Nancy's $100M Project

THE UNIVERSITY OF CHICAGO

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http://genemed.bsd.uchicago.edu

Relating Variation to Phenotype

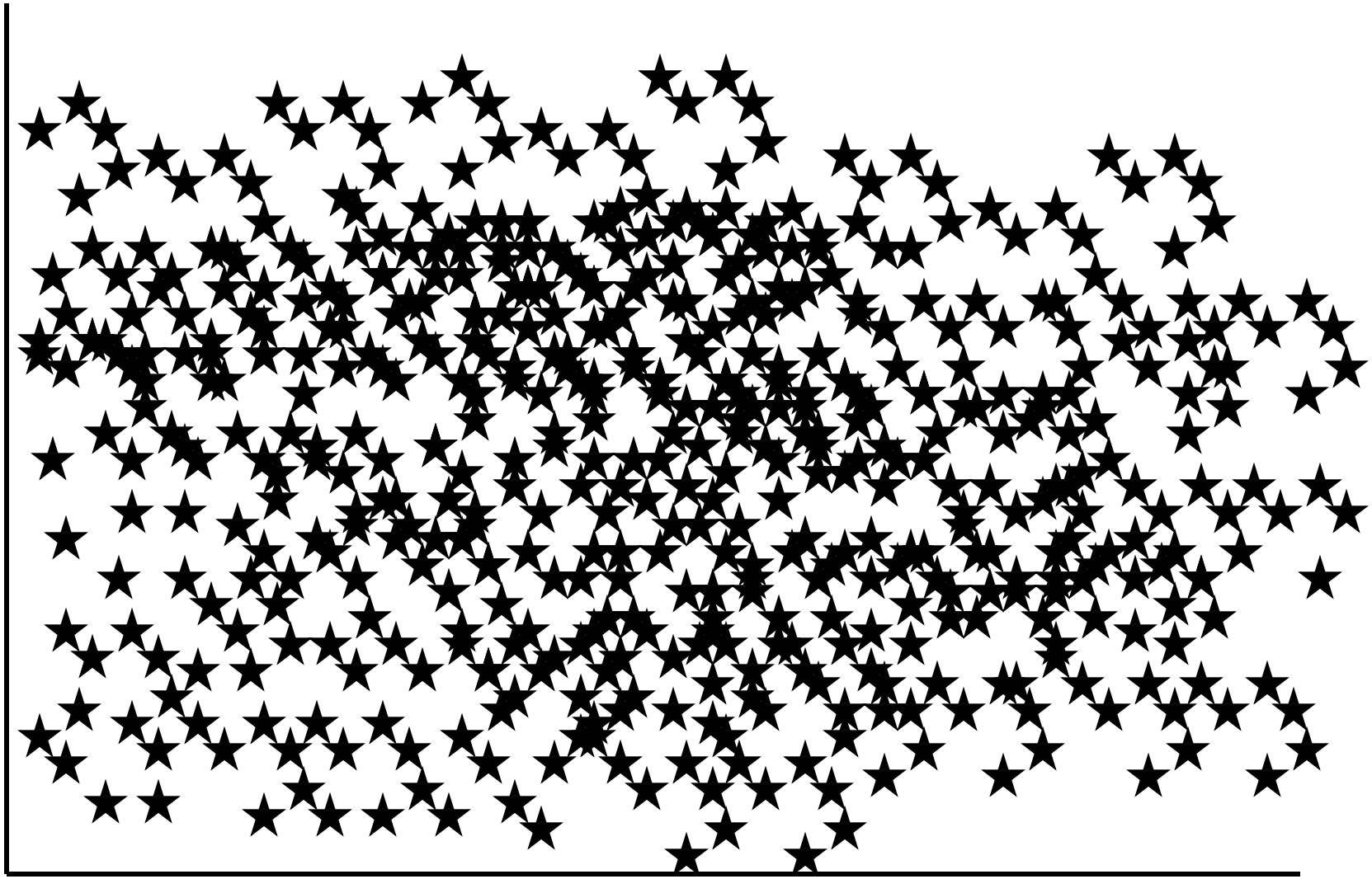
Common Variants

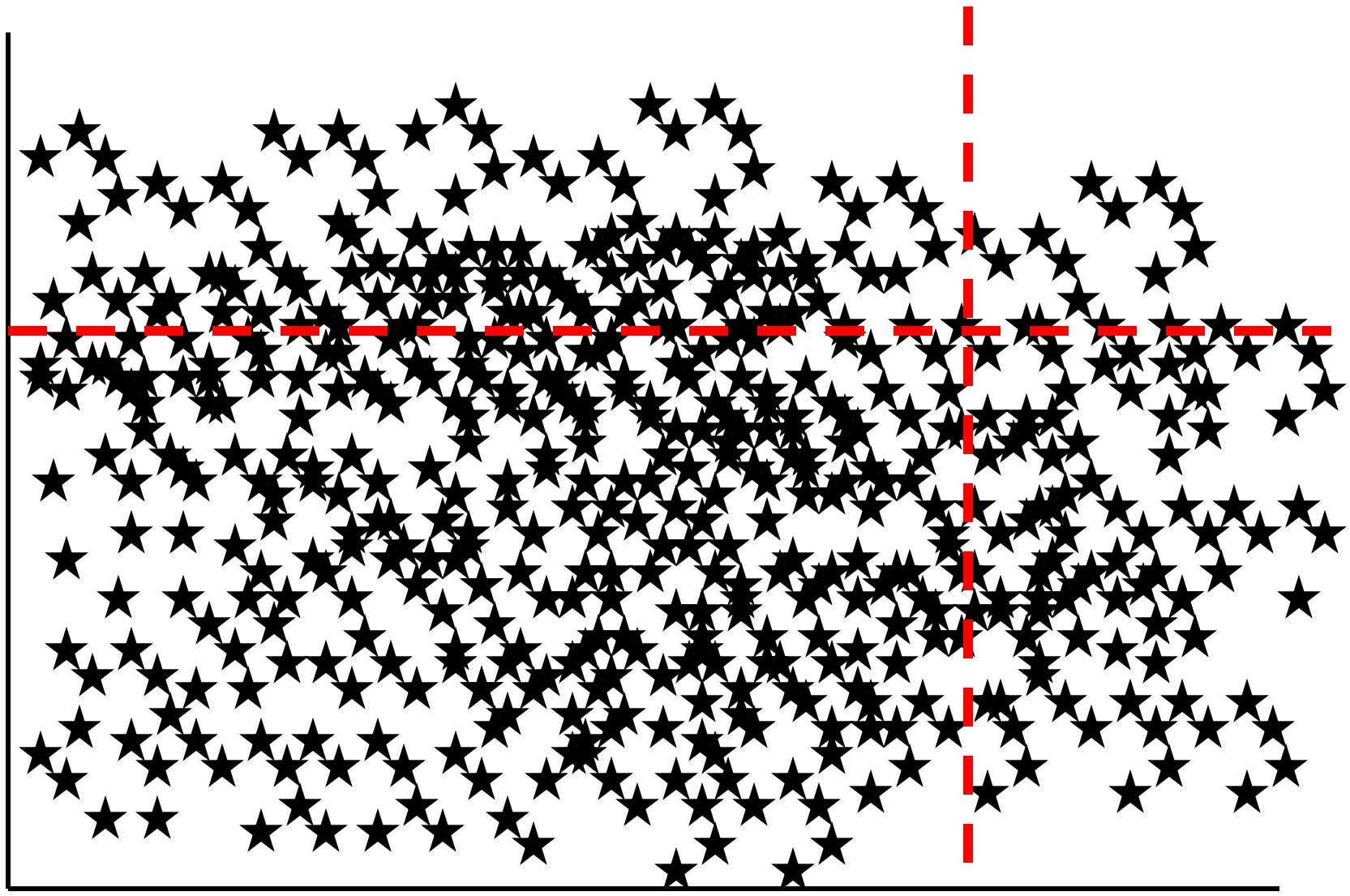
+

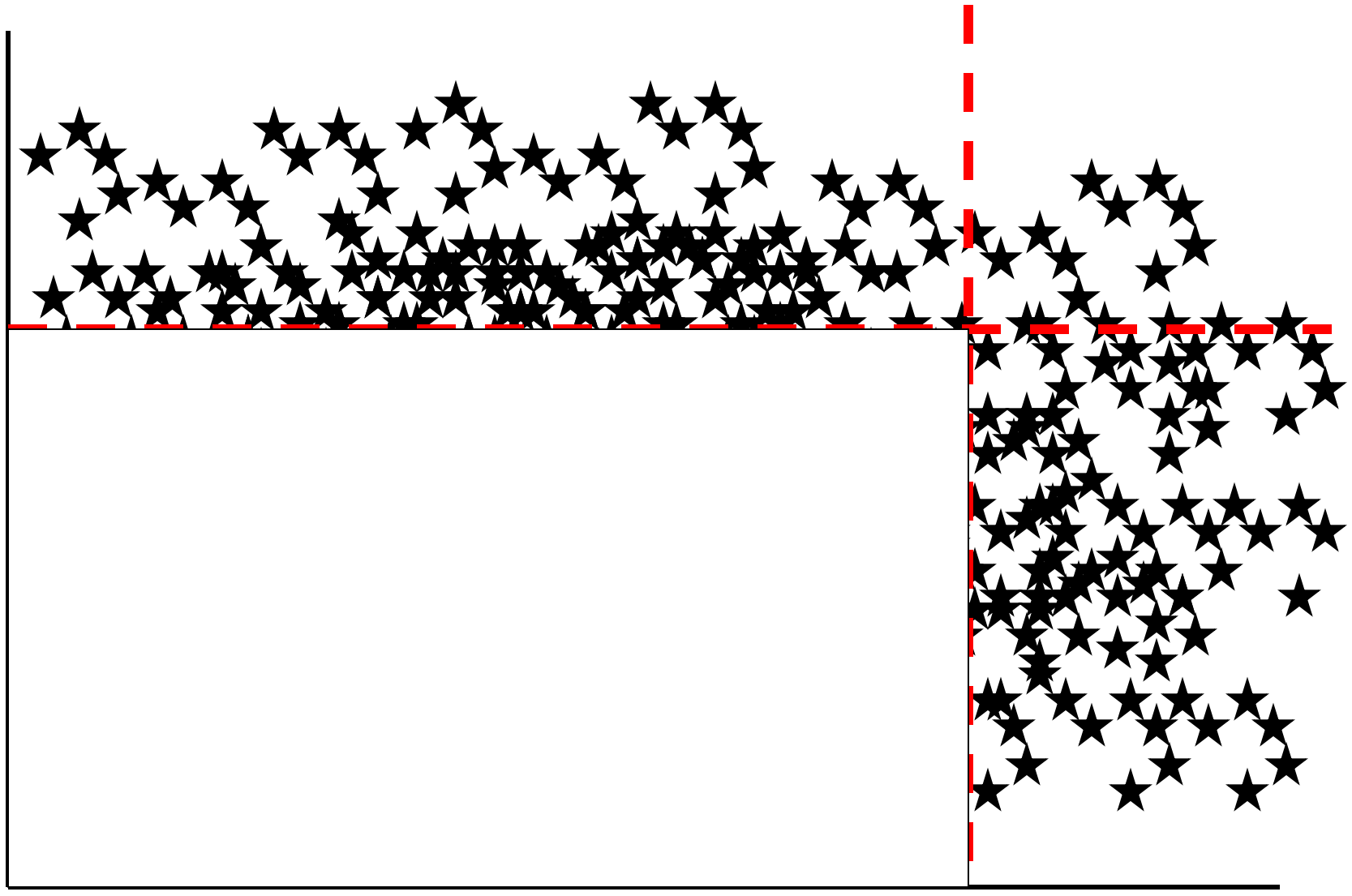
Rare Variants

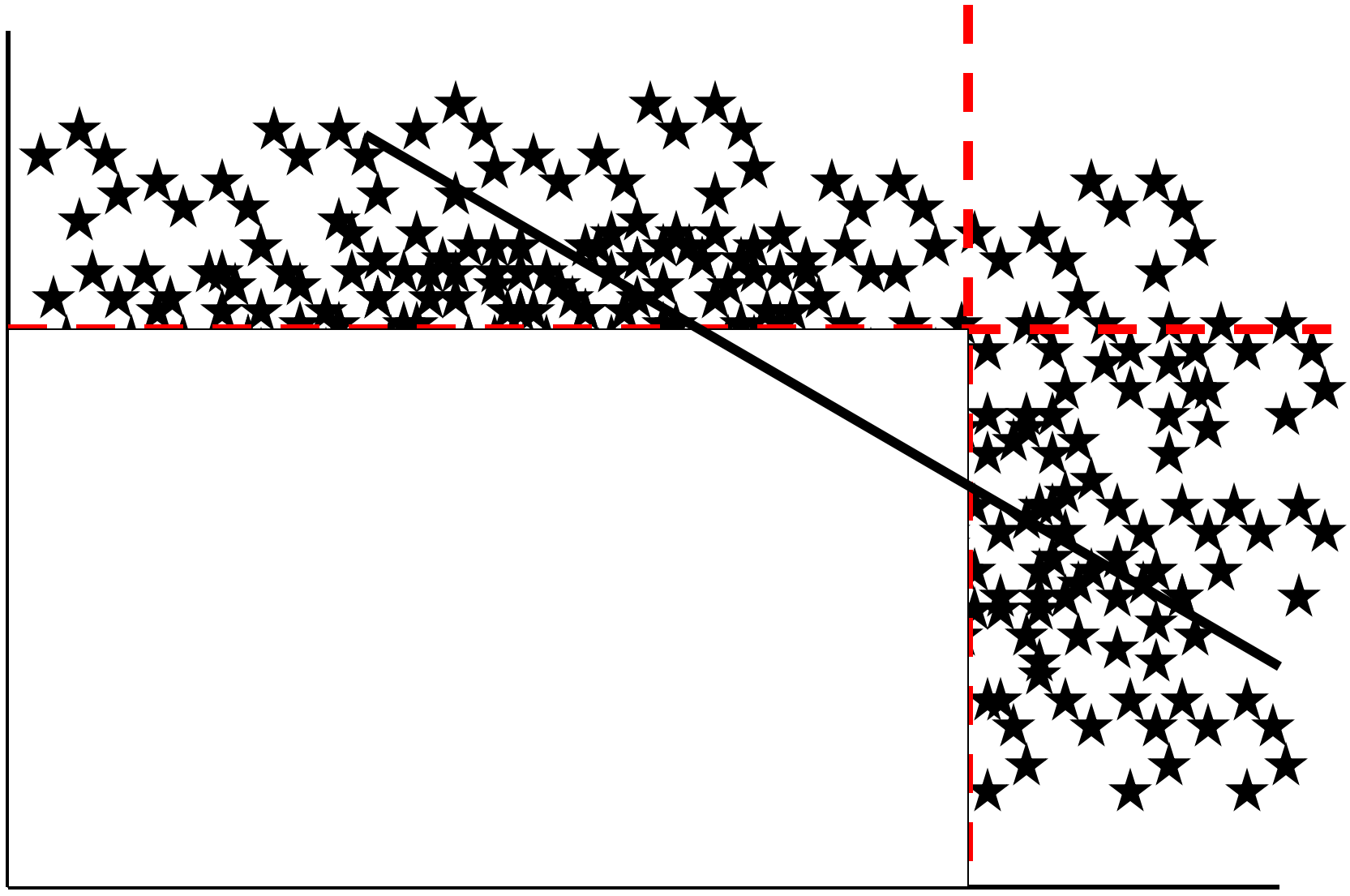
=

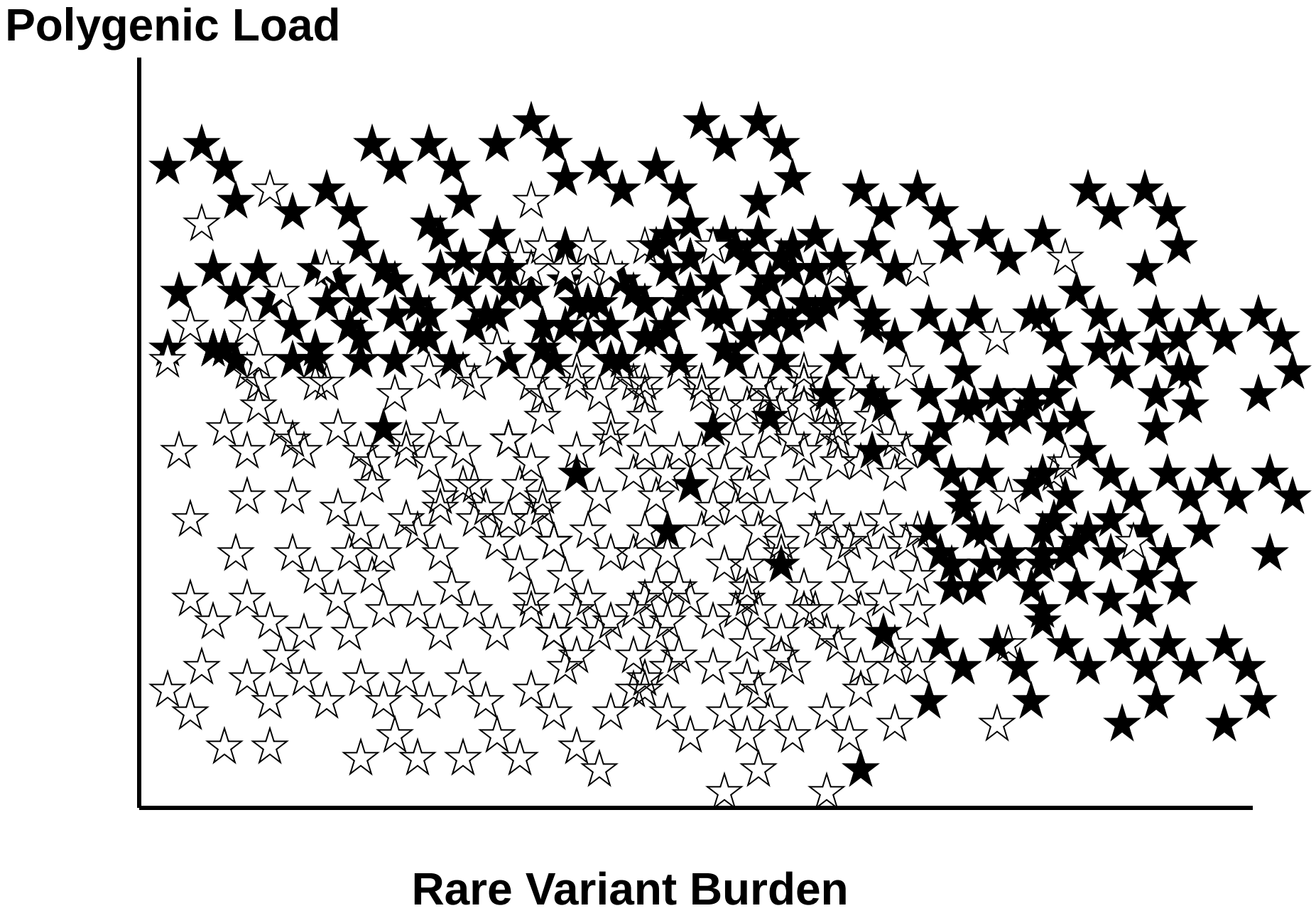
Genome Interrogation

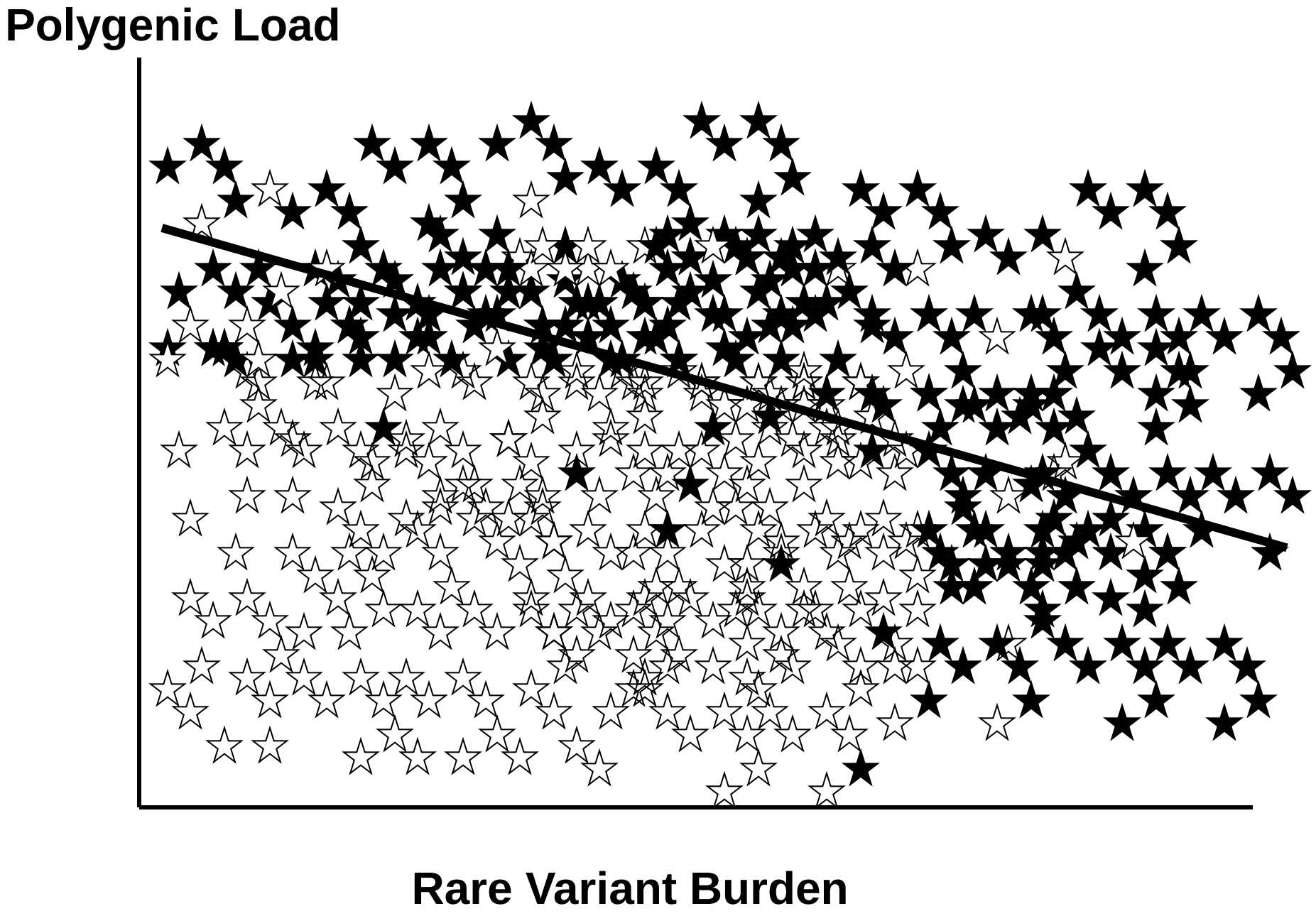









Polygenic Load
Rare Variant Burden


Polygenic Load
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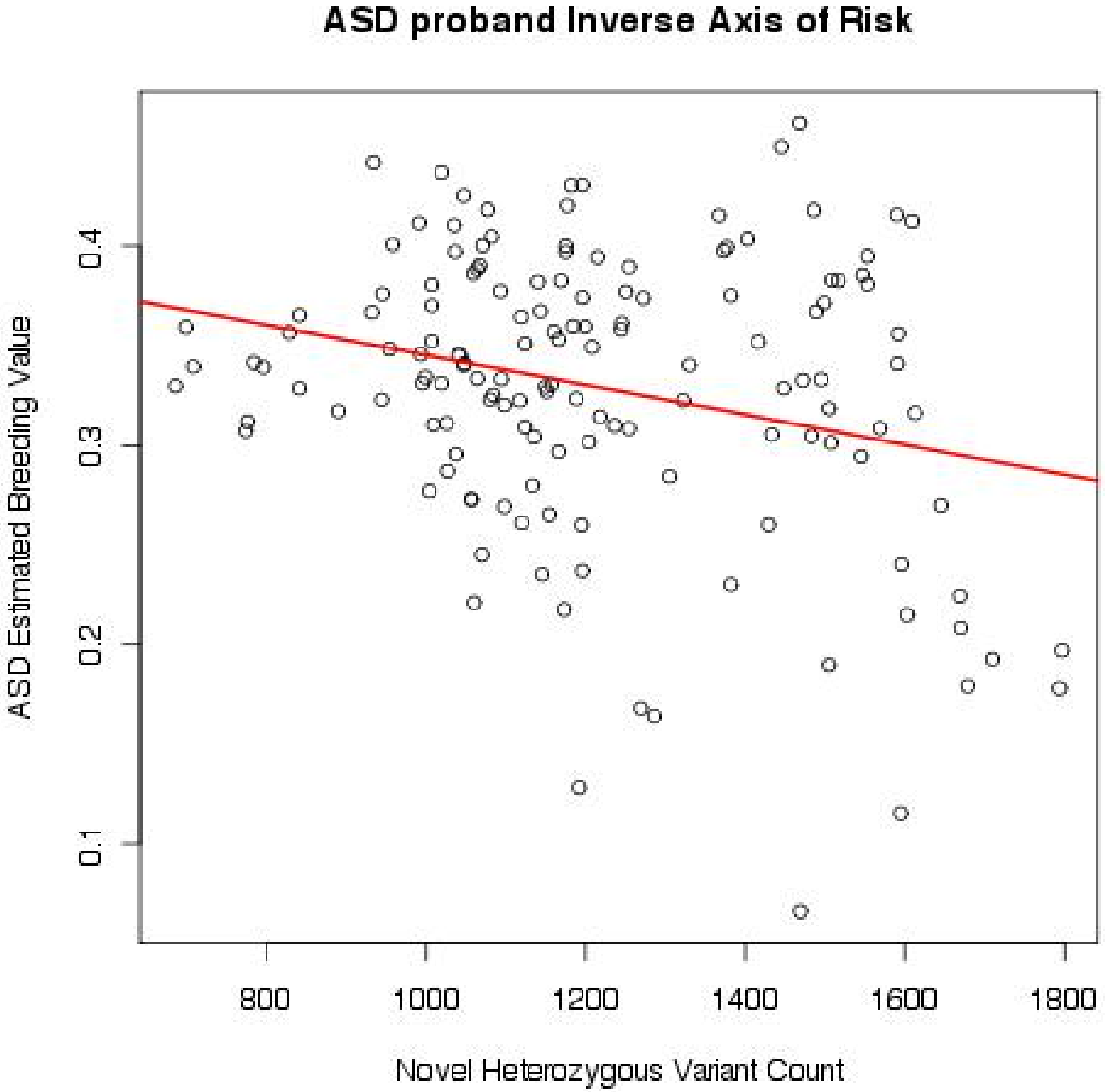

ASD proband Inverse Axis of Risk
ASD Estimated Breeding Value
0.1
0.2
0.3
0.4
800
1000
1200
1400
1600
1800
Novel Heterozygous Variant Count

Implications of Inverse Axis of Risk

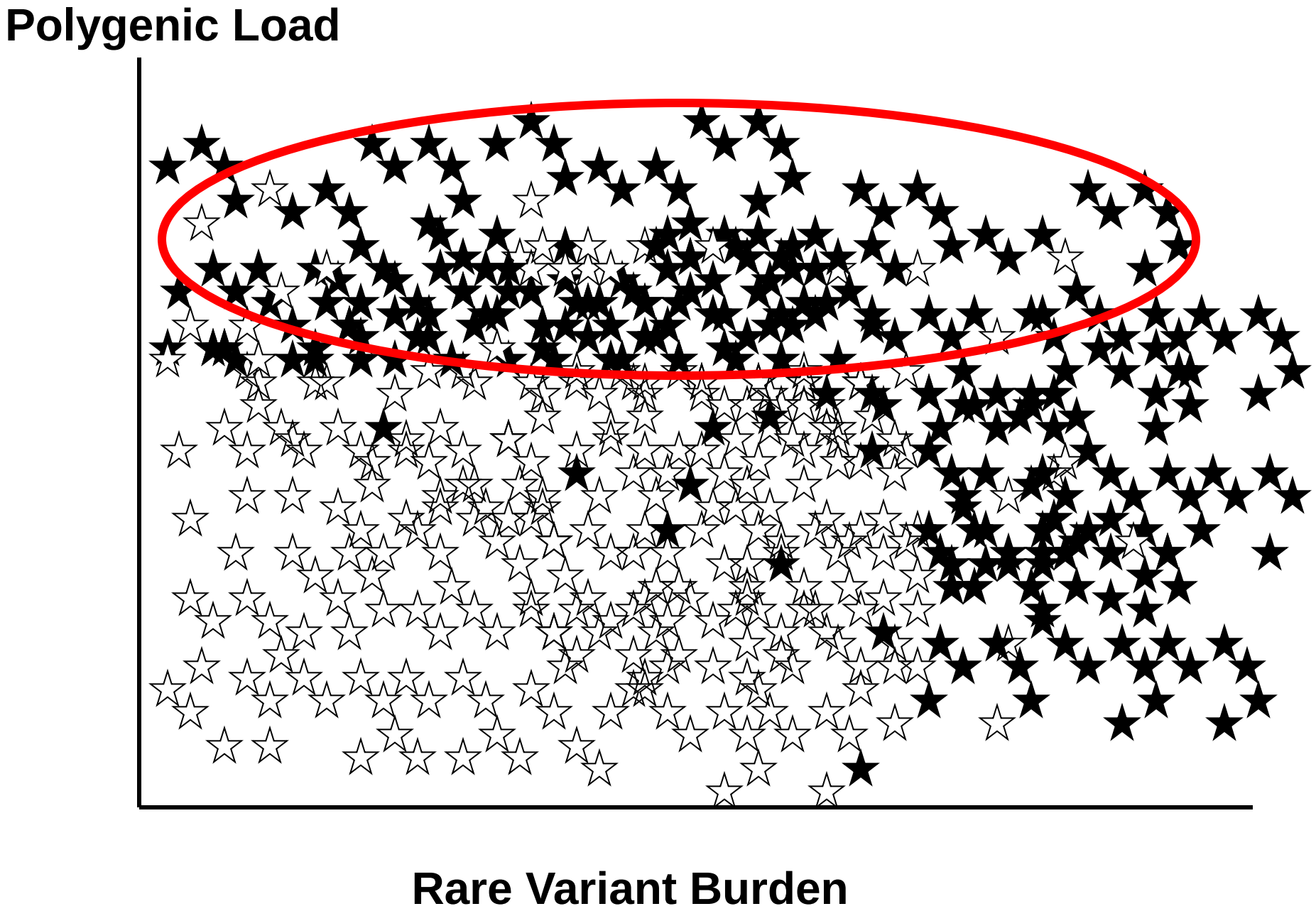
- **Study design**
  - **Sequence affecteds with low polygenic load and unaffecteds with high polygenic load**
  - **Sequencing 25K in these tails yields power comparable to sequencing 50-100K**
- **Analysis and interpretation of existing sequencing data**
  - **Weighting polygenic load to distinguish contributory *de novo* from rest**
  - **Incorporating into general analysis of rare variants to improve power**

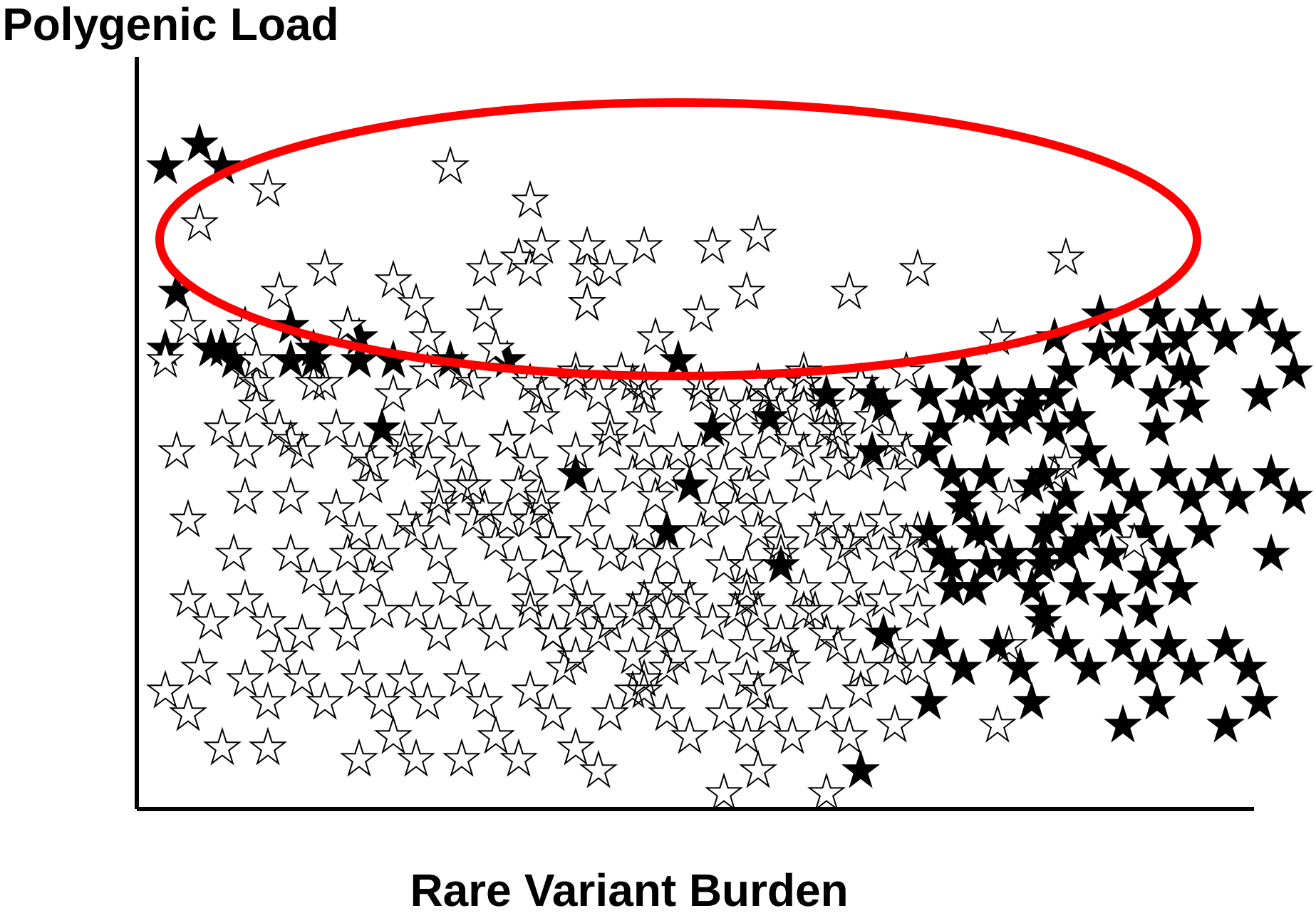
Year 1

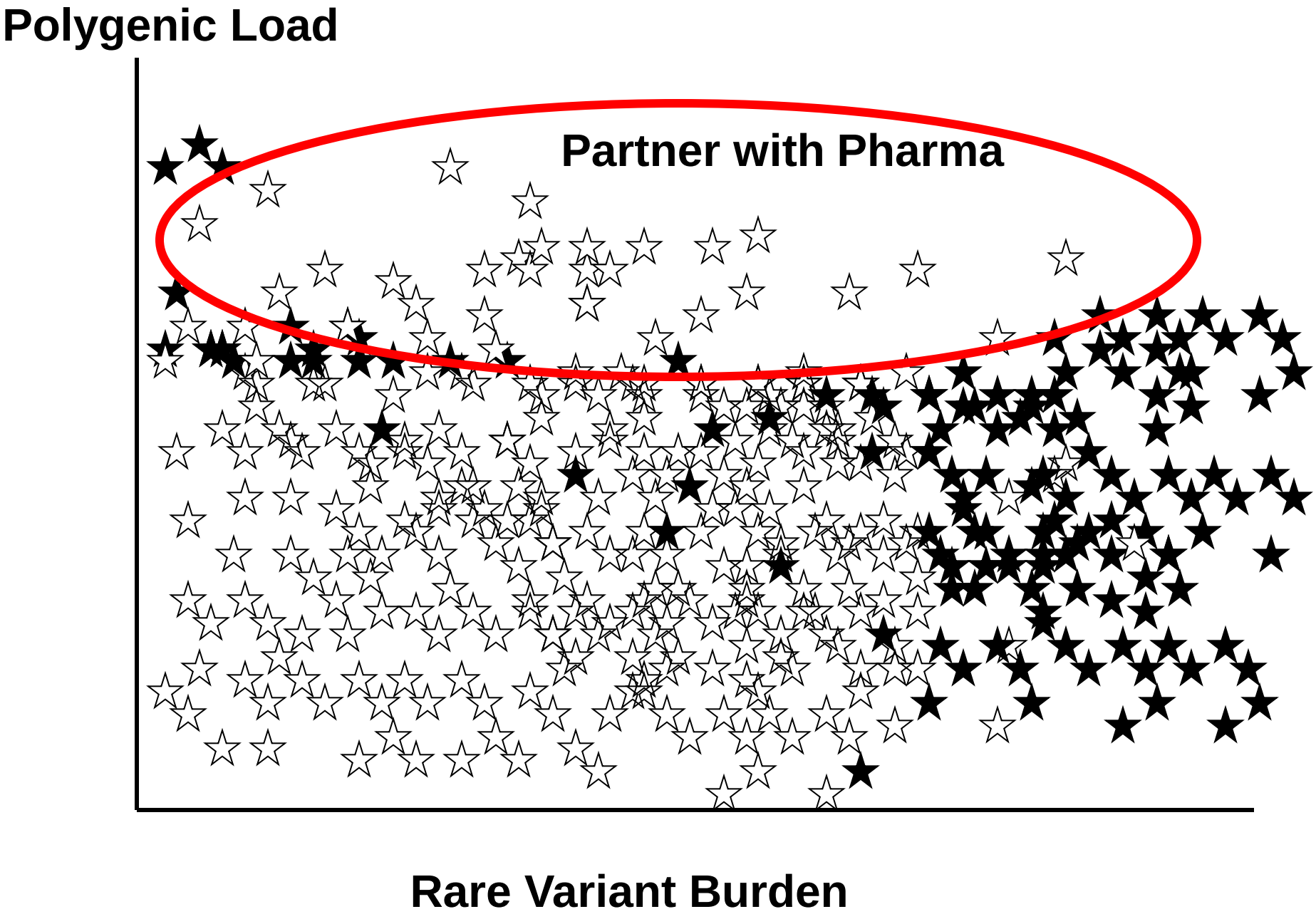
- **$20M for genotyping samples with $50 biobanking chips with GWAS and exome chip content**
  - **Emphasis on biobanks, existing cohorts, all clinical trials with samples not yet having GWAS (to be added to all existing GWAS data)**
  - **Expand impact by partnering with other NIH disease and private foundations**
  - **Prioritize use cases that enable reimbursement for CLIA / CAP cheap chips (pharmacogenomics, diagnostic oddysseys)**
- **Goal: 2-3M samples with sufficient genome interrogation for characterizing polygenic load for all common disease**

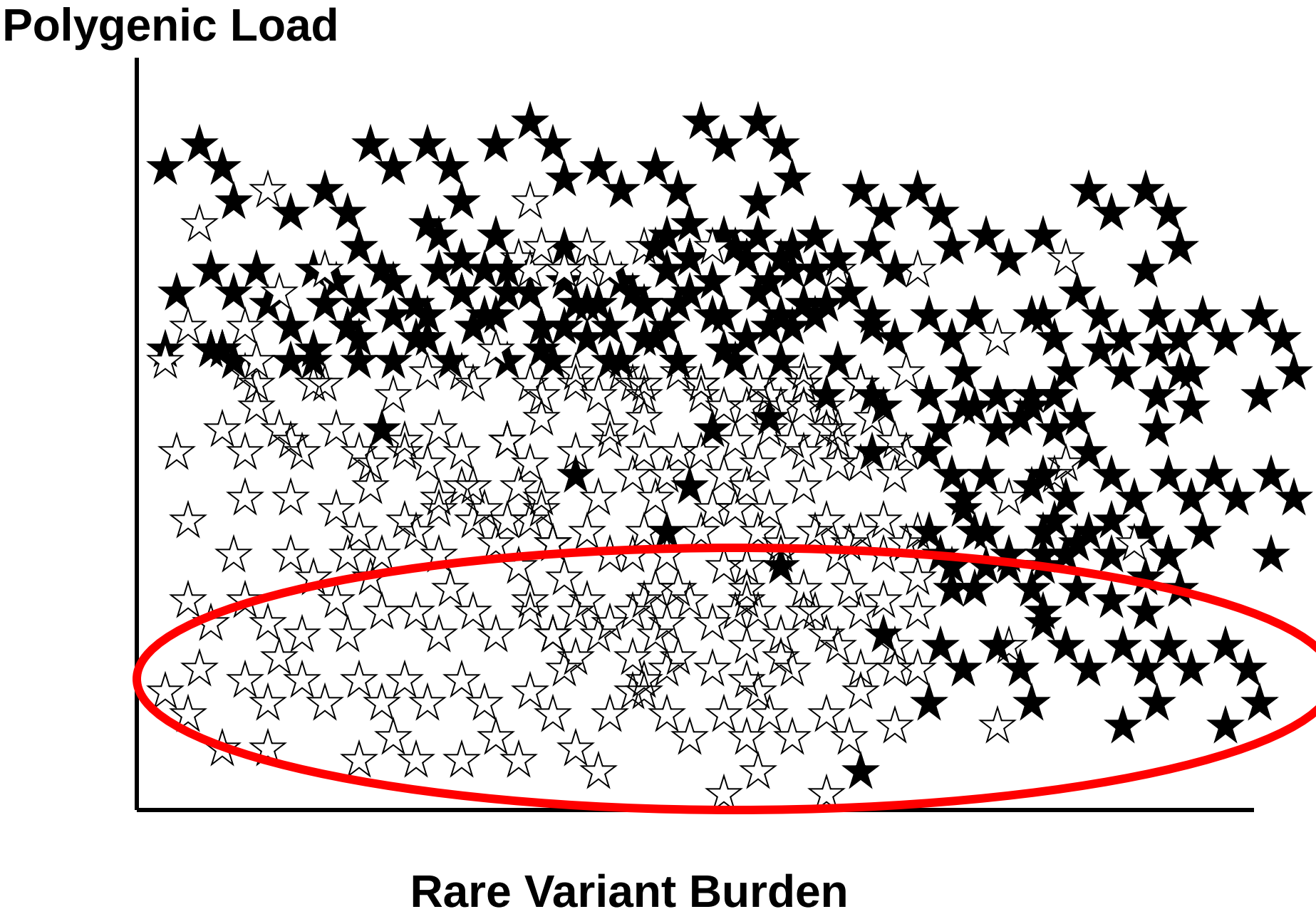
With 2,000,000 Subjects

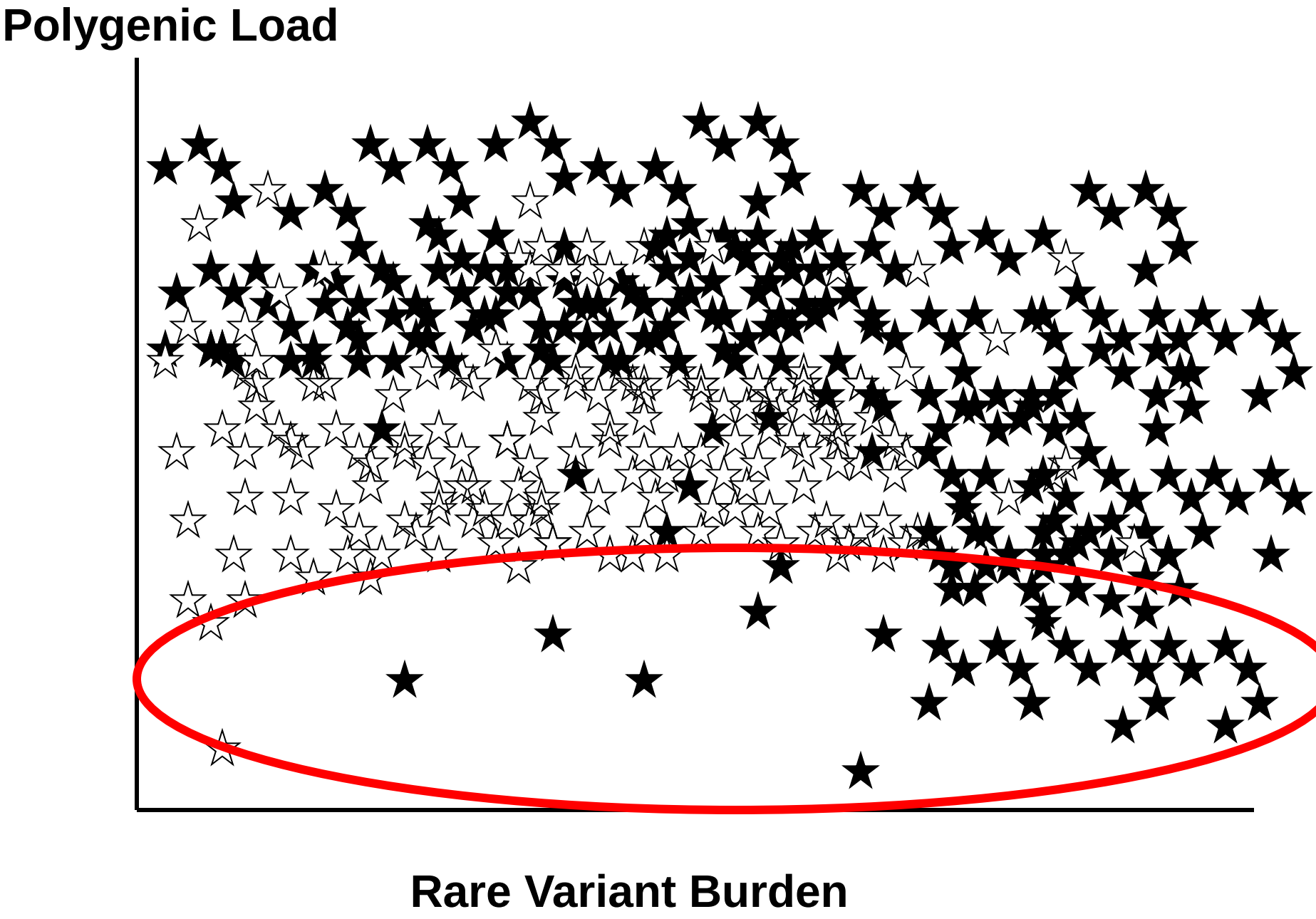
- **Expect > 400,000 with diagnoses for diseases with 20% lifetime risk**
- **Expect > 200,000 with diagnoses for diseases with 10% lifetime risk**
- **Expect > 100,000 with diagnoses for diseases with 5% lifetime risk**
- **Expect > 20,000 with diagnoses for diseases with a 1% lifetime risk**

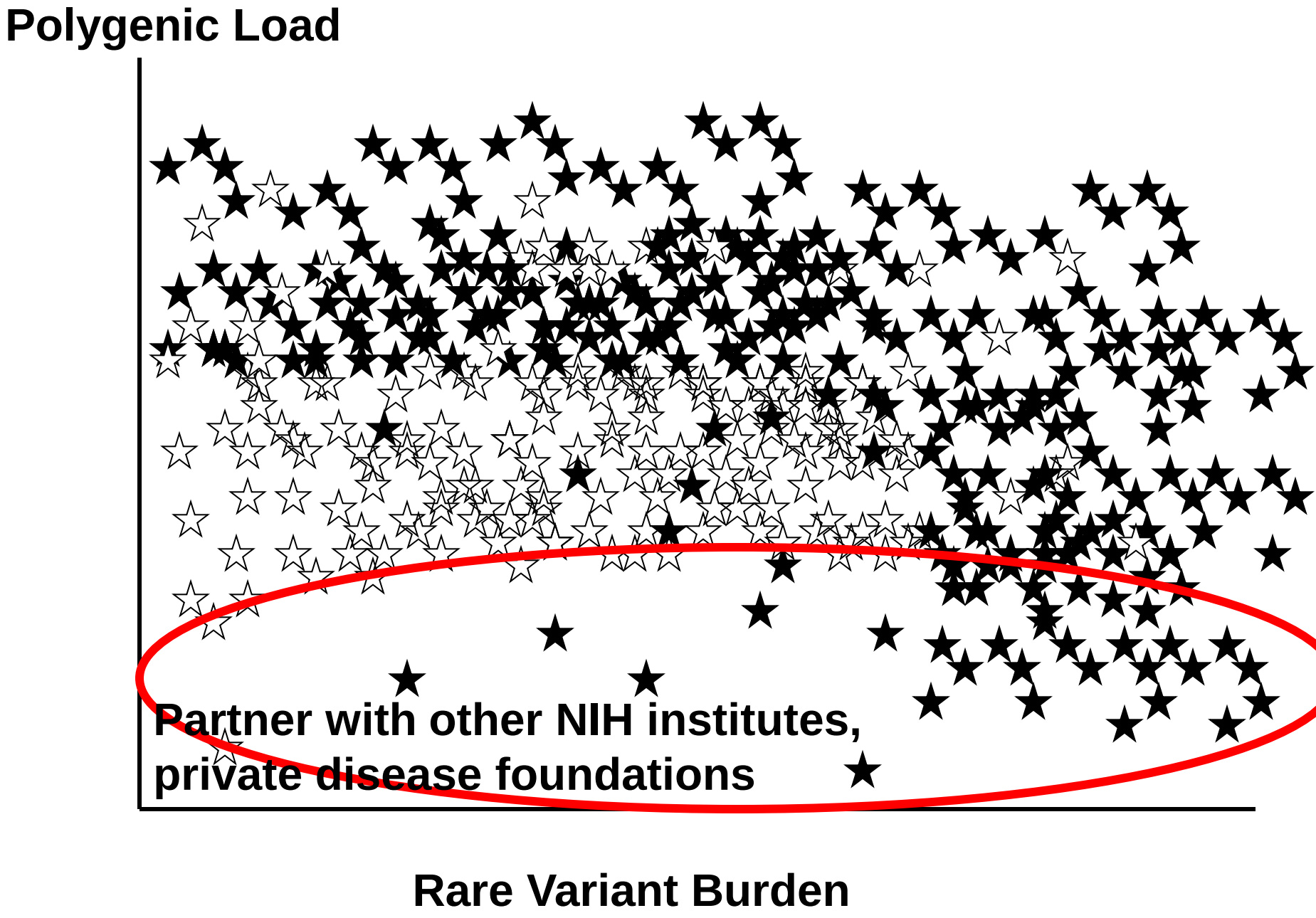

Polygenic Load
Rare Variant Burden


Polygenic Load
Rare Variant Burden


Polygenic Load
Partner with Pharma
Rare Variant Burden


Polygenic Load
Rare Variant Burden


Polygenic Load
Rare Variant Burden


Polygenic Load
Partner with other NIH institutes,
private disease foundations
Rare Variant Burden

Years 2-5

- **Sequence individuals in the “tails” for all common diseases**
- **Build “use cases” for reimbursement of CLIA / CAP whole genome sequencing**
- **Explore serial transcriptomics for clinical utility**
  - **Any circumstance with “watchful waiting”**
  - **Diagnostic oddysseys**

Deliverables

- **Sufficiently powered but highly efficient studies of rare variants in common disease**
- **Additional opportunities for research**
  - **Combine EMR usage, biomarkers, with polygenic scores and rare variants at genes shown to contribute to disease risk to improve prediction of common disease**
  - **Use available data to characterize environmental factors impacting risk “at the tails” – cost-effective prevention**

Cox Lab

Eric Gamazon

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(Bridget)

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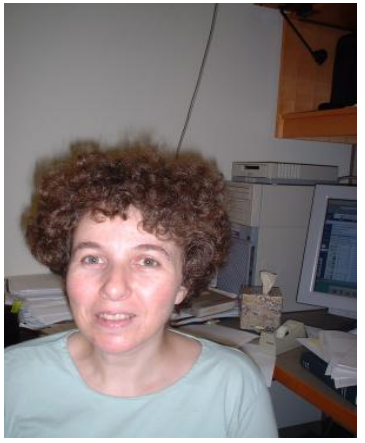
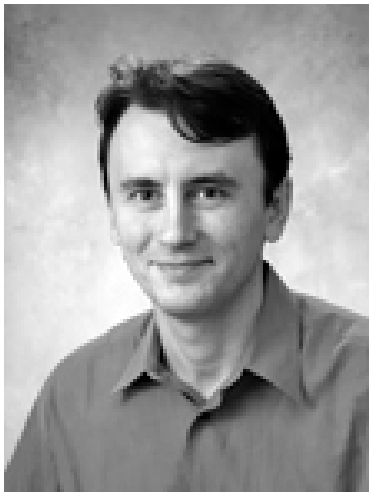


Anna Pluzhnikov

Colleagues & Collaborators



Dan Nicolae

M. Eileen Dolan

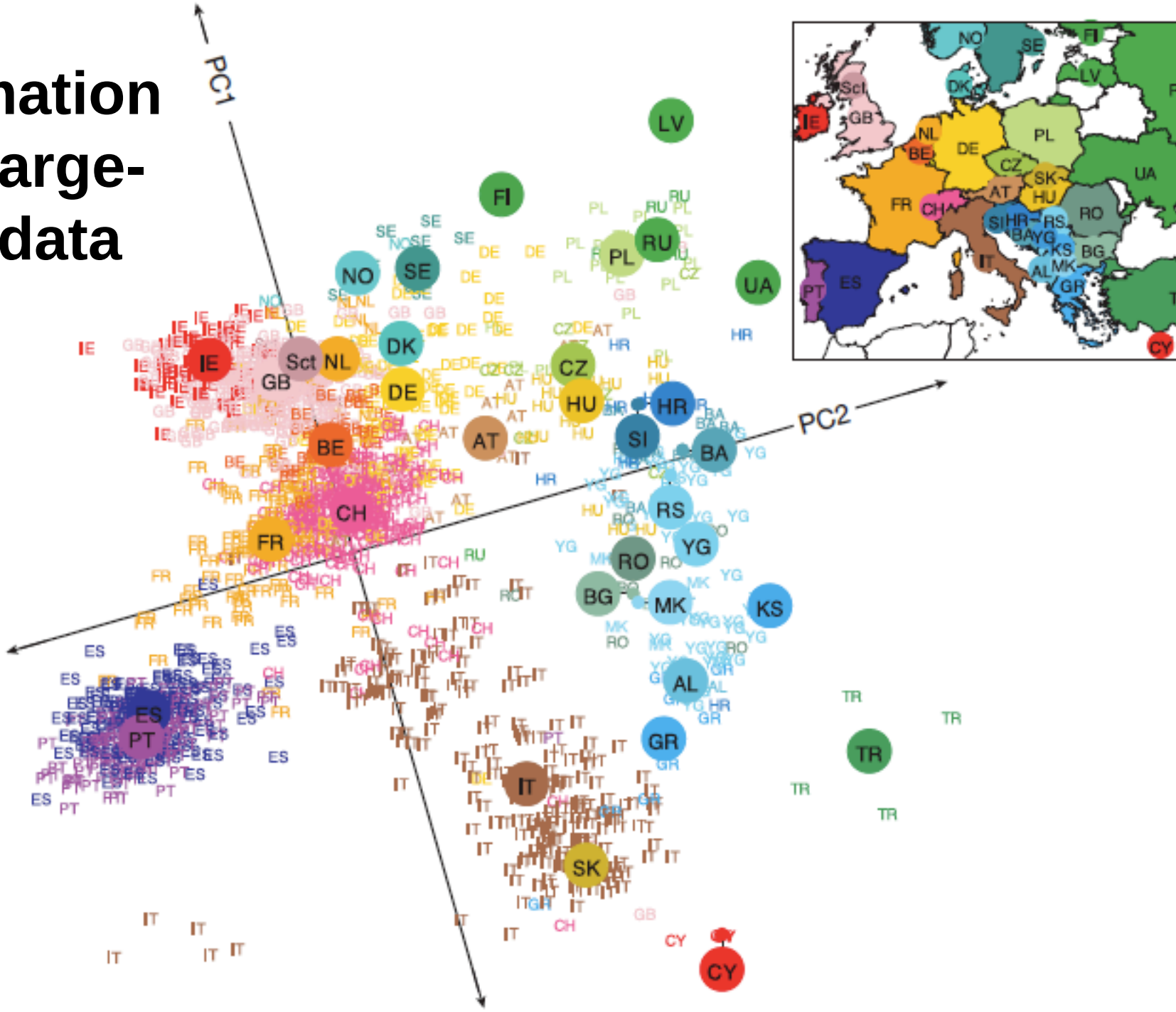
Haky Im

Bob Grossman

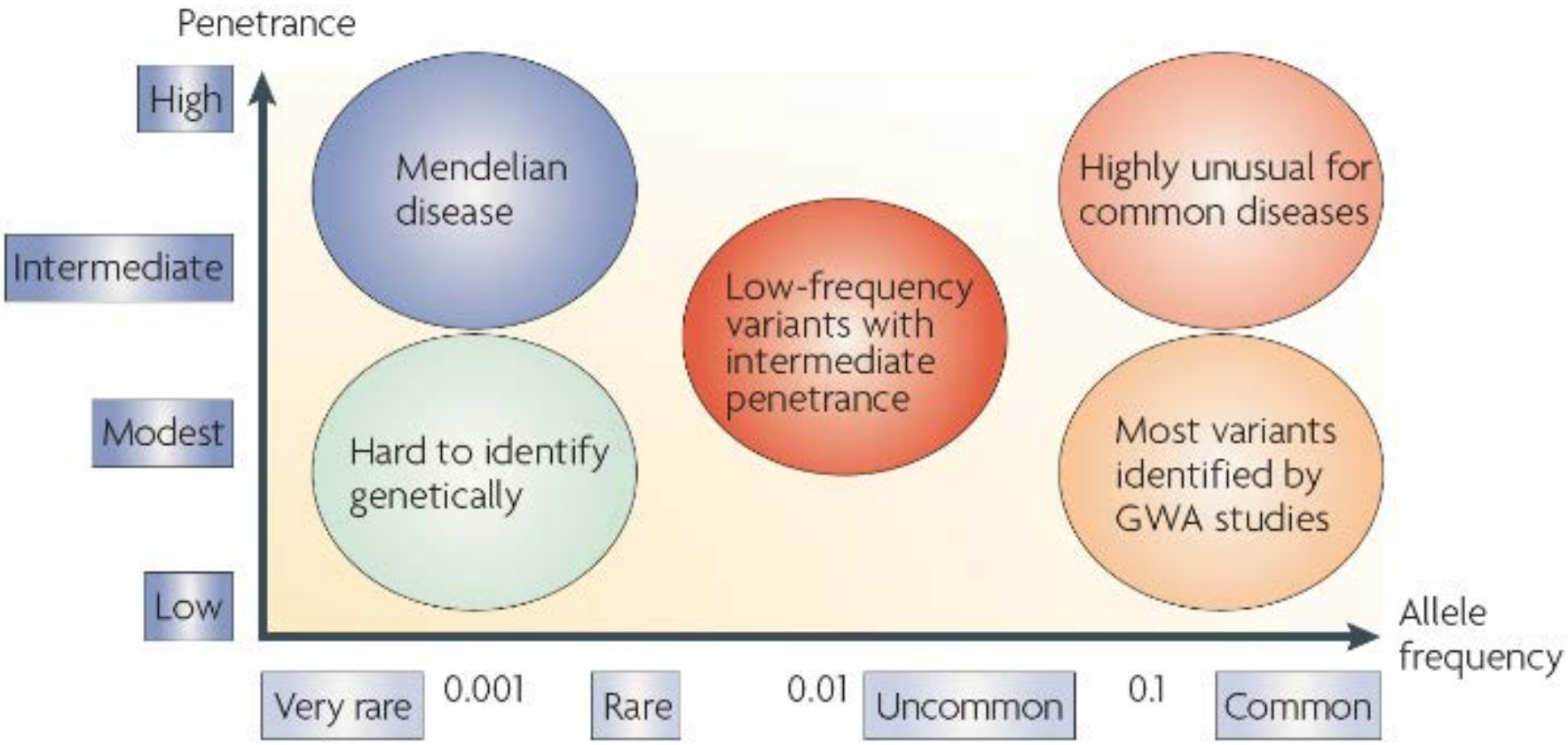
Chun-yu Liu

Andrey Rzhetsky

Information from large-scale data

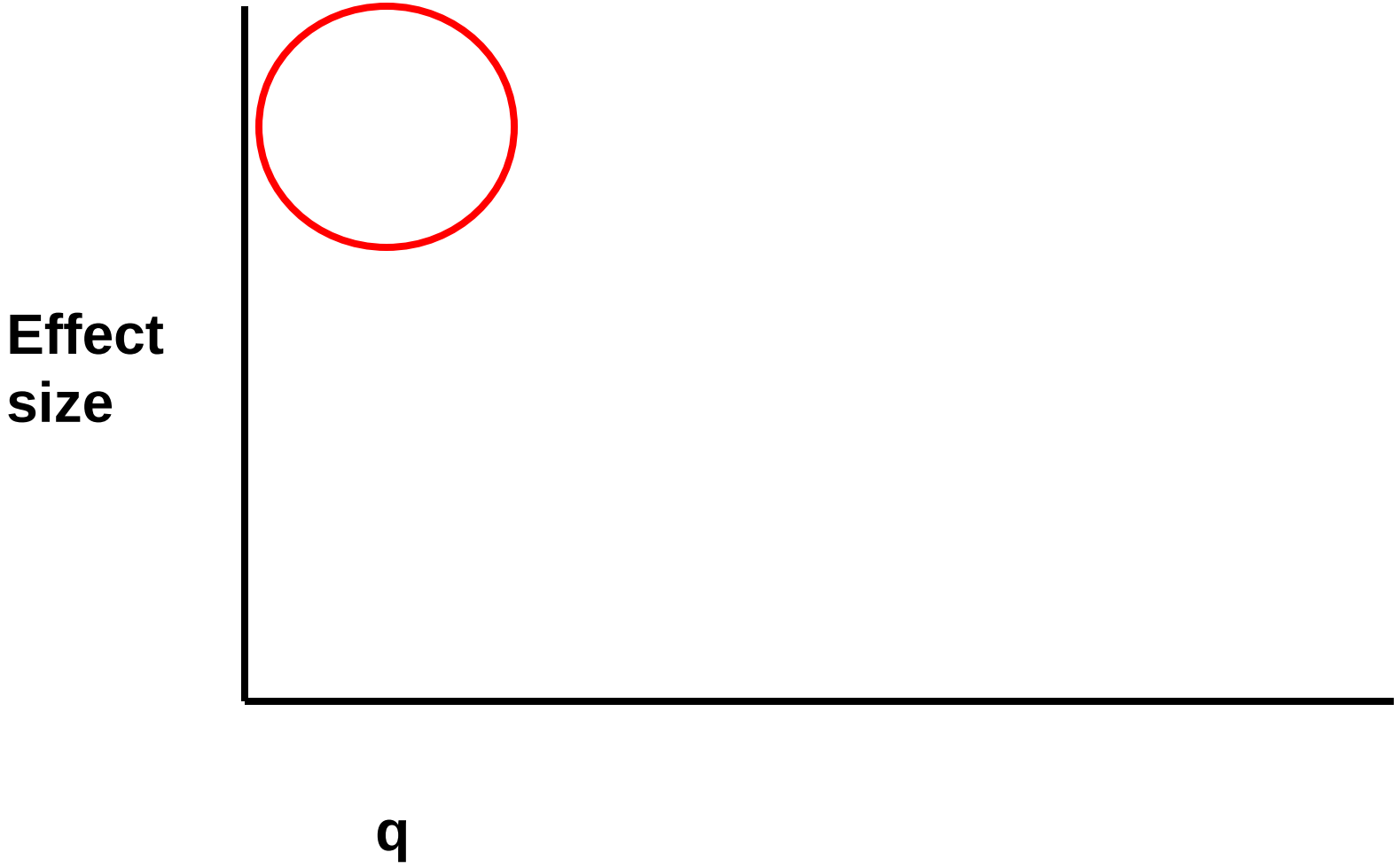


Relationship Between MAF and Effect Size



Lobo, I. (2008) Multifactorial inheritance and genetic disease. Nature Education 1(1):5

Relationship between MAF and Effect Size



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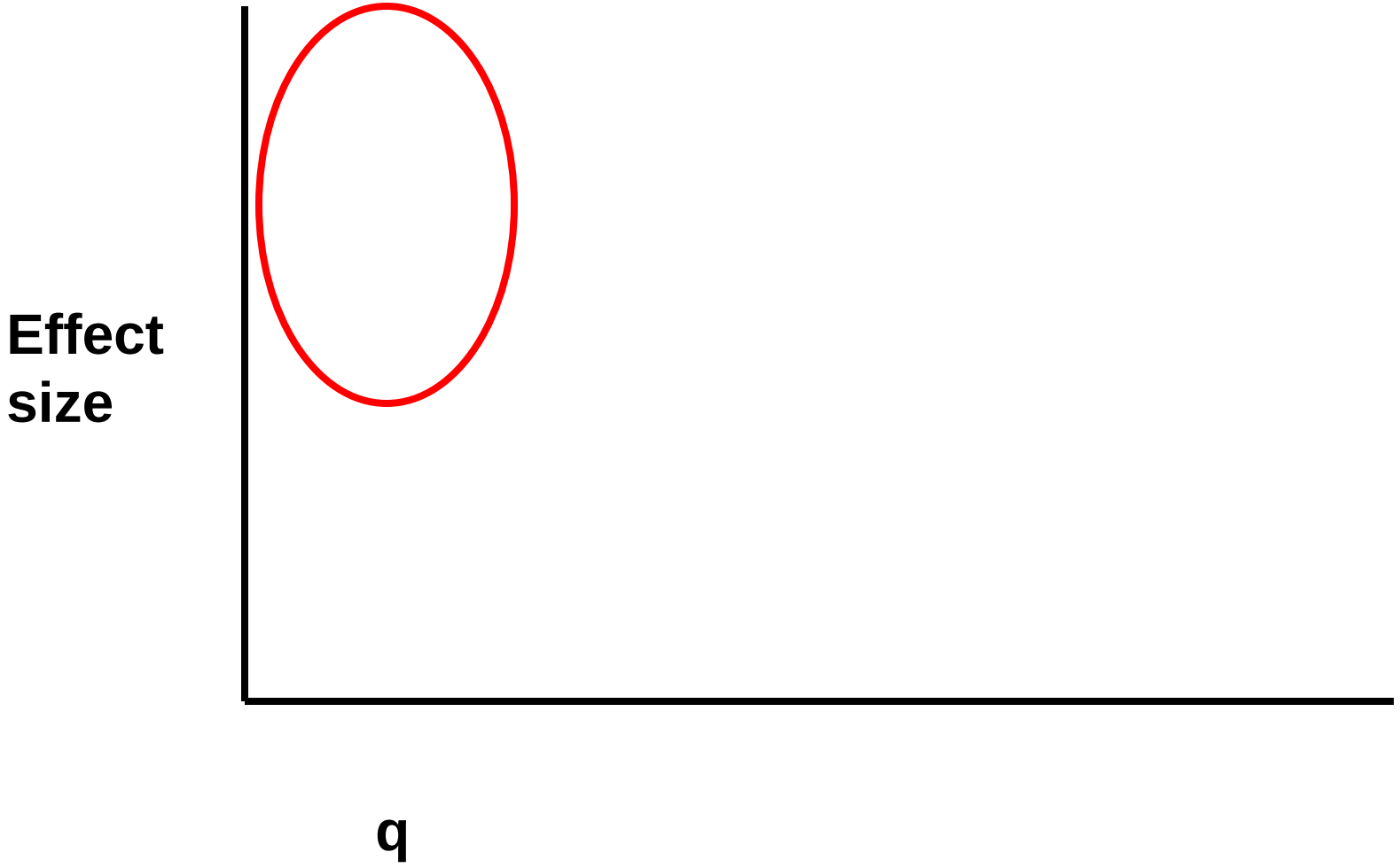

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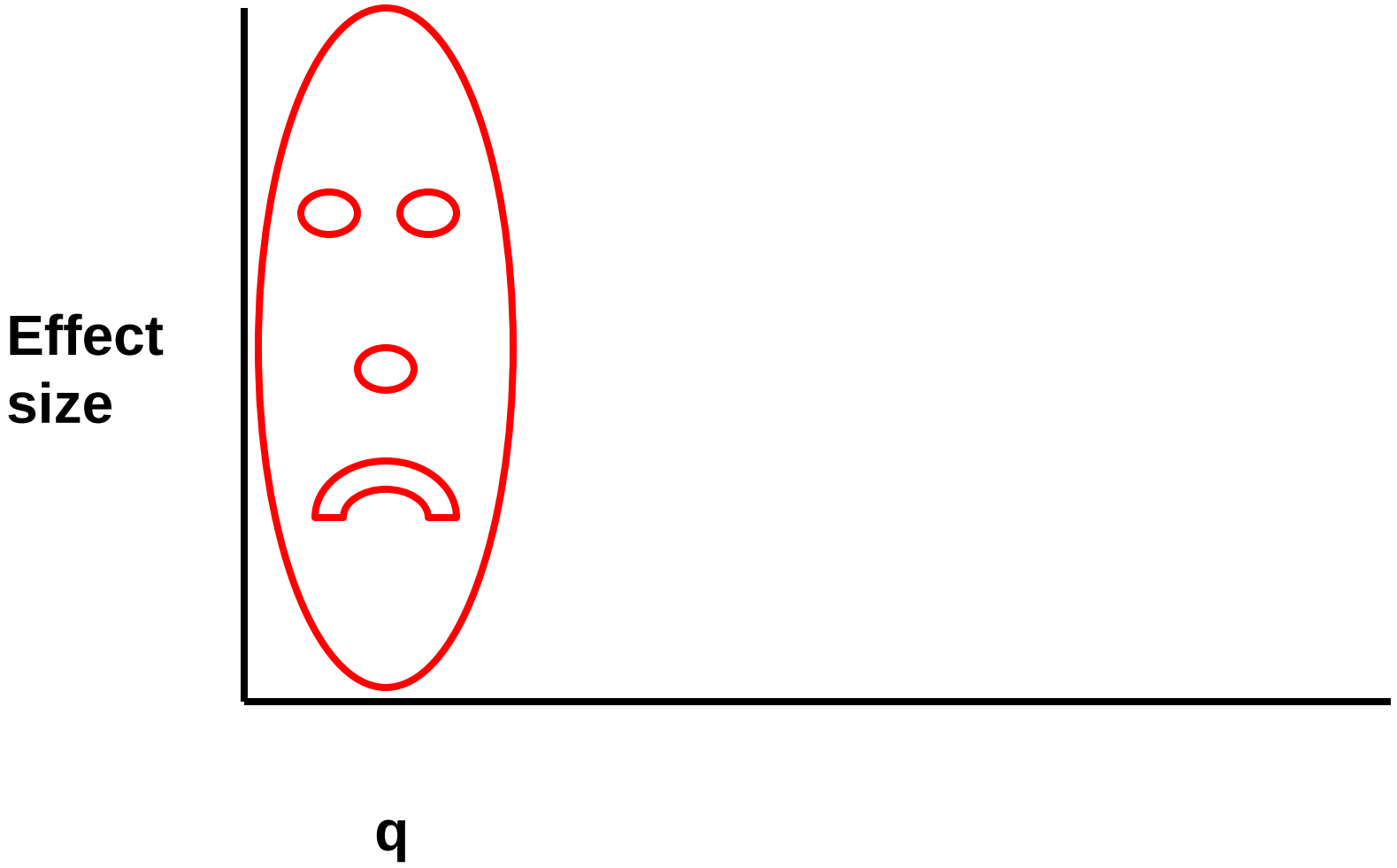

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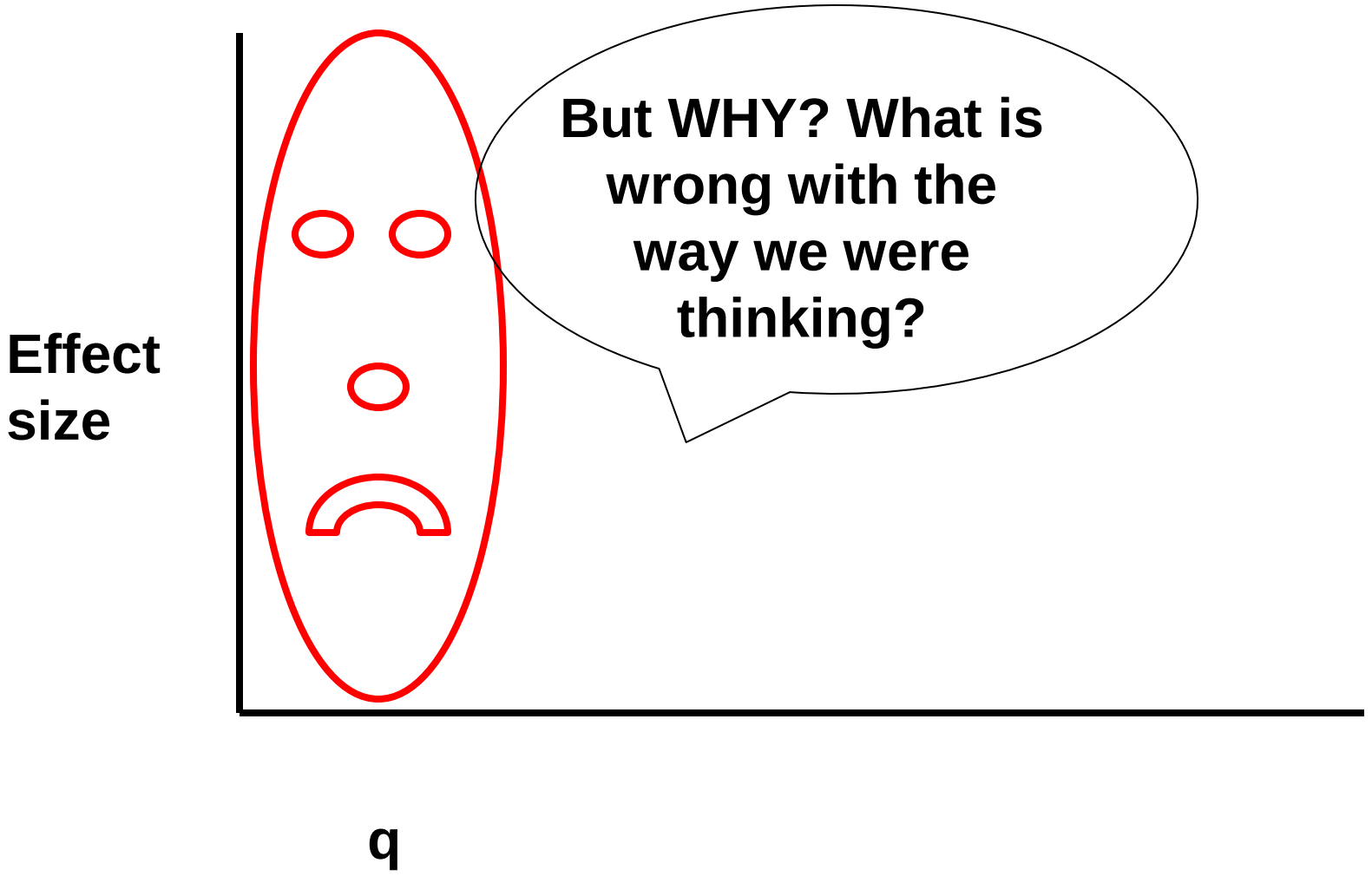
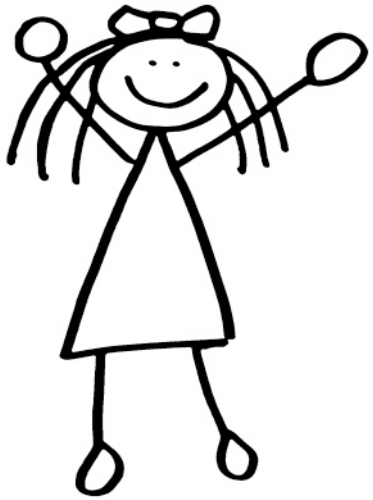
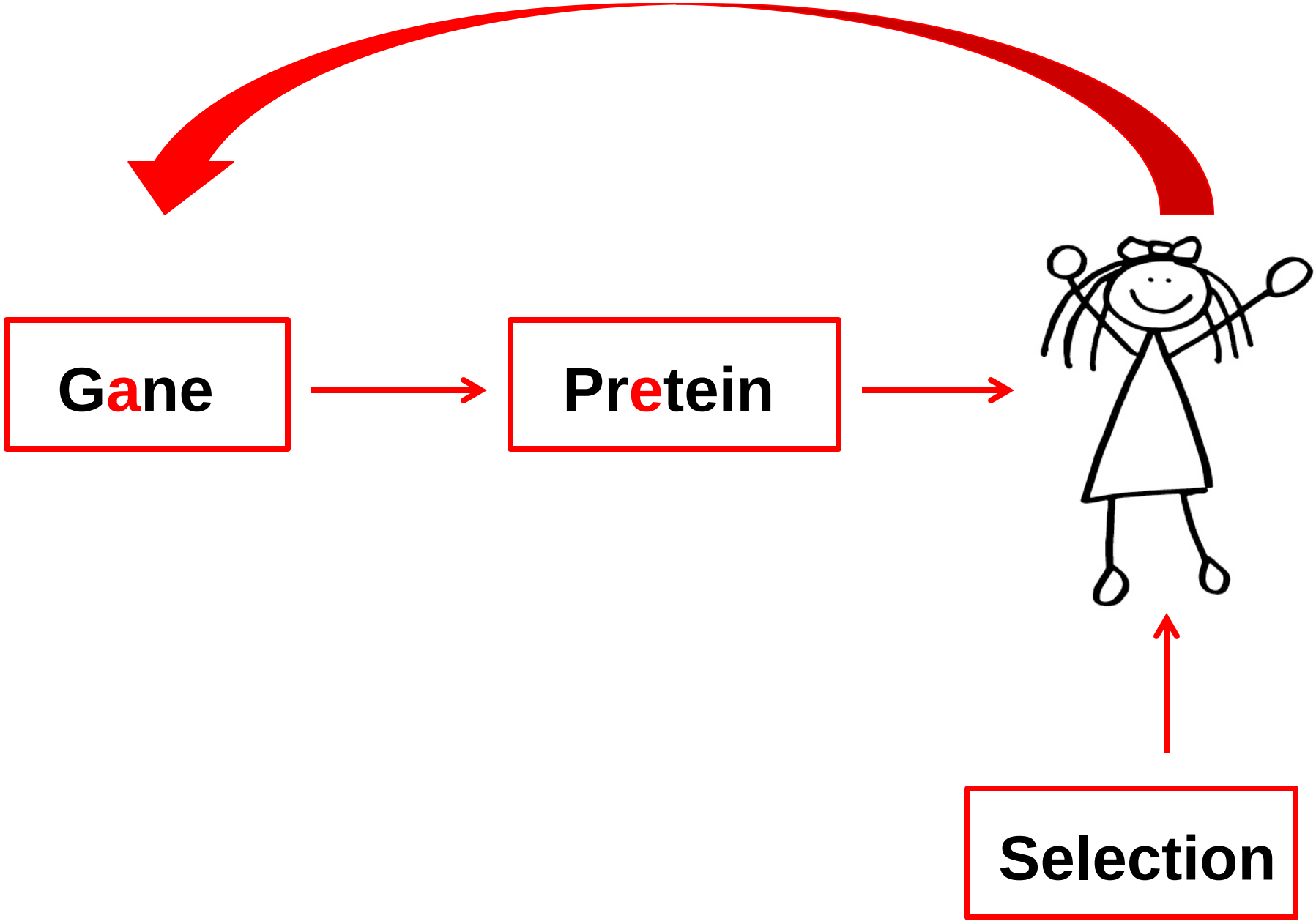
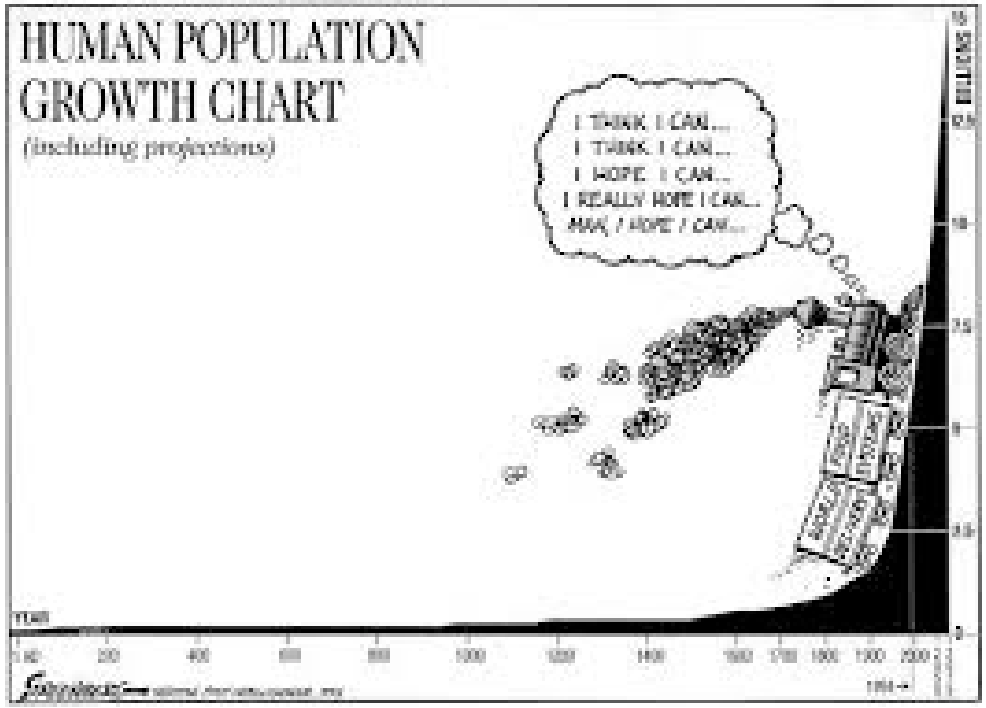


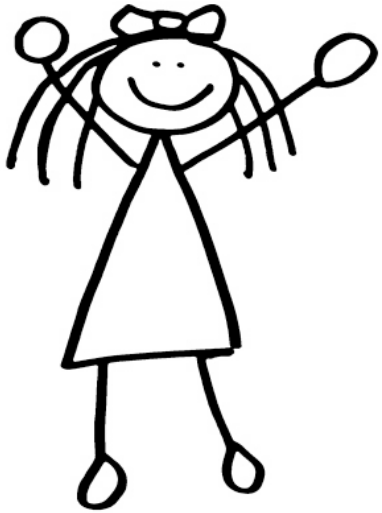
Gene → Protein →




Gane
Pretein
Selection



Gane → **Pretein** →



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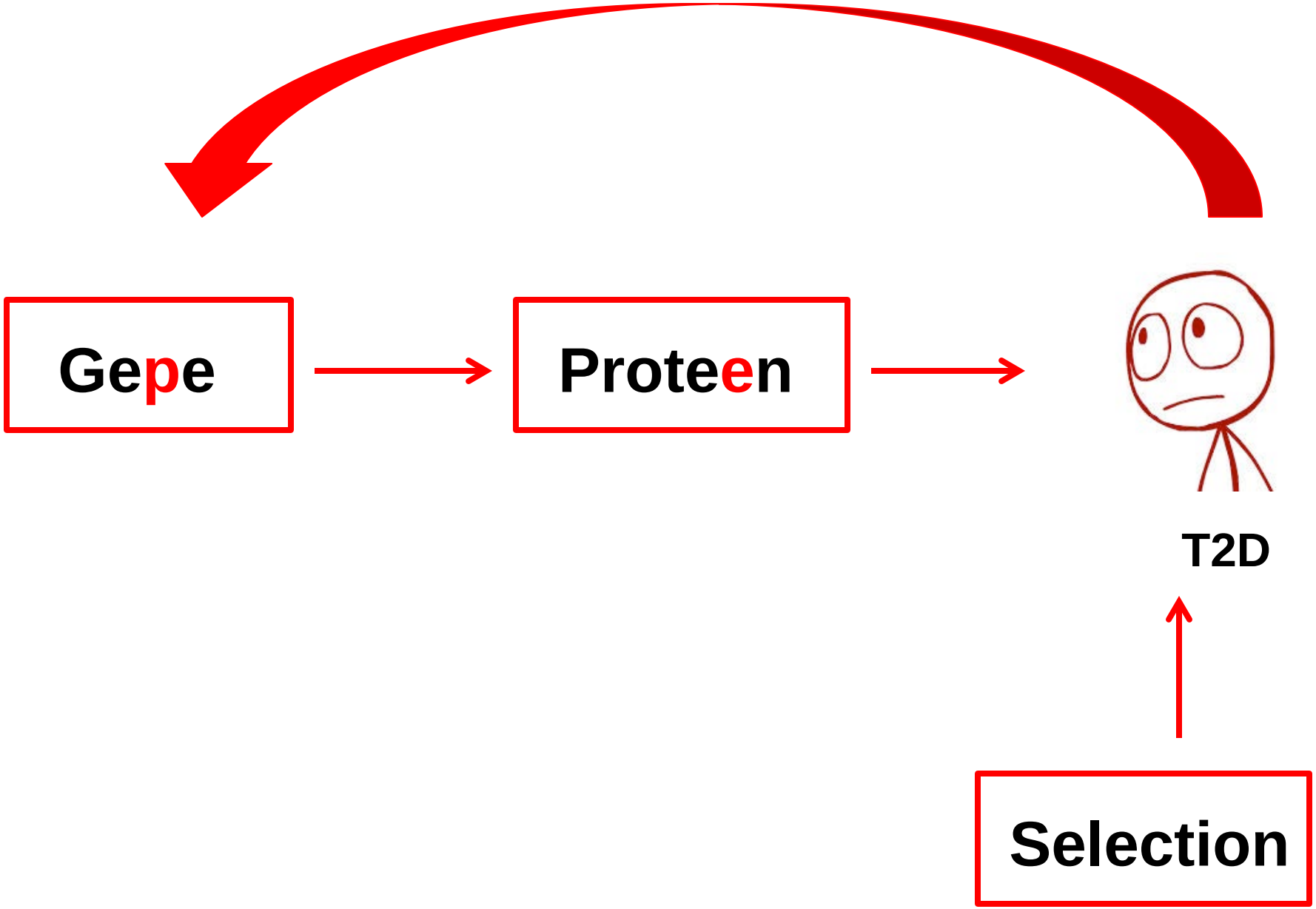
A Nondegenerate Code of Deleterious Variants in Mendelian Loci Contributes to Complex Disease Risk

Blair DR, Lyttle CS, Mortensen JM, Bearden CF, Jensen AB, Khiabanian H, Melamed R, Rabadan R, Bernstam EV, Brunak S, Jensen LJ, Nicolae D, Shah NH, Grossman RL, Cox NJ, White KP, Rzhetsky A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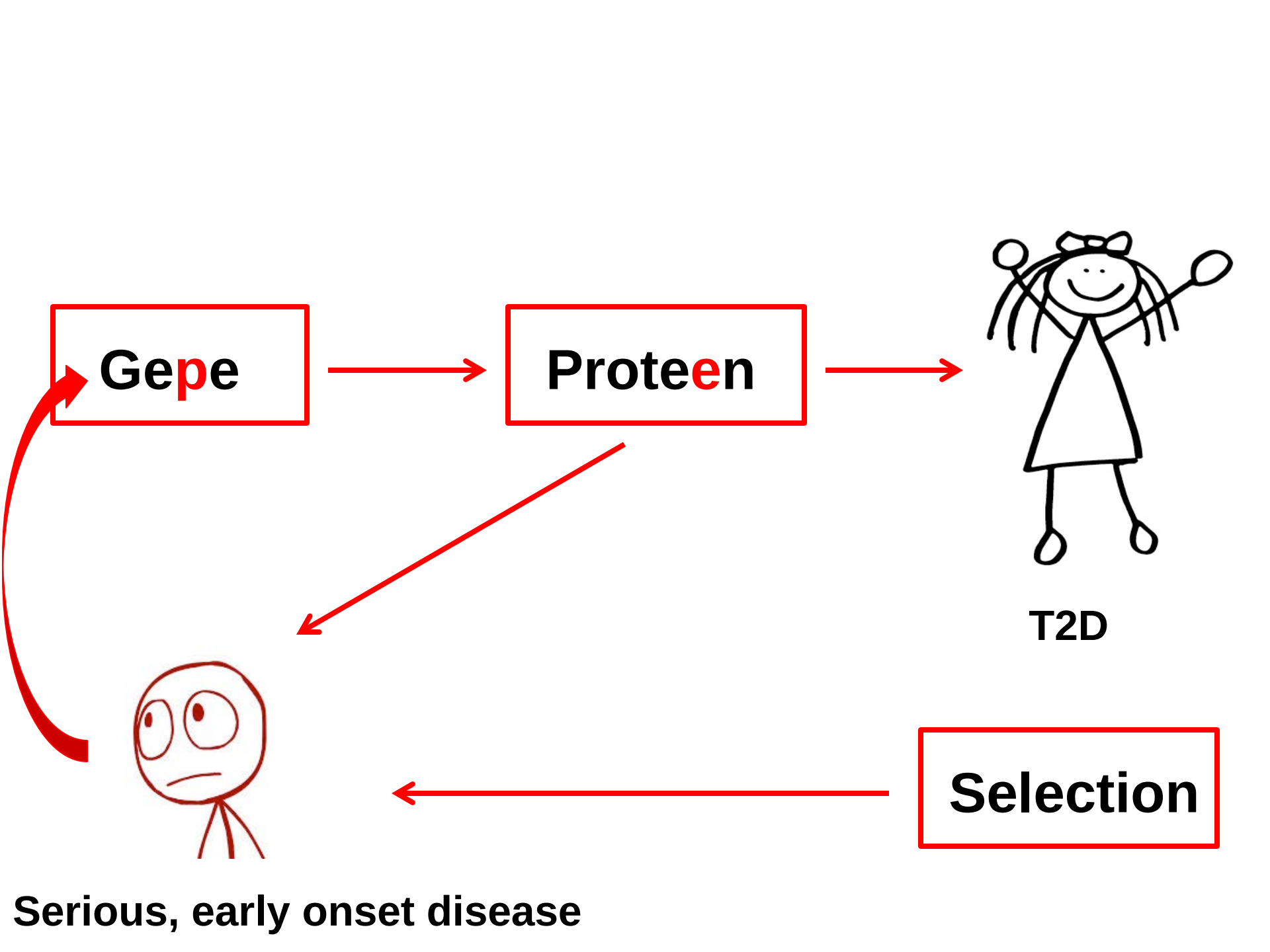
T2D
Selection


Gepe
Proteen
T2D
Selection
Serious, early onset disease