Genome-wide strategies for detecting multiple loci that influence complex diseases

Jonathan Marchini, Peter Donnelly, Lon R Cardon

Presented by Jeff Kilpatrick

Introduction

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- Large collections of human data now available
- Massively parallel genotyping can produce data for over a million genetic markers per person -- fast

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  2. Compile list of genes near significant markers

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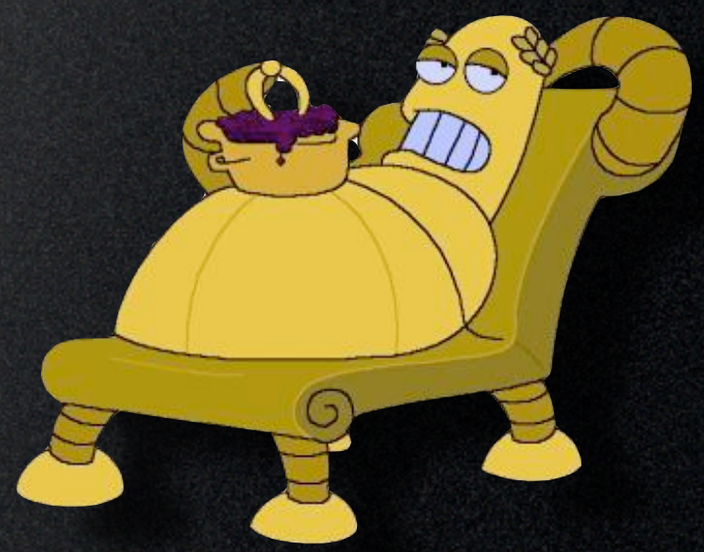
  4. Grow fat and wealthy with a supermodel spouse



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  - Evidence suggests interactions contribute broadly to complex traits
  - Frequency distribution of marker variants affects their statistical power

Introduction

- This paper explores two questions
  - Is there hope for consistently detecting such effects?
  - How do we design and analyze genome-wide association studies?

The Plan Today

- Interaction models
- Analysis strategies
- Power analysis
- Loose ends

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Interaction Models

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- Model: a mathematical description of how genes confer risk

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- Example: “exactly two disease variants from two susceptibility loci are required”

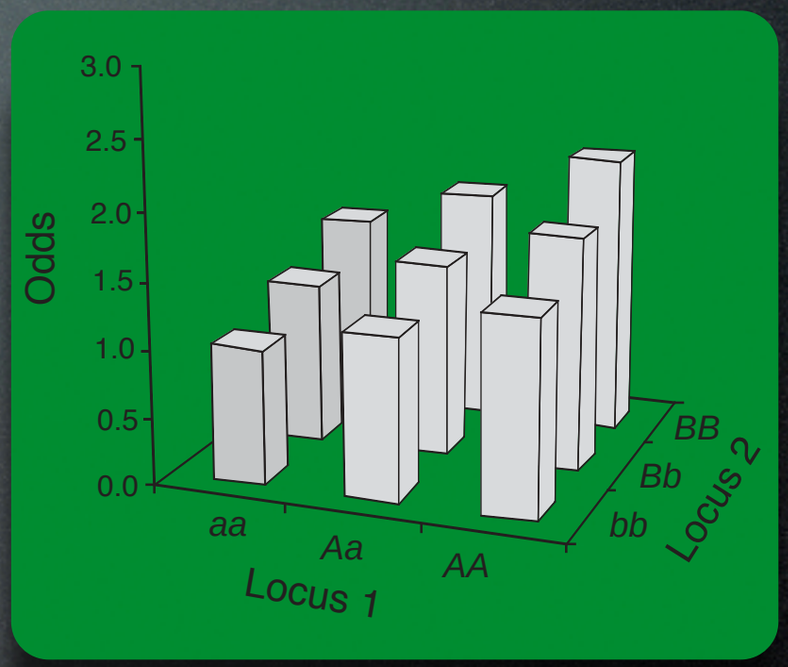
Interaction Models

- The example:

	AA	Aa	aa
BB			✓
Bb		✓	
bb	✓		

Interaction Models

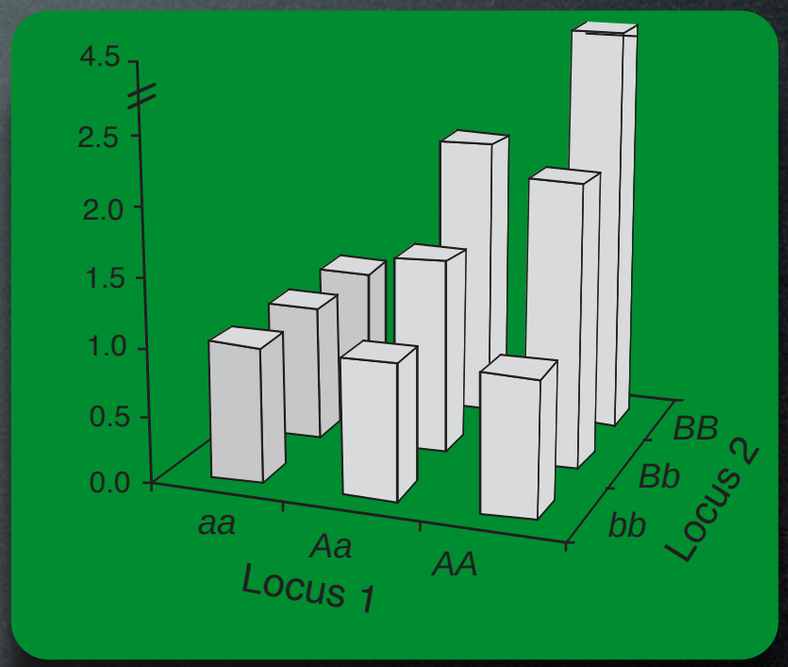
- Adding a disease variant at either marker multiplicatively increases risk
- Loci do not interact



Model 1: multiplicative within and between loci

Interaction Models

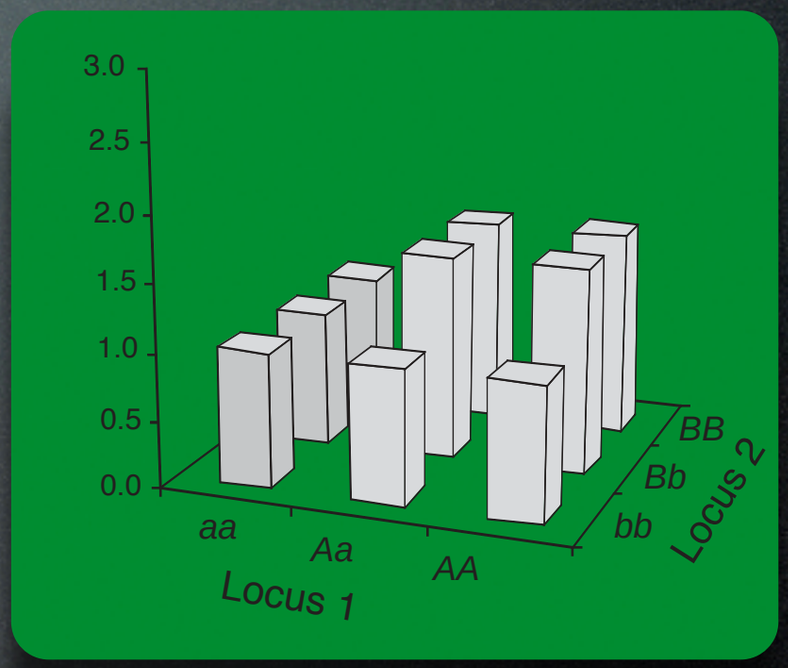
- Neither locus alone is sufficient
- Multiple risk alleles from different loci increase risk linearly



Model 2: two-locus interaction multiplicative effects

Interaction Models

- Neither locus alone is sufficient
- Presence of risk variants from both markers increases elevates risk to constant level



Model 3: two-locus interaction threshold effects

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- Power analysis
- Loose ends

Analysis Strategies

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- Tests cost time. Time is money.
- Tests cost significance

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  - Requires n^2 tests
  - Will discover all pairwise interactions, assuming their effects survive correction for multiple tests

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  - Search for mildly associated loci
  - All pairs of selected loci are tested

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- Calculations assume L = 300,000 markers, with two (unobserved) causative loci
- Bonferroni correction applied

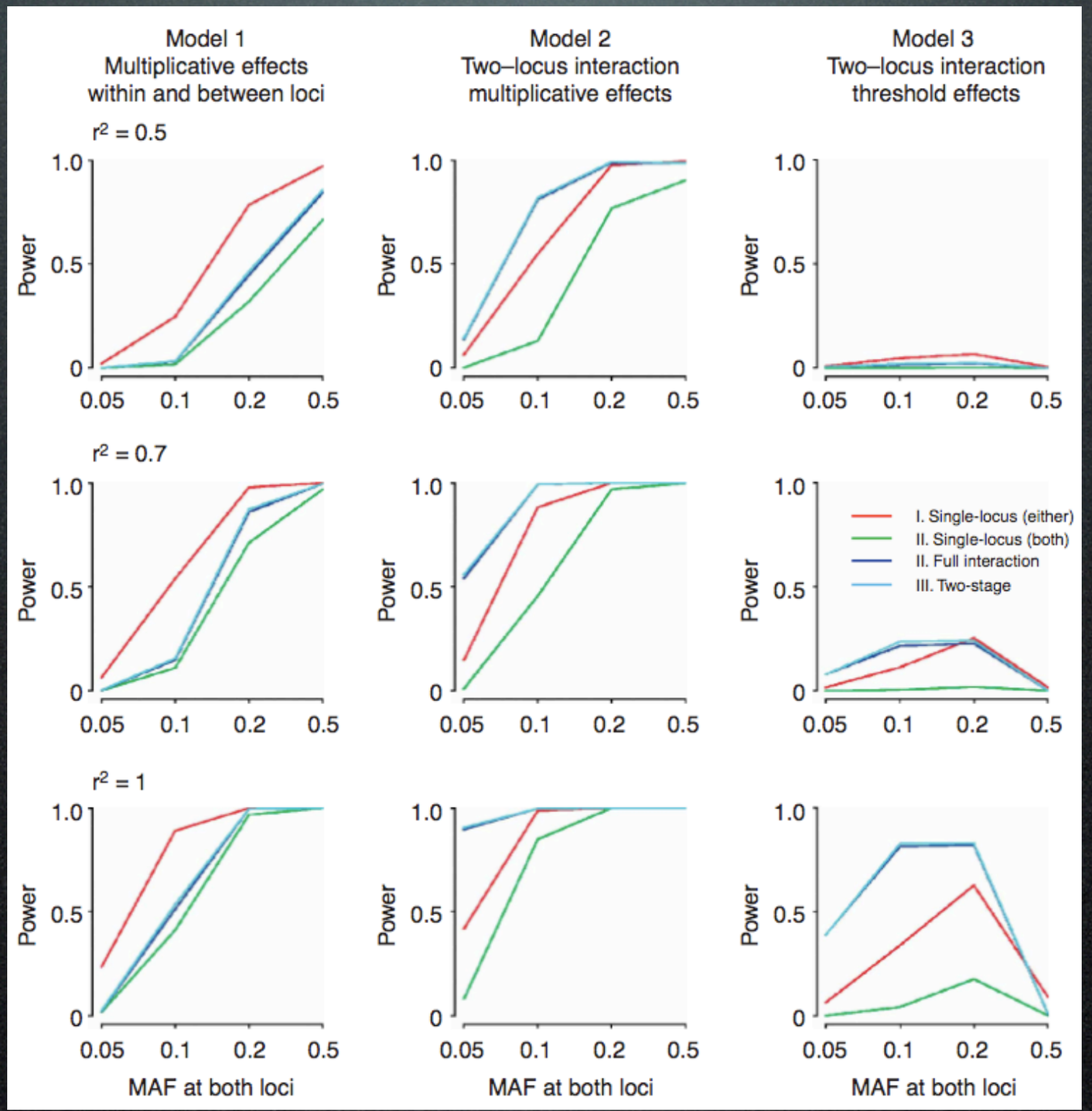
Power Analysis

Distance to disease locus

High

Medium

Low



Dreamland (either locus)

Dreamland (both loci)

Styx (both loci)

The Compromise (both loci)

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- Power strongly correlated with minor allele frequency and LD

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- Styx approach took 33 hours on ten nodes with 300,000 markers and 2,000 subjects

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Loose Ends

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- Different allele frequencies between initial and follow-up cohorts

Loose Ends

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Loose Ends

- This study understates usefulness of interaction searches
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- Permutation testing would be more accurate

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- All non-exhaustive interaction searches may miss some effects
- Complete enumeration is too expensive for higher order effects
- The Compromise provides the best of both worlds in most studies

Questions