

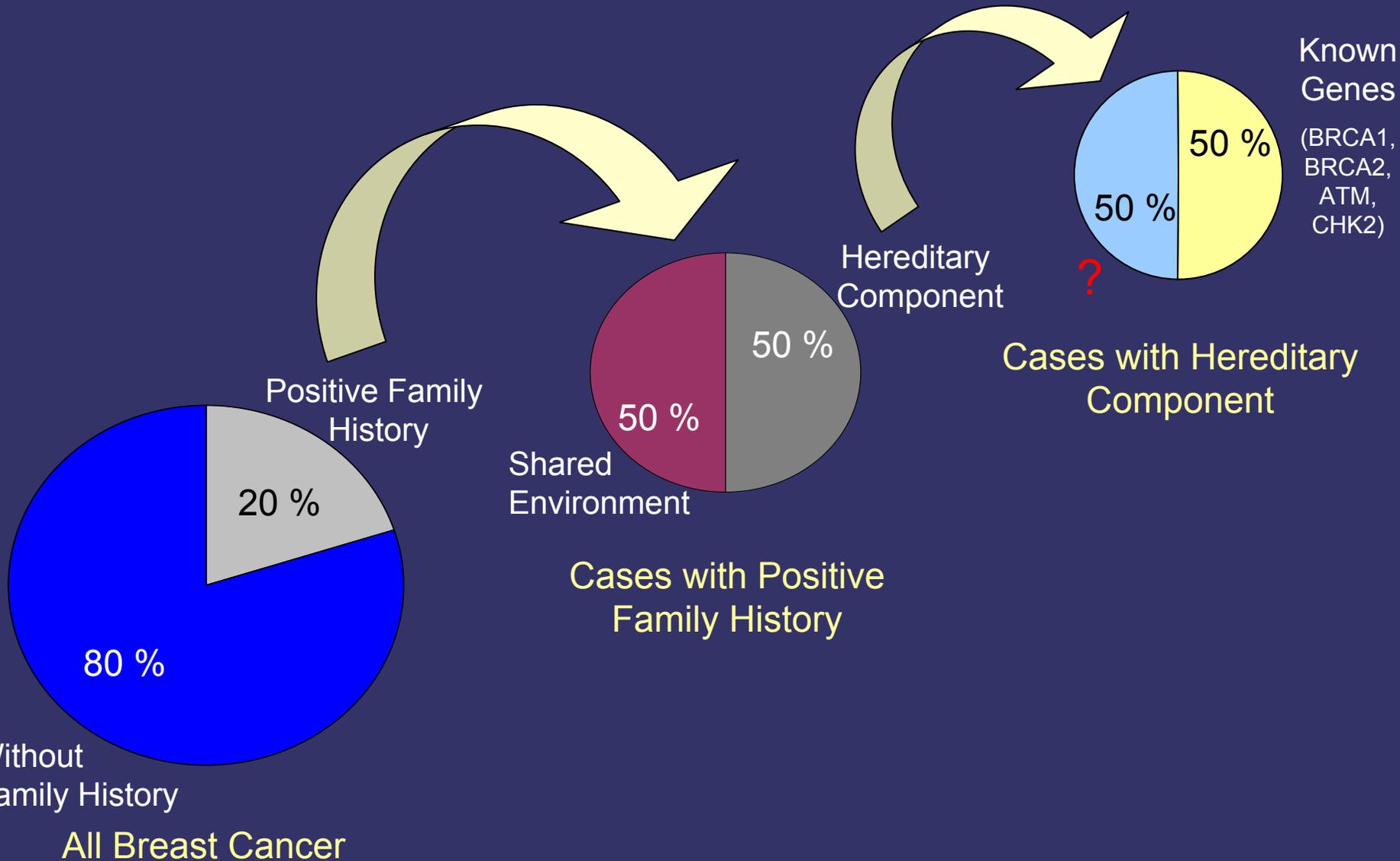
Genomewide Association in Early-onset Breast Cancer

Habibul Ahsan

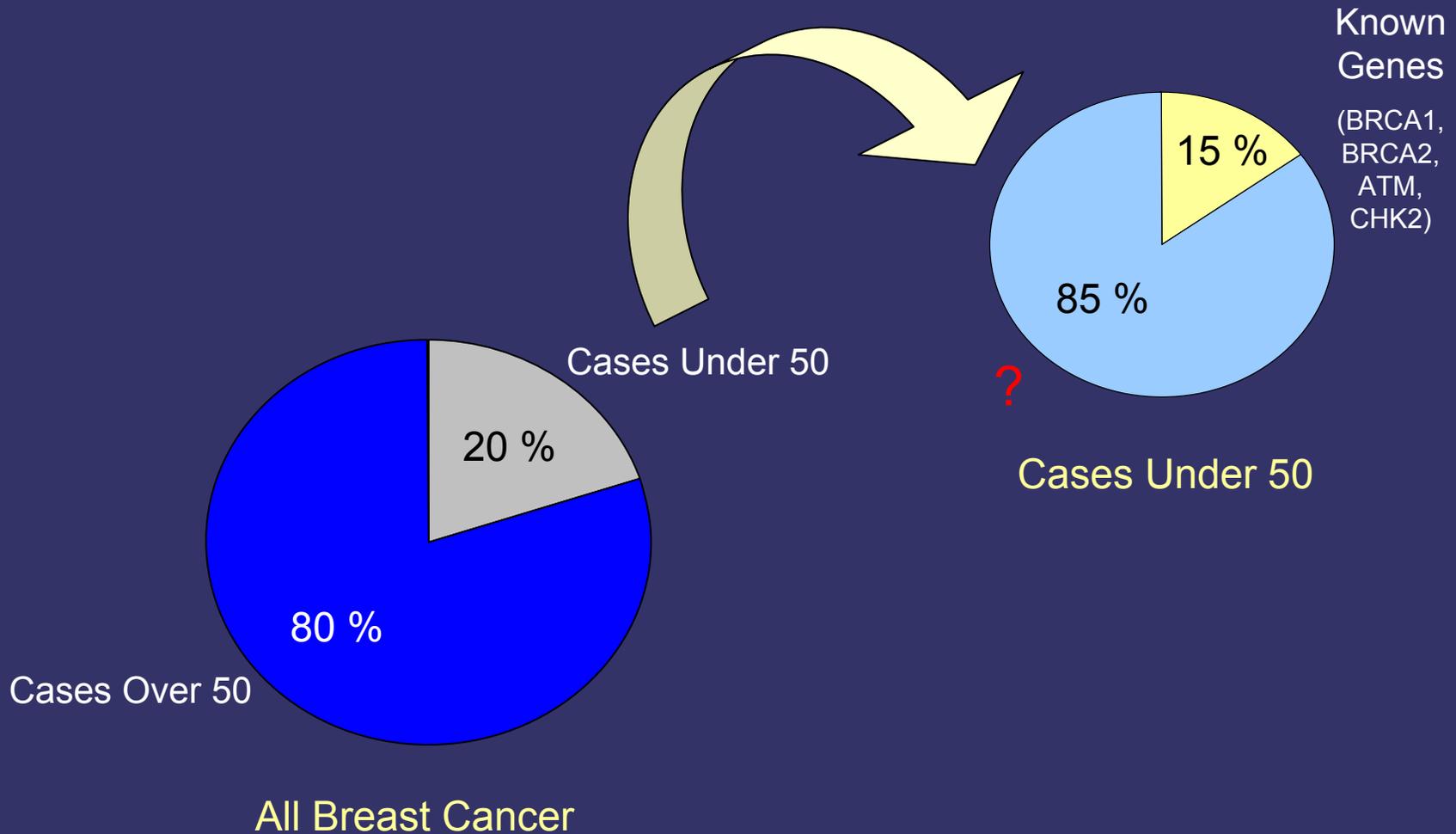
Alice Whittemore

On Behalf of Breast CFR

Family History and Genetic Susceptibility to Breast Cancer



Age at Onset and Genetic Susceptibility to Breast Cancer



Study Focus and Setting

- Early-onset (<50 years)
- BRCA1 & BRCA2 mutation negative
- Non-Hispanic Caucasian
- Incident cases of invasive breast cancer
- Population-based ascertainment
- Both population and sister controls

From:

- Australia (John Hopper)
- Canada (Irene Andrulis)
- California, USA (Esther John)
- Germany (Jenny Chang-Claude)

Proposed Genotyping Platforms (Currently Available)

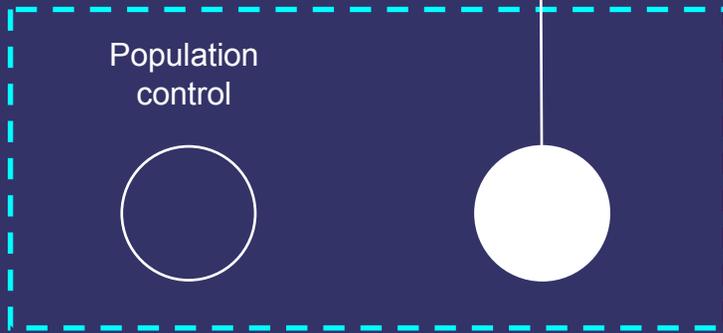
- Affymetrix 500k SNP panel
 - 523,200 randomly-spaced SNPs
- ParAllele 20k ns cSNP panel
 - 20,127 non-synonymous cSNPs

Aims

- **Phase I – Discovery Phase:** Identify the most promising alleles associated with breast cancer in a *two-stage case-control* study comparing 1500 cases and 1500 controls.
- **Phase II – Confirmatory Phase:** Confirm Phase I associations and attempt to identify the disease-causing alleles in an *independent sister-pair* study comparing 830 cases and their 830 unaffected sister controls.

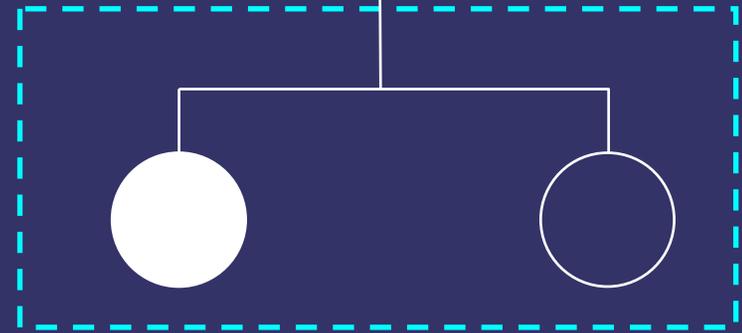
Study Design

Phase I



1500 cases / 1500 population controls

Phase II



830 cases / 830 unaffected
sister controls

Phase I (Two-stage Discovery Phase)

Stage I

1,000 non-Hispanic White early-onset breast cancer cases & 1,000 matched population controls

↓
genotype for

Affymetrix 500k SNPs
+
ParAllele 20k ns cSNPs

↓
analysis yields

Promising SNPs

Stage II

500 non-Hispanic White early-onset breast cancer cases & 500 matched population controls

↓
genotype for

All promising SNPs from Stage I

↓
genotyped by

ParAllele custom 10k SNP panel

Combined Phase I Analysis

1,500 non-Hispanic White early-onset breast cancer cases & 1,500 matched population controls

↓
All promising SNPs from Stage I
↓
analysis yields

Significant SNPs

Phase II (Confirmatory Phase)

830 early-onset breast cancer cases and their 830 unaffected sisters of same or higher age

↓
genotype for

All Phase I significant SNPs
+
Set of surrounding SNPs to characterize haplotypes
+
All candidate SNPs in the same haplotypes

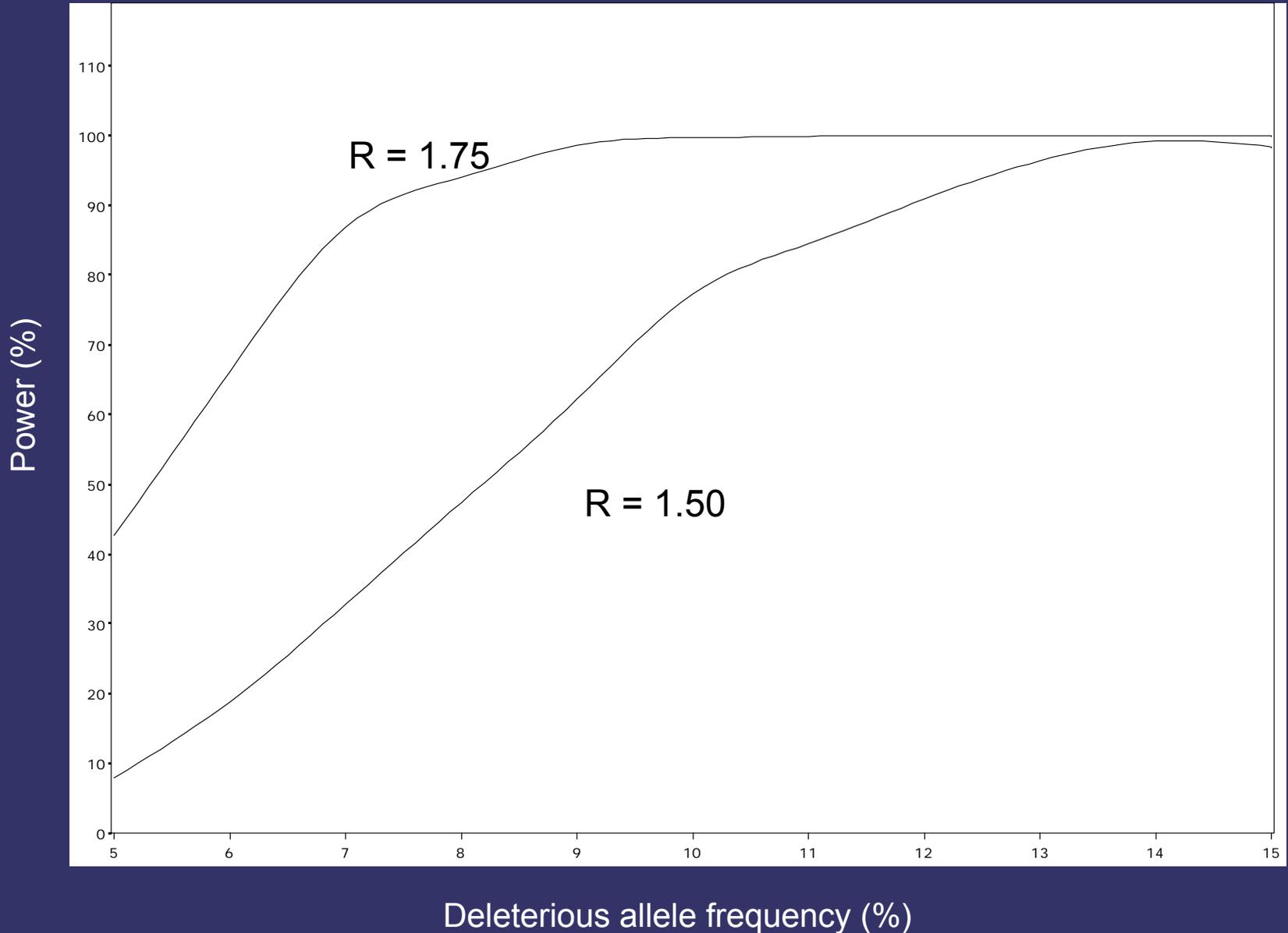
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genotyped by

ParAllele custom 3k SNP panel

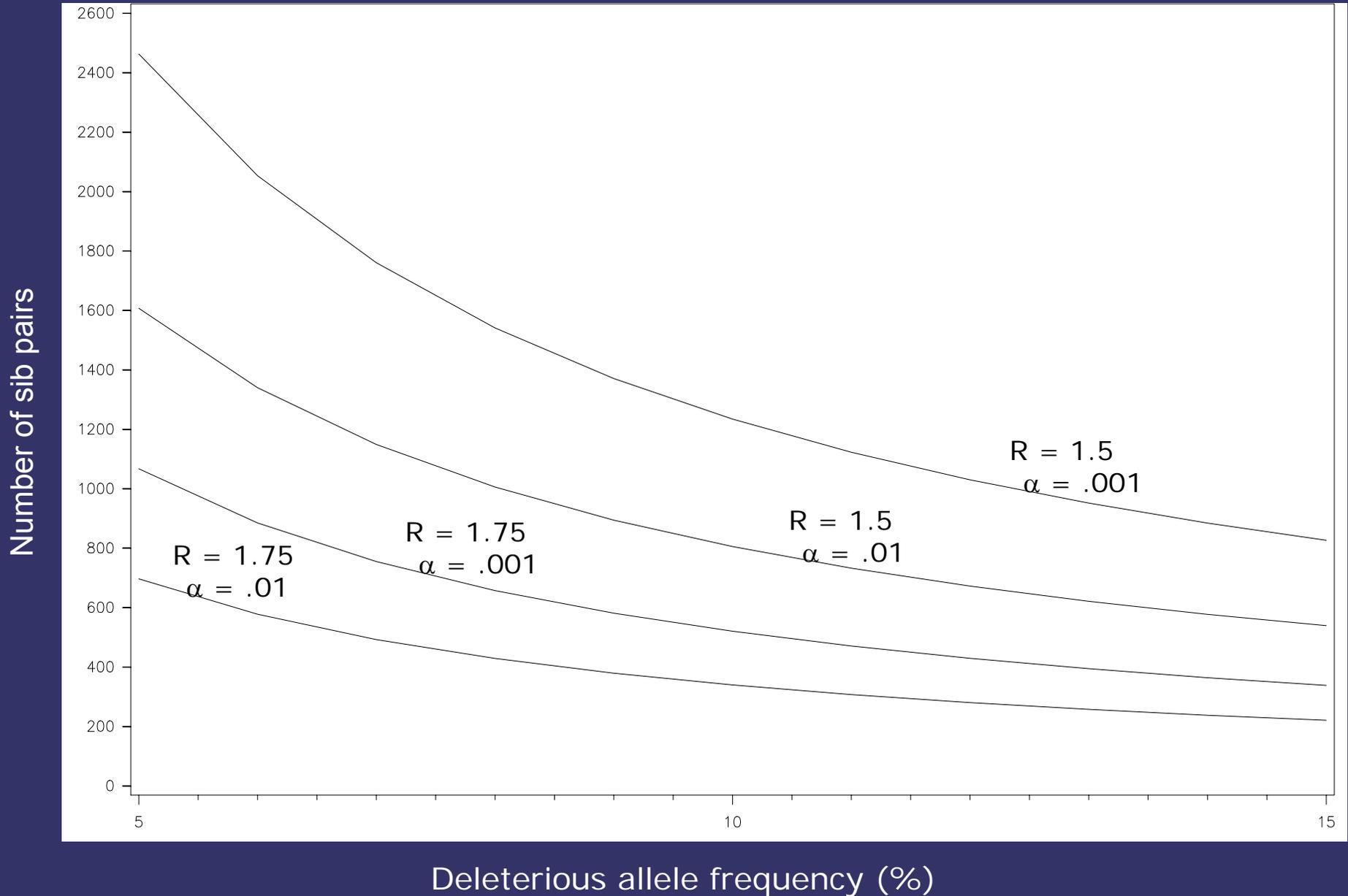
↓
analysis yields

Confirmed causal SNPs and haplotypes for breast cancer

Simulated power of Phase I study to detect an untyped causal locus whose variant allele has additive effects, with a heterozygote relative risk R



Numbers of sister case-control pairs needed to detect a causal allele with additive effects with 80% power, type-1 error rate α , & a heterozygote relative risk R



Pilot GWA Case-control Study

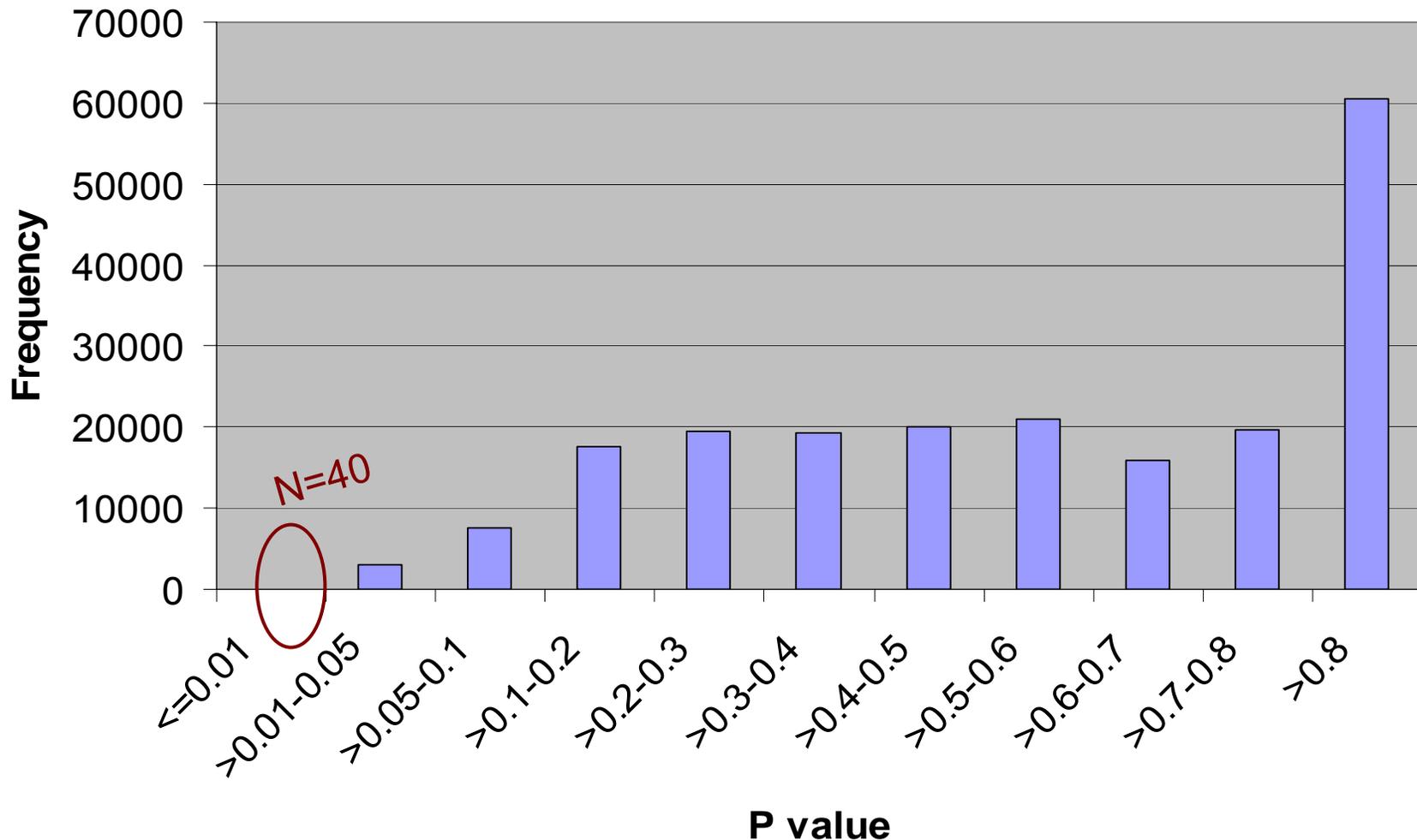
[Age <40, Non-Hispanic White, BRCA1/2-negative]

Quality Control Parameters

		Canada (n=20)		California (n=20)		Germany (n=20)	
		mean	95% CI	mean	95% CI	mean	95% CI
DNA 260/280 ratio	controls	1.92	1.88 - 1.96	1.92	1.89 - 1.95	1.82	1.76 - 1.87
	cases	1.92	1.88 - 1.95	1.88	1.84 - 1.93	1.81	1.77 - 1.84
Purified PCR conc ng/uL	controls	2005.57	1624.44 - 2386.69	2265.35	2101.37 - 2429.32	2078.15	1855.05 - 2301.24
	cases	1834.59	1341.34 - 2327.83	2207.74	1915.05 - 2500.42	2199.91	2092.03 - 2307.78
Purified PCR 260/280 ratio	controls	1.89	1.86 - 1.92	1.89	1.86 - 1.92	1.90	1.86 - 1.94
	cases	1.89	1.83 - 1.95	1.90	1.88 - 1.92	1.89	1.86 - 1.93
Genotype call rate	controls	91.36%	89.51 - 93.22%	87.69%	86.31 - 89.07%	88.21%	85.65 - 90.77%
	cases	91.18%	89.26 - 93.11%	89.75%	86.24 - 93.25%	88.94%	87.07 - 90.80%
Heterozygote call	controls	27.23%	26.46 - 28.01%	28.06%	27.07 - 29.06%	26.38%	25.51 - 27.24%
	cases	26.51%	25.64 - 27.38%	26.97%	25.63 - 28.30%	26.47%	25.15 - 27.79%
AFFX-5Q-123/456 ratio	controls	3.03	2.73 - 3.34	2.39	2.18 - 2.60	2.42	2.07 - 2.77
	cases	3.34	3.06 - 3.62	2.26	1.92 - 2.60	2.75	2.44 - 3.06
AFFX-5Q-789/456 ratio	controls	4.98	4.66 - 5.31	3.68	3.36 - 3.99	4.16	3.73 - 4.59
	cases	5.31	4.81 - 5.82	3.82	3.38 - 4.27	4.36	3.76 - 4.96
AFFX-5Q-ABC/456 ratio	controls	6.07	5.69 - 6.46	4.46	4.07 - 4.86	5.32	4.76 - 5.88
	cases	6.54	5.75 - 7.34	4.96	4.55 - 5.37	5.35	4.44 - 5.93

Pilot GWA Study Results

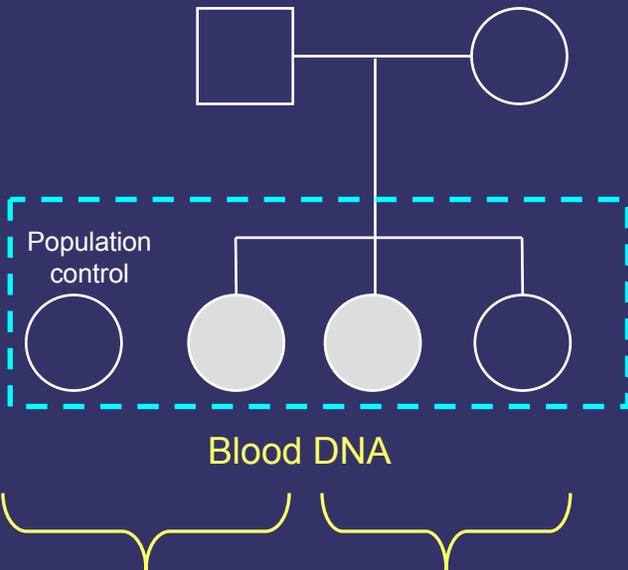
Distribution of p-values from CLR analysis



Plans for Integrated Genomewide Studies in BCFR:

3 Complementary Studies:

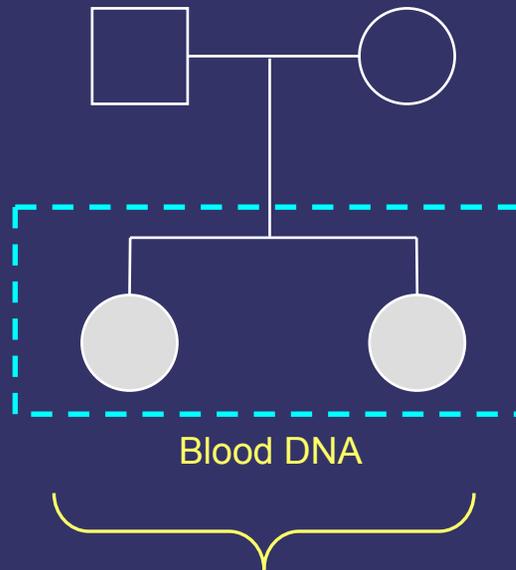
Association Scan



Case-control design

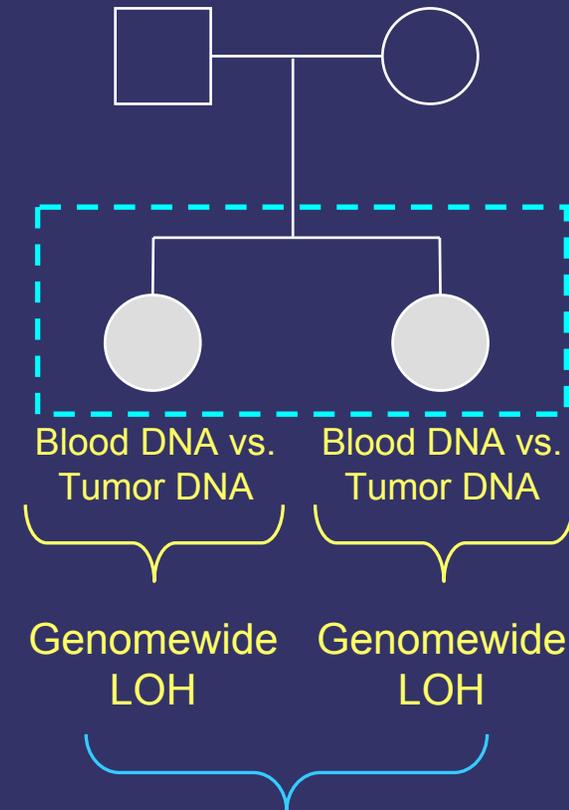
(Under 50 Cases with Sister
& Population Controls)

Linkage Scan



Affected sister-pair design

LOH Scan



Genetic Susceptibility
to LOH

Acknowledgements

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