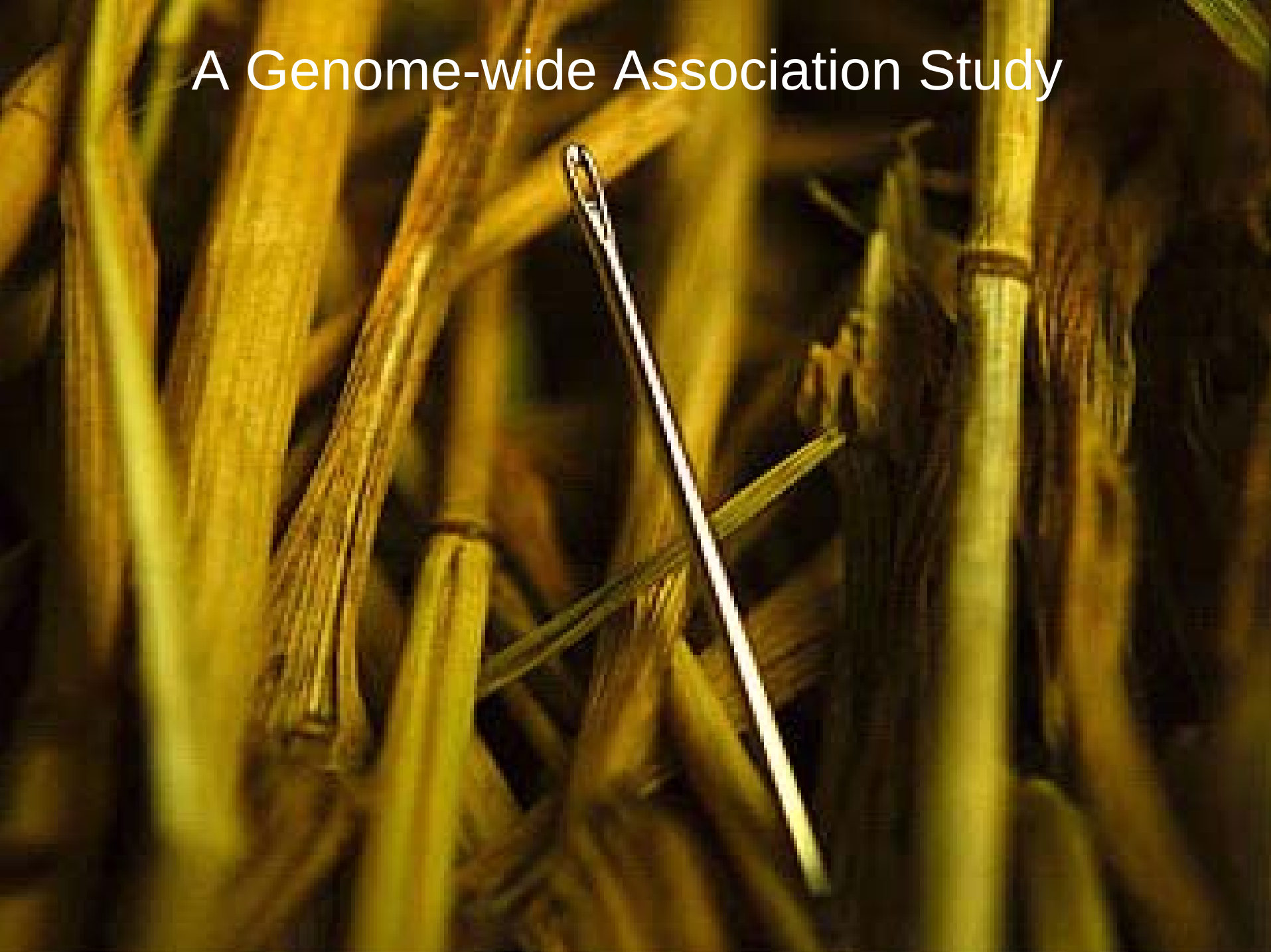
Assessment of Risk for Colon Tumors In Canada (ARCTIC)

Brent Zanke
Steve Gallinger
Celia Greenwood
Michelle Cotterchio
Tom Hudson

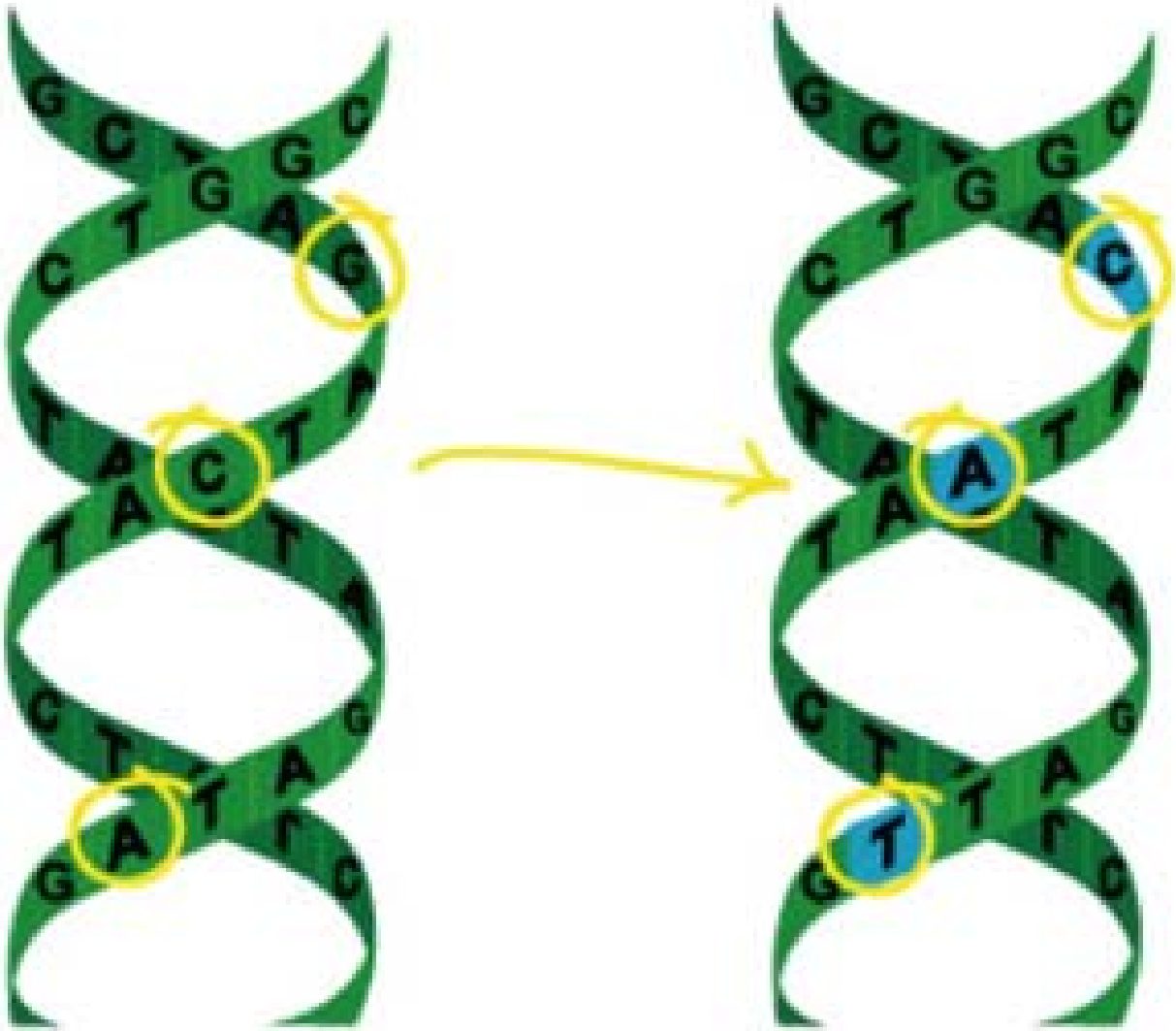
Toronto/Montreal

A Genome-wide Association Study



Associating inherited (DNA) variation with biological variation

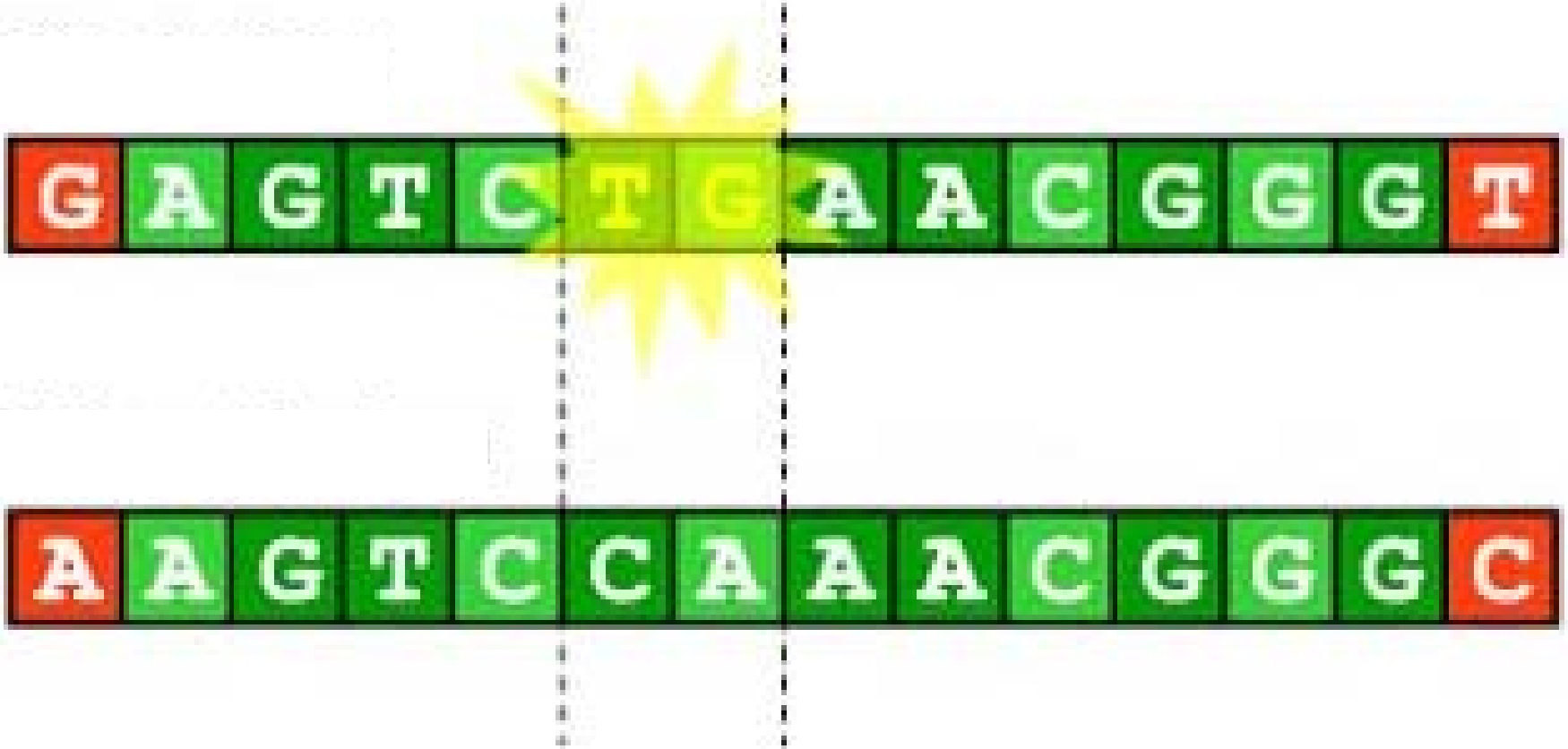
- Each person's genome is slightly different
- Some differences alter biological function
- Questions:
  - How much variation exists?
  - Which differences matter?



SNP Statistics

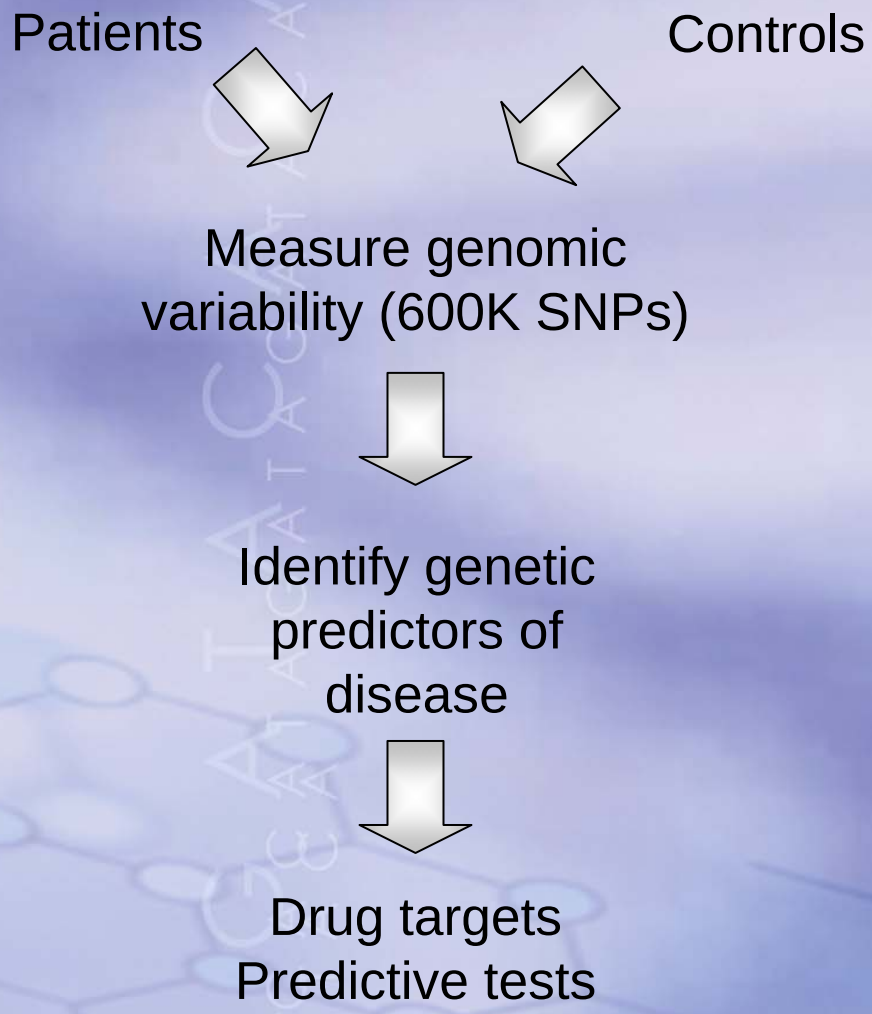
- Estimated SNPs in human genome: 10 million
- Number that have been seen twice: about two million

Finding the genetic contribution to human disease

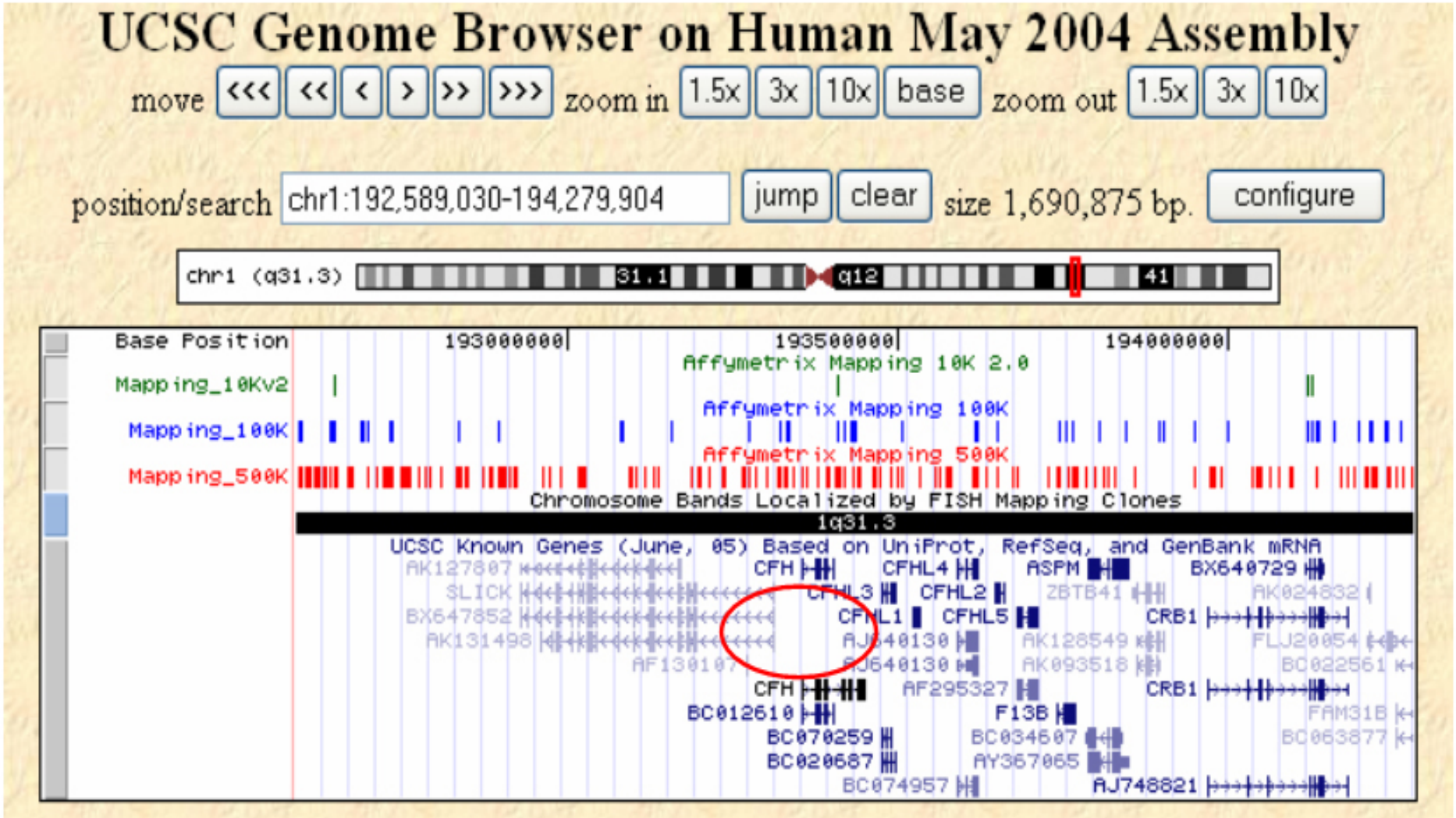


Through the identification of SNP markers that distinguish diseased from healthy individuals (red), true disease-causing genetic changes (yellow) can be identified by fine sequencing.

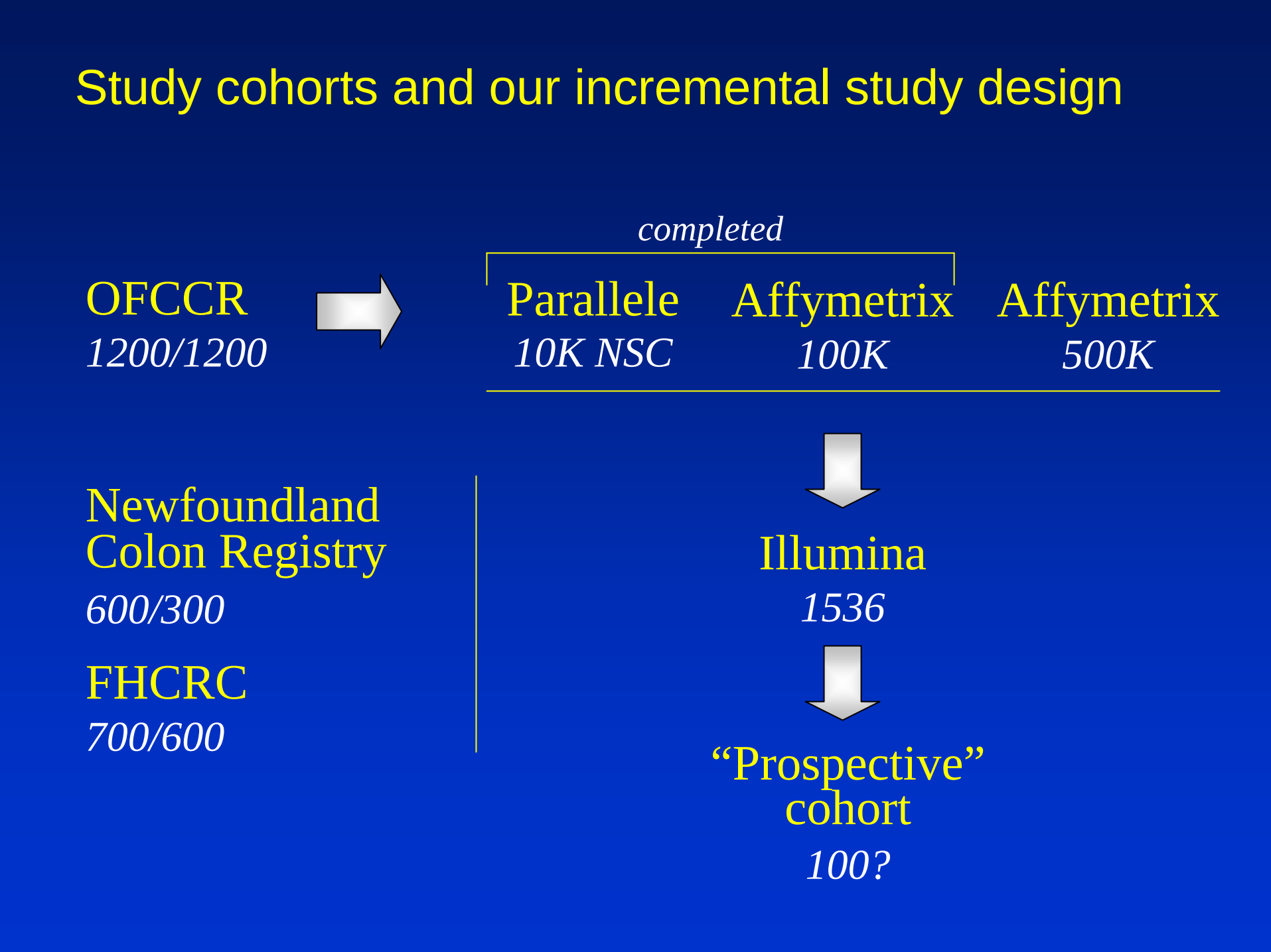
Assessment of Risk of Colon Tumors In Canada (ARCTIC Project)



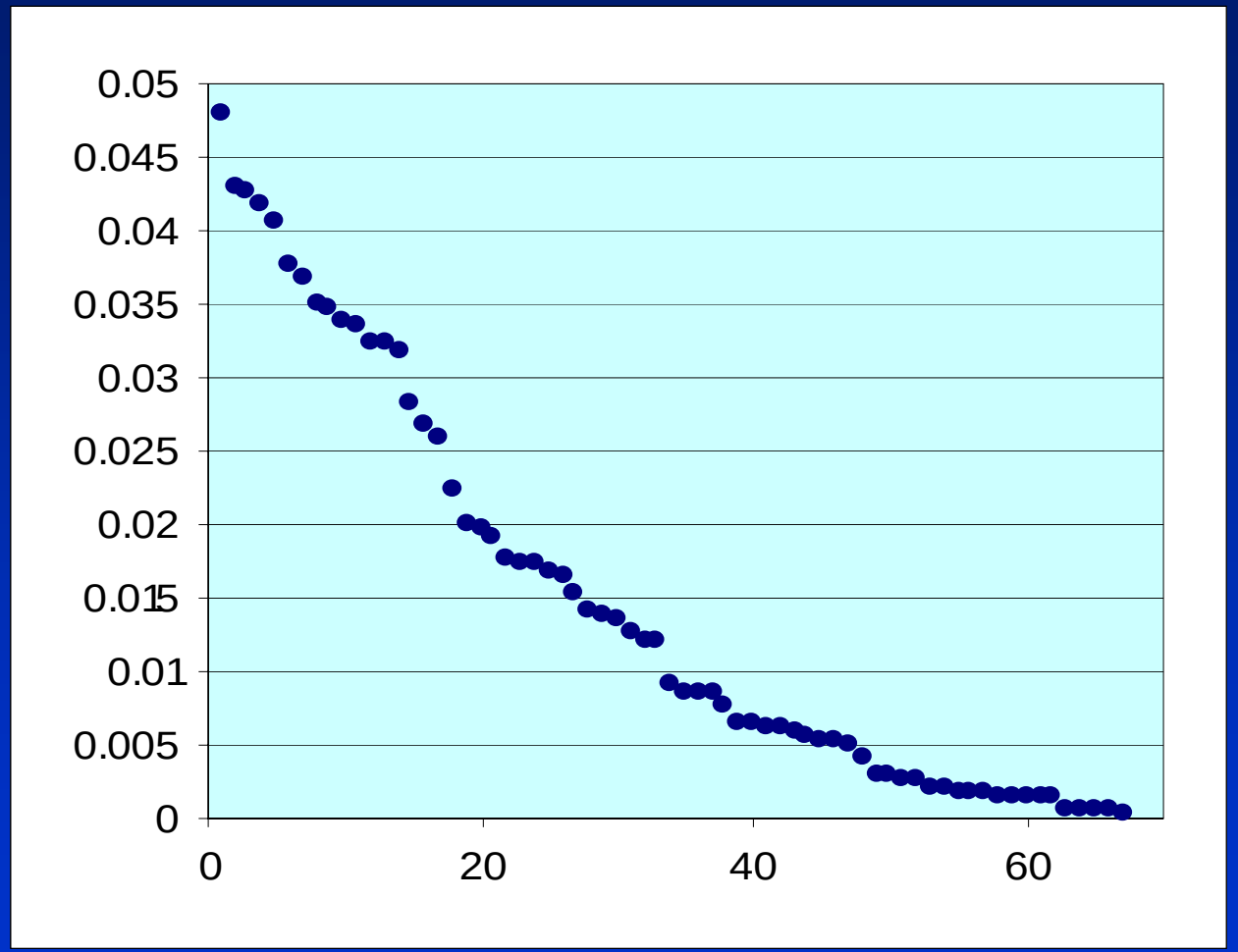
Comparison of 10K, 100K and 500K SNP coverage in the UCSC Genome Browser. Circled gene is Complement Factor H, identified in a 100K association Study.

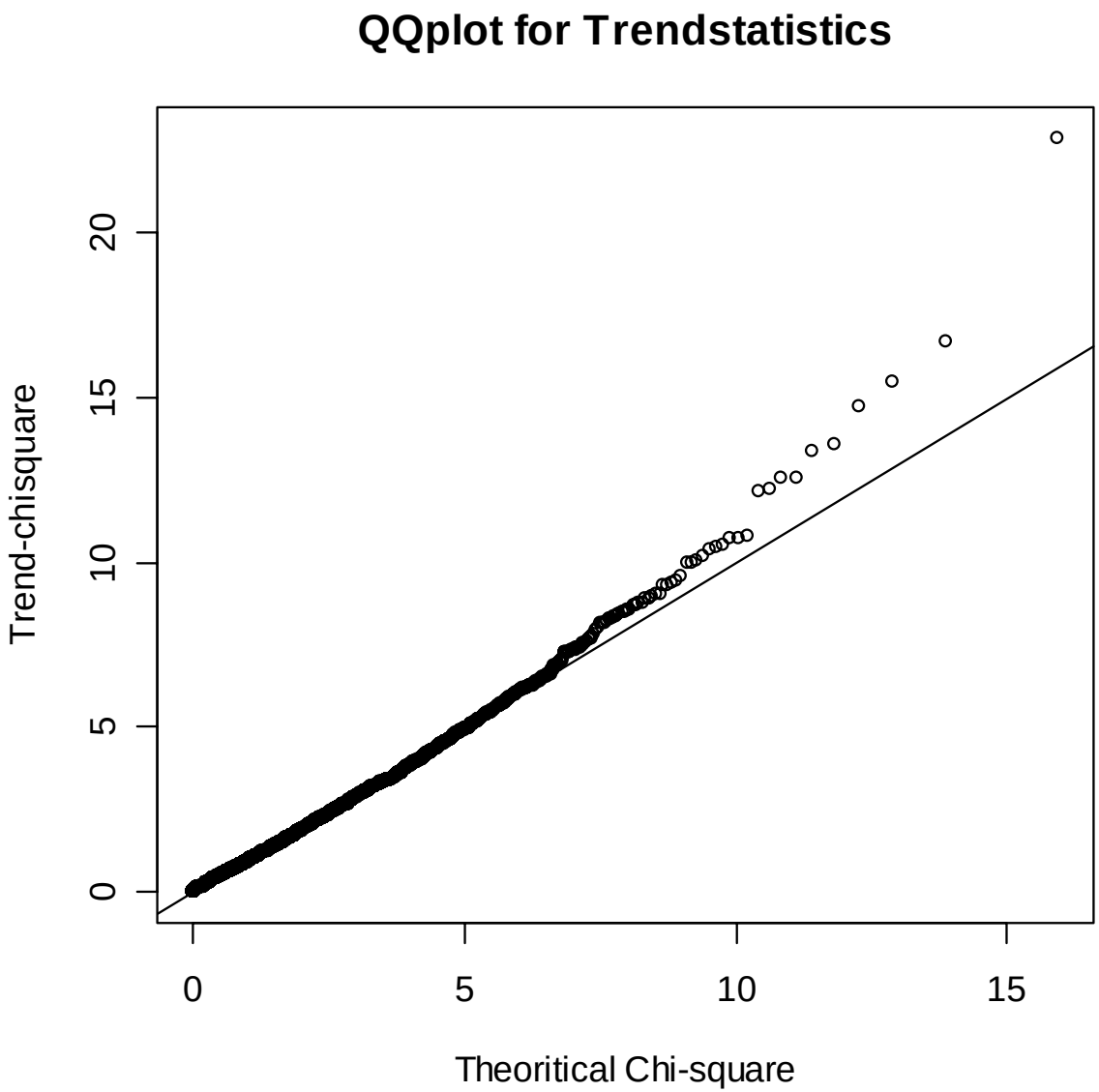


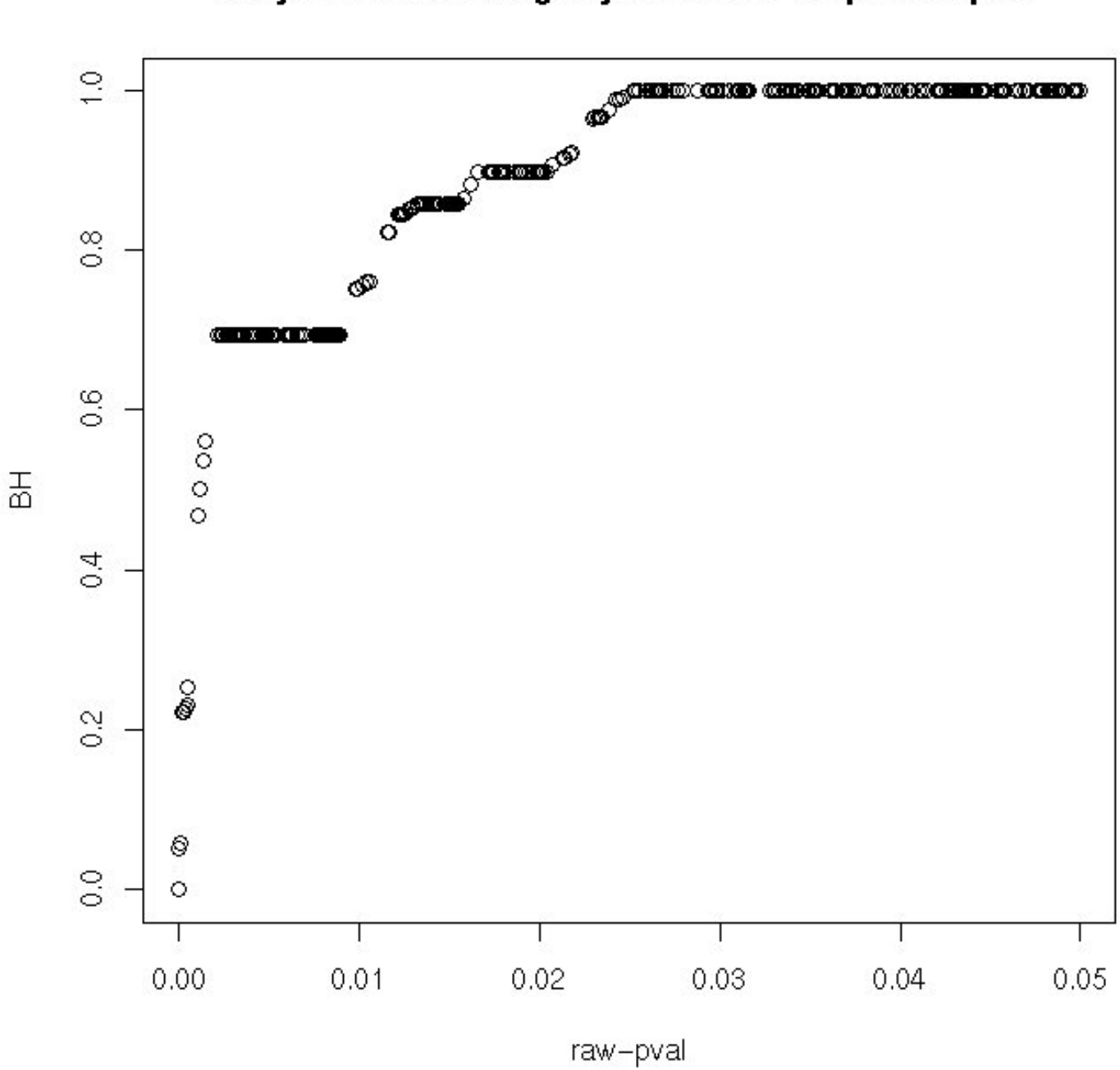
Study cohorts and our incremental study design



DNA repair gene polymorphisms correlating with colon cancer phenotype




QQplot for Trendstatistics
Trend-chisquare
0
5
10
15
20
0
5
10
15
Theoritical Chi-square


Benjamini–Hochberg adjustment of Emp. Max. pval
BH
raw–pval
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.01
0.02
0.03
0.04
0.05

DNA Repair SNP Subset

Toronto cohort 68 SNPs (1200 cases:1200 controls)

French cohort 65 SNPs (340 cases + 270 APC:700 controls)

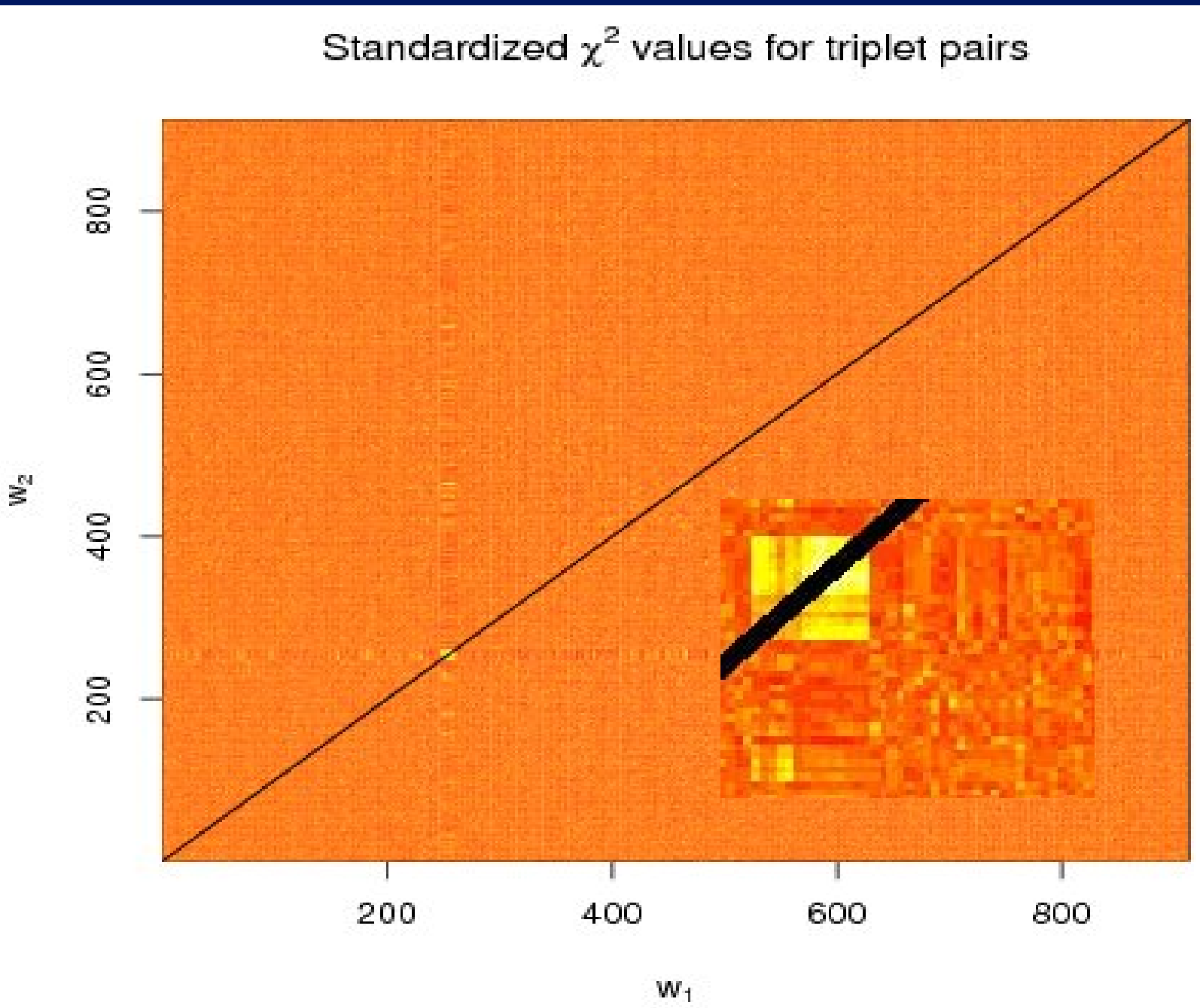
17 SNPs in common ($p < 0.05$)

Validation: p values, full model:

SNPs	Nfld (450:370 cases:controls)	Seattle (700:700 cases:controls)
rs1074078	0.19	0.07
rs2270543	0.12	0.60
rs9875030	0.0002 (TNIK)	0.86
rs7341420	0.07	0.11
rs1125008	0.95	0.87
rs1573034	0.17	0.69
rs2488336	0.33	0.30
rs2234978	0.55	0.55
rs7095466	0.66	0.07
rs206143	0.73	0.43
rs1799943	0.88	0.55
rs4451921	0.75	0.86
rs2521348	0.83	0.67
rs2048707	0.18	0.64
rs718742	0.63	0.08
rs9844740	0.07 (TNIK)	0.99
rs891554	0.82	0.40

Approach to Statistical Analysis

* Univariant analysis - permutation testing/Chi^2
* Univariant analysis - haplotype assignment
* Multivariant parwise testing of single SNPs
* Multivariant parwise haplotype testing
* Multivariant decisions trees (Tree View)


Standardized χ^2 values for triplet pairs
200
400
600
800
w_2
200
400
600
800
w_1

Value of the ARCTIC Project

- ✓ **Save lives with the development of a predictive genetic test for colon cancer**
- ✓ **Potentially predict response to expensive and toxic drugs prospectively**