A Common Inversion Under Selection in Europeans

Stefansson, Hreinn *et al.* (2005) Nature Genetics – 37: 127-137

Presenter: Tom Conway

Evolution (02:131) Spring 2013

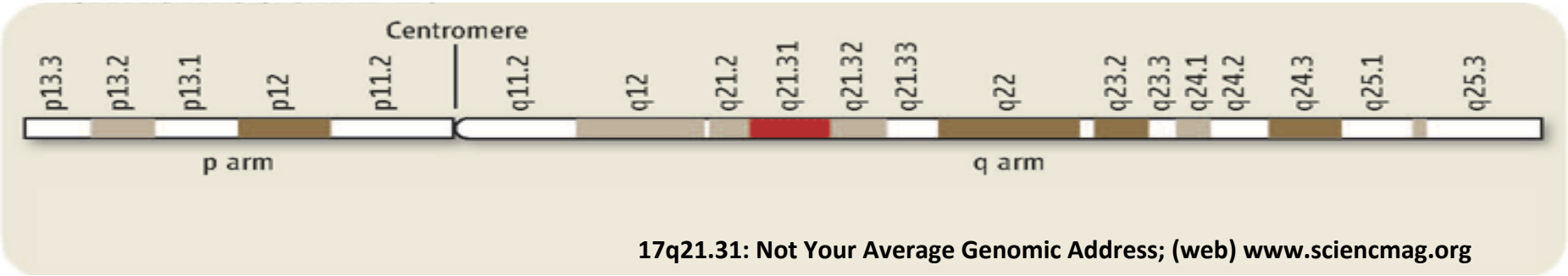
Week 9: March 26, 2013

Significance of Studying Genetic Variation Among Humans

- Gain insight into:
  - Organization of the human genome
  - Phenotypic and reproductive impact of variation
  - The evolutionary history of humans

Chromosome 17

- Region 17q21.31



17q21.31: Not Your Average Genomic Address; (web) www.sciencmag.org

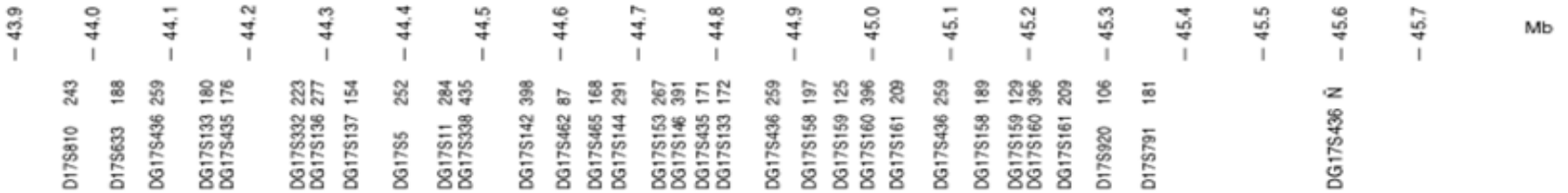
- Previous Studies
  - **Genes**
    - Corticotropin Releasing Hormone Receptor 1 (*CRHR1*)
    - **N-ethylmaleimide-sensitive factor (*NSF*)**
    - **Microtubule-associated Protein tau (*MAPT*)**
      - **H1 and H2 Haplotypes**
    - **Strong Linkage Disequilibrium (LD)**

Objectives

1. Detect and describe variation between H1 and H2 haplotypes

2. Show that the H2 lineage is undergoing positive selection in the Icelandic population
   - Evolutionary history
   - Signs of positive selection
     - Has the frequency of H2 increased?
     - Does H2 increase fitness by increasing offspring #?

Detecting Structural Differences



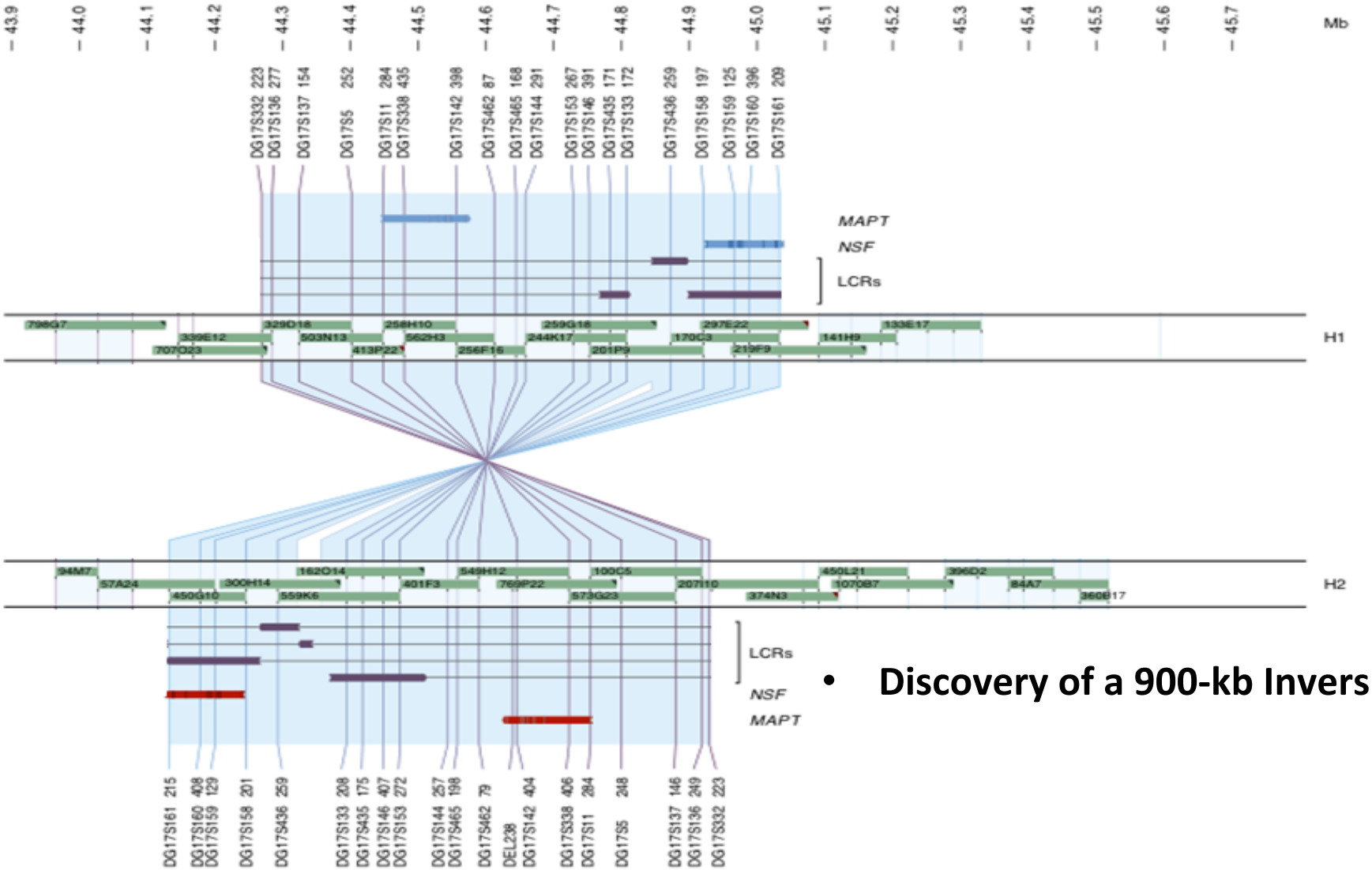
- **Contigs generated**

  - **Contigs – short, overlapping DNA sequences used to map longer DNA segments**

- **Contigs genotyped for 60 microsatellite markers**
  - **Assembled to form physical maps**

Stefannson et al. (2005) Figure 1 (modified)

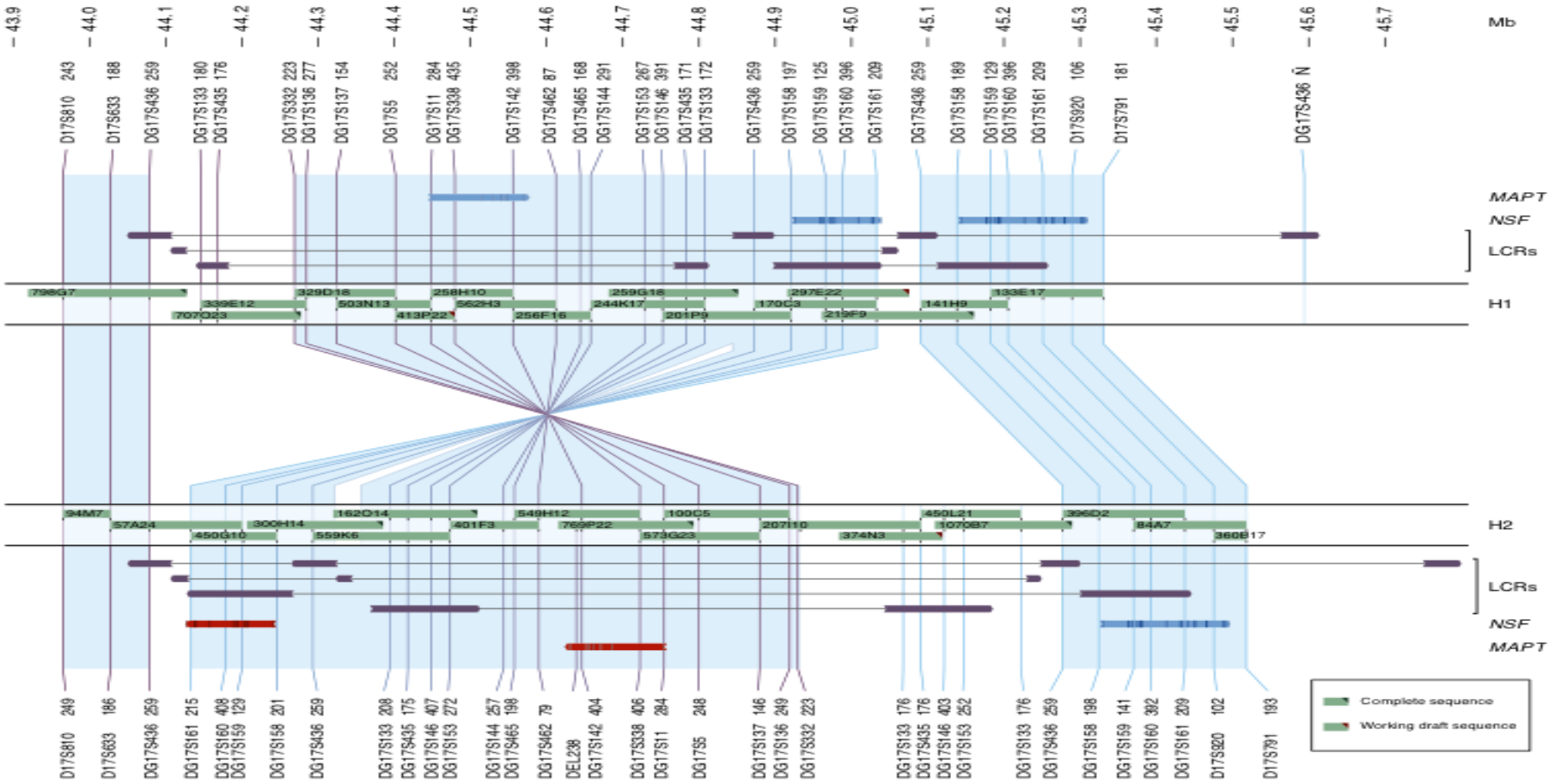
Detecting Structural Differences



- **Discovery of a 900-kb Inversion**

Stefannson et al. (2005) Figure 1 (modified)

Detecting Structural Differences



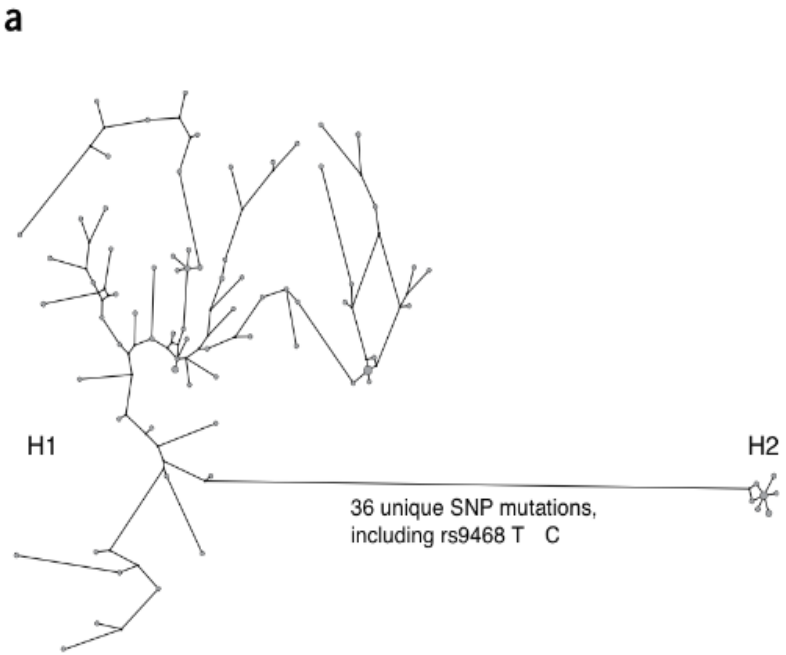
Stefannson et al. (2005) Figure 1

NSF Gene Duplication

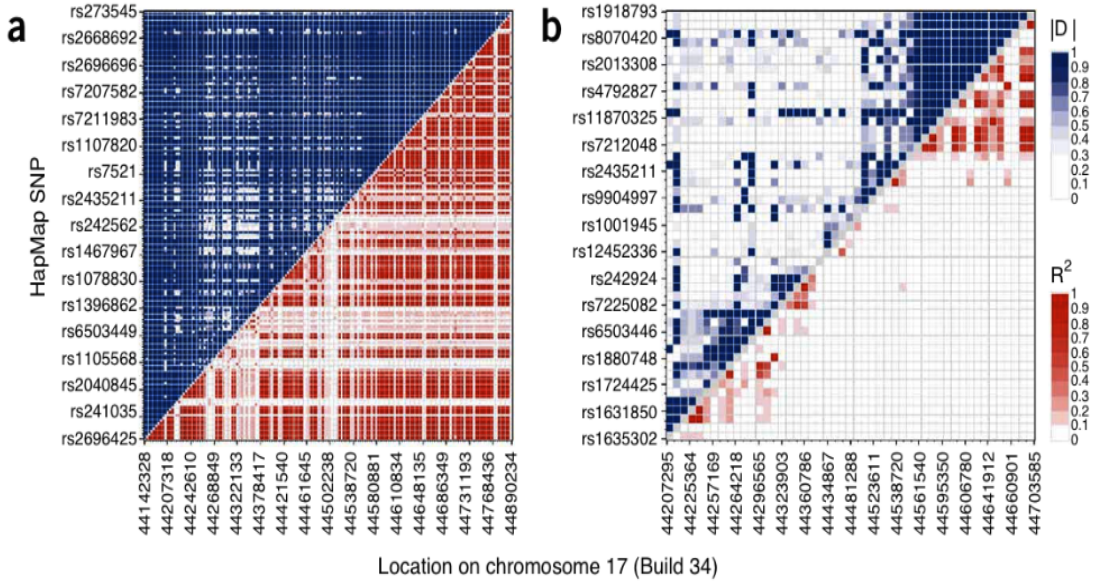
- Exons 1 – 13
  - H1
    - 127-kb duplication 100-kb upstream from full *NSF* gene
  - H2
    - 280-kb inverted duplication 1-Mb upstream from full *NSF* gene

Differences Used to Distinguish H1 and H2

- 424-kb nonduplicated inverted region
  - H2 differs from H1 by 6 microsatellite alleles and 36/95 SNPs
- H2 haplotypes are extremely homogenous with strong LD
  - no recombination between H1 and H2
    - Supports use of microsatellites **(DG17S142)** and SNP markers

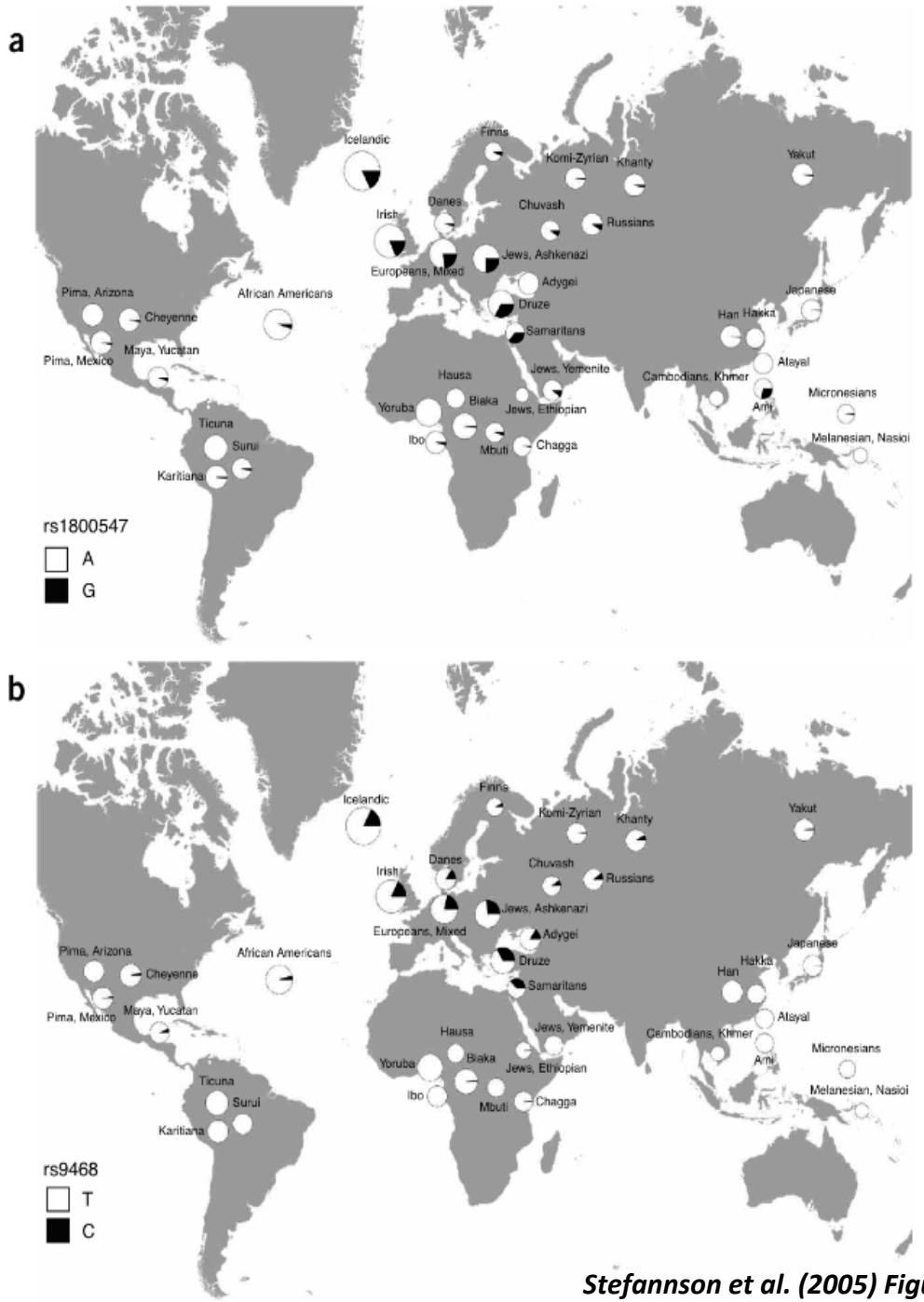


Stefannson et al. (2005) Figure 3a



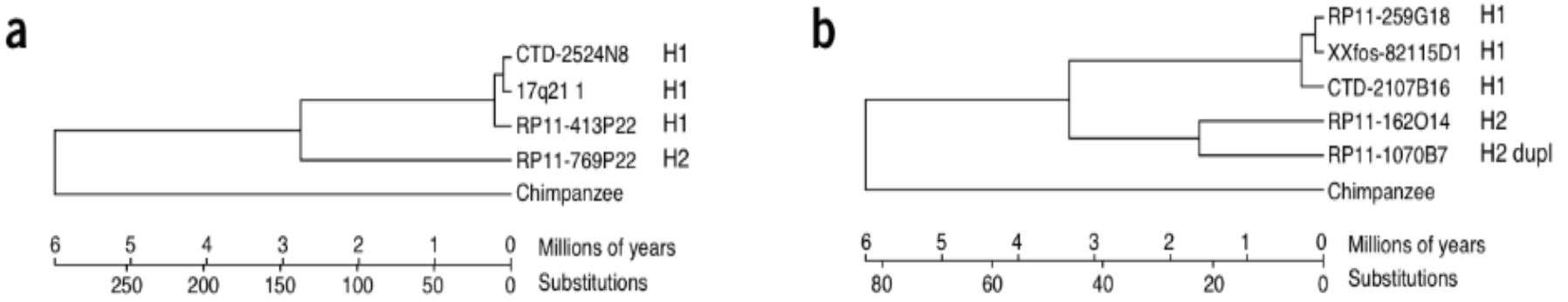
Stefannson et al. (2005) Figure 4

- Frequency of H2
  - **21 % European ancestry**
  - 6% African ancestry
  - 1% Asian ancestry



Stefannson et al. (2005) Figure 5

Evolutionary History H1 and H2 Lineages:
Time of Divergence



Stefannson et al. (2005) Figure 2

Maximum Parsimony Trees – divergence time estimated using # of differentiating mutations and assuming common rate

- **(a)** 77-kb region; **(b)** 32-kb region
  - Assume chimp-human divergence occurred 6 Mya and equal rates of evolution

- Divergence of H1 and H2: 0.3444% → Est. time of divergence ≈ 3 Mya
  - Unusually ancient

- **Homogeneity, Ancient Divergence, and Frequency of H2**
  - **Ancient balancing selection → Strong positive selection**

Evolutionary History of H1 and H2 Lineages

- Rule out neutral evolution as source of diversity
  - Simulations Under Four Demographic Scenarios
    - Compared relative diversity of microsatellites
  - Observations of H2 were Incompatible with expectations of neutral evolution
    - Including recent expansion via bottleneck

Evidence for Positive Selection of H2 Chromosomes in Iceland

- 29,137 Icelanders born between 1925 and 1965
  - 16,959 females; 12,178 men
  - Genotyped for **DG17S142**

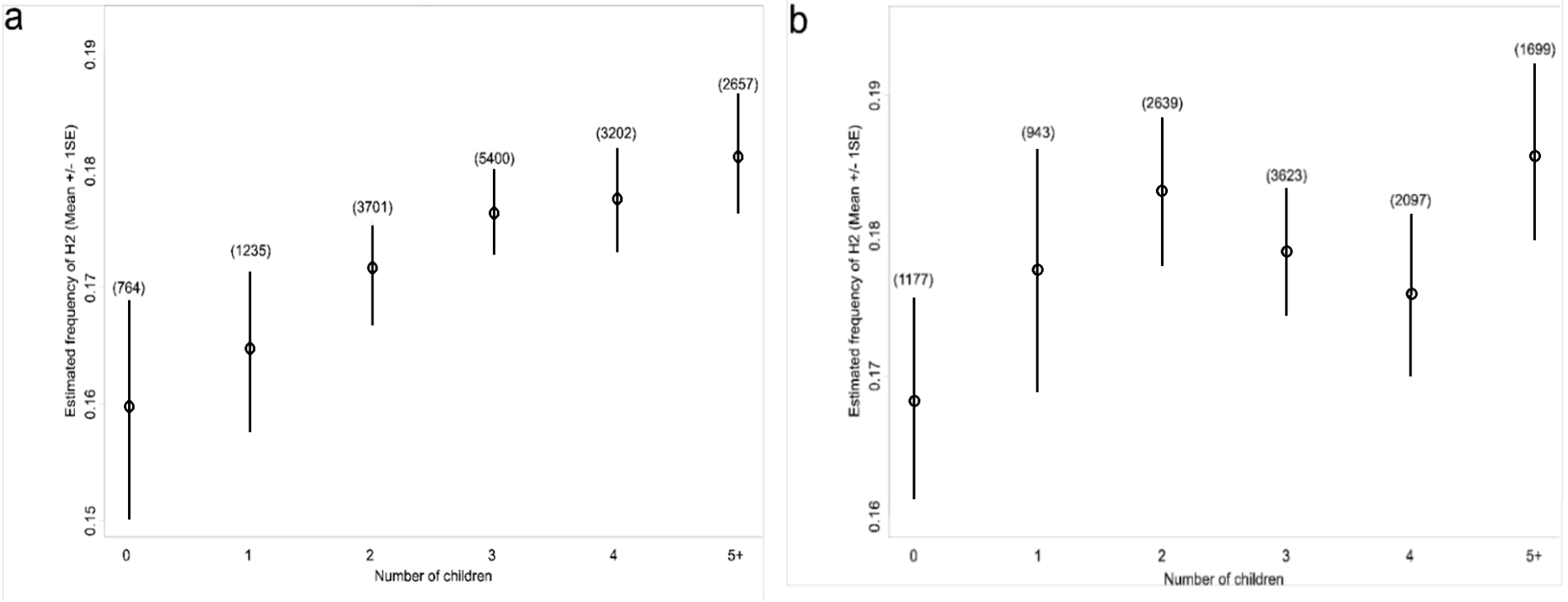
- Additive Effect Model - (0 copies < 1 copy < 2 copies)
  - H2 homozygotes do not have more children than heterozygotes

    - **Reject Additive Model**

Evidence for Positive Selection of H2 Chromosomes in Iceland

- Dominant Effect Model
  - Heterozygotes and H2 homozygotes have same # of children
  - Estimated effect of H2
    - Increase of 0.0796 children for average carrier
      - **+ 0.0907 for females**; + 0.0679 for males
    - **H2 CARRIERS HAVE FITNESS ADVANTAGE OVER NONCARRIERS**
- Unable to confirm/reject balancing selection
  - Few H2 homozygotes in sample

Evidence for Positive Selection of H2 Chromosomes in Iceland



Stefannson et al. (2005) Supplementary Figure 7

- **(a)** Women
  - As # of children rises so does the frequency of H2
    - Trend ends at 5 children
- **(b)** Men

Evidence for Positive Selection of H2 Chromosomes in Iceland

- Transmission Disequilibrium
  - Could be accountable for high frequency of H2
    - Is H2 is more likely than H1 to be transmitted to offspring by heterozygote parent?
  - Genotyped 5,529 parent-offspring trios
    - 3,286 trios with a heterozygous parent
      - H2 transmitted 1,641 times
  - No evidence for transmission disequilibrium

Evidence for Positive Selection of H2 Chromosomes in Iceland

- Mothers with higher recombination rates tend to have more children

- 5,012 women, spouse, and ≥ 2 children
  - 1000 genome-wide linkage markers
  - Regressed estimated recombination rate on # of H2 copies carried by mother
    - Rates increase 0.472 Morgans per copy
      - Across entire genome
  - No correlation in males

Evidence for Positive Selection of H2 Chromosomes in Iceland

- Results
  - Estimated effect of H2 through recombination:
    - May be underestimated
      - Only able to estimate rates in women with 2+ children
    - + 0.00564 more children for a carrier relative to a noncarrier
    - 0.00564 < 1/10 of 0.0907 (total effect)
      - Other pathways influenced by H2

Known Issues

- Unusually Ancient Divergence (3 Mya)
  - Anatomically modern human
    - Origin - 150,000 years ago
  - Origin of genus *Homo*
    - 2.5 million years ago

- Two Possible Explanations
  1. H1 and H2 maintained in ancestral gene pool
     - Balancing selection countering drift
  2. Divergence in isolated hominin populations
     - Introduced to *Homo sapien* gene pool before migration out of Africa

Conclusion

1. **Detect and describe variation between H1 and H2 haplotypes**
   - 900-kb inversion discovery; Partial duplication of *NSF* gene
     - Potential source of variation in gene expression patterns
   - H2 is extremely homogenous with strong LD

2. **Show that the H2 lineage is undergoing positive selection in the Icelandic population**
   - Signs of positive selection
     - High frequency of H2 only among Icelanders and other European populations
     - H2 increases fitness of carrier by increasing number of offspring
       - Recombination rate

- Increased frequency of H2 founder chromosomes by positive selection
  - **Not ruled out:**
    - More complex selection history
    - Extreme founder effect
- **Prediction:**
  - Selection for H2 is same throughout European populations

References

- Stefansson, Hreinn *et al.* 2005. A Common Inversion Under Selection in Europeans. Nature Genetics - 37: 127-137
- Pennisi, E. 2008. 17q21.31: Not Your Average Genomic Address. Science - 7: 842-845.

Tables 1 and 2

Table 1 Relationship between number of children and H2 carrier status

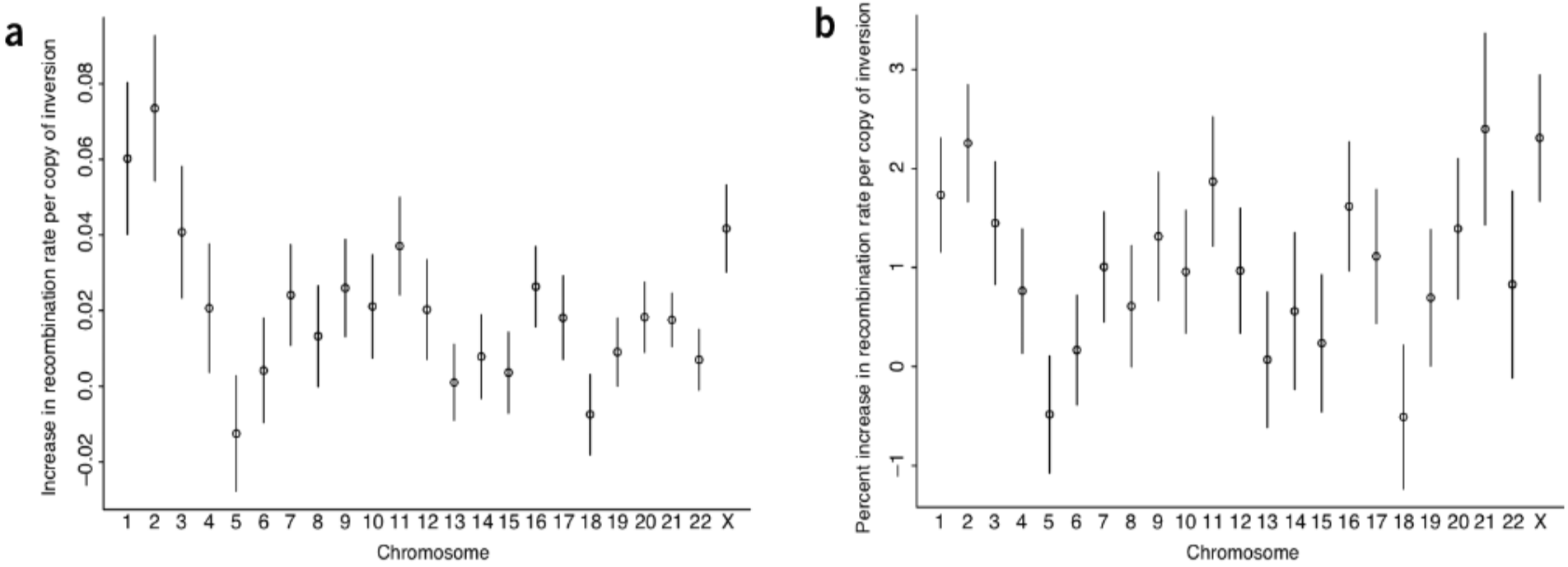
Cohort	Predictor	Estimate	Standard error	*P* value
Combined	Year of birth	−0.0340	0.0008	0.0000
	Carrier of H2	0.0796	0.0259	0.0025
	Sex	0.2360	0.0190	0.0000
Female	Year of birth	−0.0331	0.0010	0.0000
	Carrier of H2	0.0907	0.0338	0.0068
Male	Year of birth	−0.0349	0.0012	0.0000
	Carrier of H2	0.0679	0.0375	0.0719

Table 2 Relationship between recombination rates and the number of H2 chromosomes carried

Response (recombinations)	Predictor	Estimate	Standard error	*P* value
Total	Number of H2	0.4721 (1.04)	0.1180	0.0002
	Year of birth	−0.0024	0.0064	0.7037
	Average age at birth of offspring	0.0838	0.0152	0.0000
Telomeric	Number of H2	0.0257 (2.24)	0.0092	0.0047
	Year of birth	−0.0006	0.0005	0.2130
	Average age at birth of offspring	0.0077	0.0012	0.0000
Nontelomeric	Number of H2	0.4465 (1.01)	0.1160	0.0004
	Year of birth	−0.0018	0.0062	0.7724
	Average age at birth of offspring	0.0760	0.0149	0.0000

Stefannson et al. (2005) Tables 1 and 2

Figure 6



Stefannson et al. (2005) Figure 6

Supplementary Figure 1

Stefannson et al. (2005) Supplementary Figure 1

Supplementary Table 2

Demographic scenario	Population size history (N_e)	Null distribution of ASD_{avg} ratio Median	Central 95% range	Empirical P-value
Constant	10^4	0.21049	0.01845-3.23677	0.0014
Ancient expansion 5,000 generations ago	10^4->10^7	0.46236	0.09737-2.23115	<0.0002
Recent expansion 200 generations ago	10^4->10^7	0.21481	0.02194-3.70106	0.0012
Expansion 800 generations ago after dramatic bottleneck 960 generations ago	10^4 -> 400 -> 10^7	0.17514	0.01669-5.7328	0.002

Stefannson et al. (2005) Supplementary Table 2