 million SNP markers

## Whole genome association:

- identify the candidate regulatory regions despite the problem of multiple testing?

# WHOLE GENOME ASSOCIATION

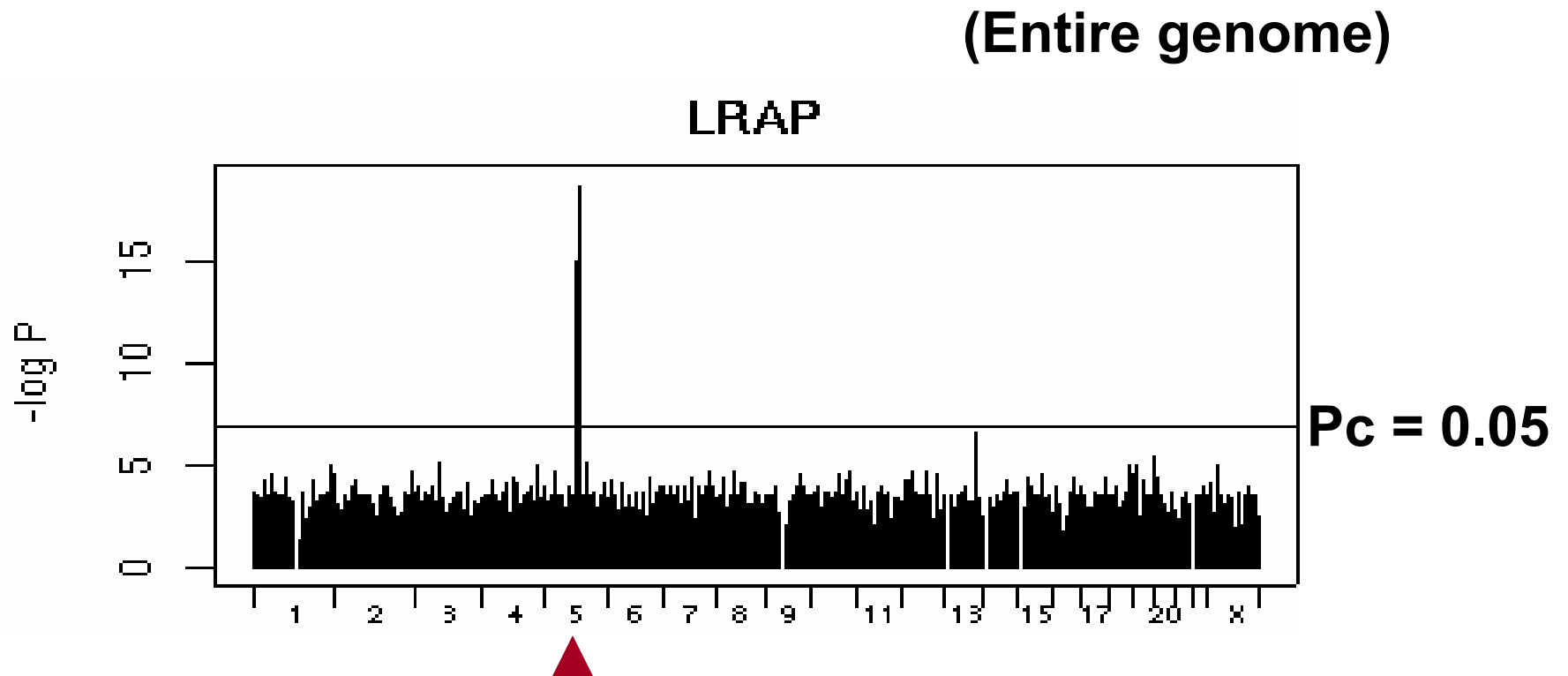
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## **57 unrelated CEPH grandparents**

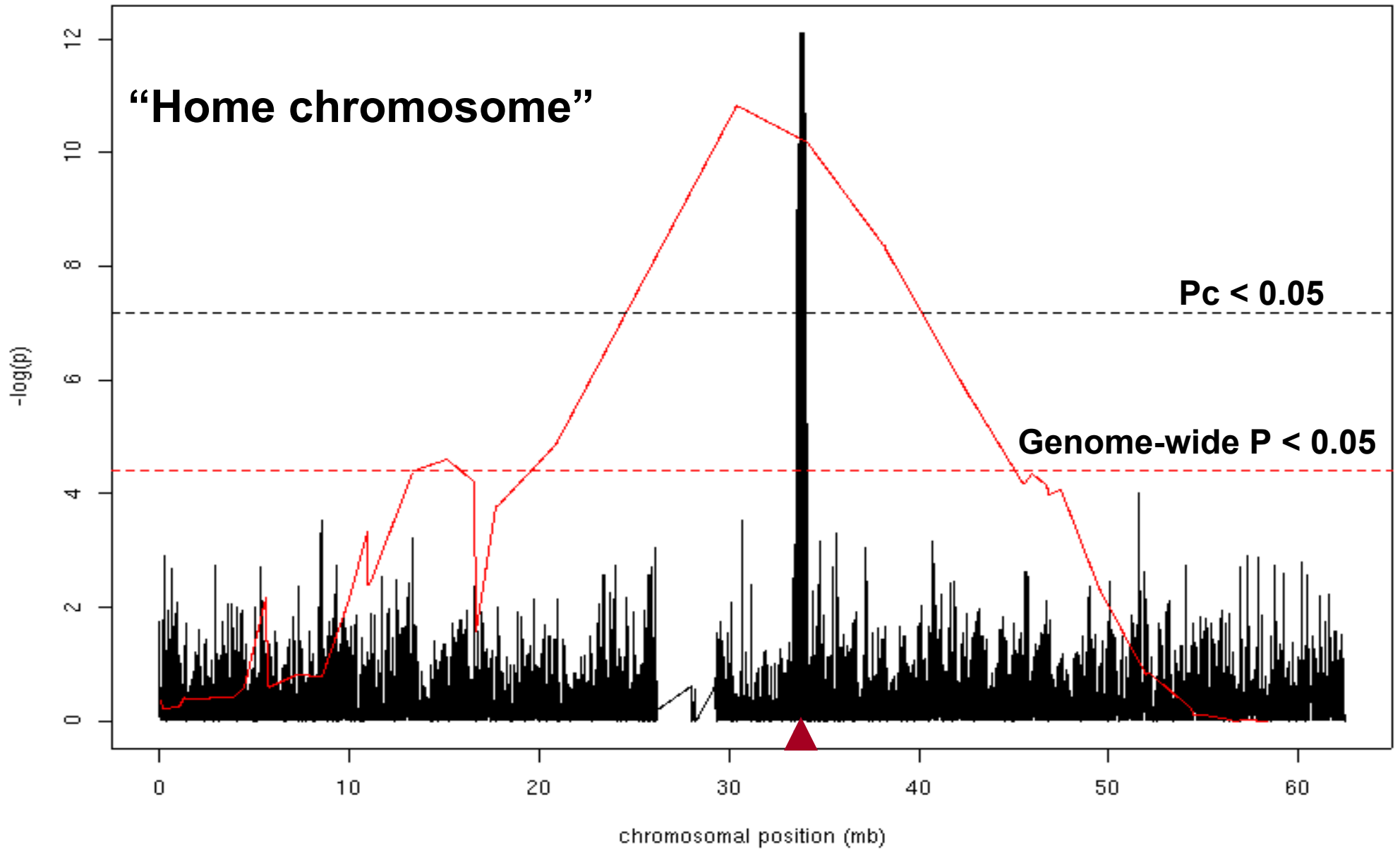
- **Phenotypes: expression levels for 27 genes, selected by highly significant linkage results**
- **Genotype: 770,394 SNP from HapMap (excluded missing data, monomorphic markers)**
- **Expression level (dependent variable) was regressed on SNP genotype (coded 0, 1, 2)**
- **P-value: Bonferroni correction for multiple testing**

# RESULTS

- 14 of the 27 phenotypes: at least one significant marker ( $P < 0.05$ ) after correction



CPNE1 Chromosome 20



# Complex Diseases - Goal

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**Want to know:**

**All the locations (genes, determinants) make**

- **Some people more**
- **Some people less**

**susceptible to the disease**

**(reality: still usually analyze one gene at a time)**

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