

Breast Cancer Susceptibility Alleles in ATM and CHEK2

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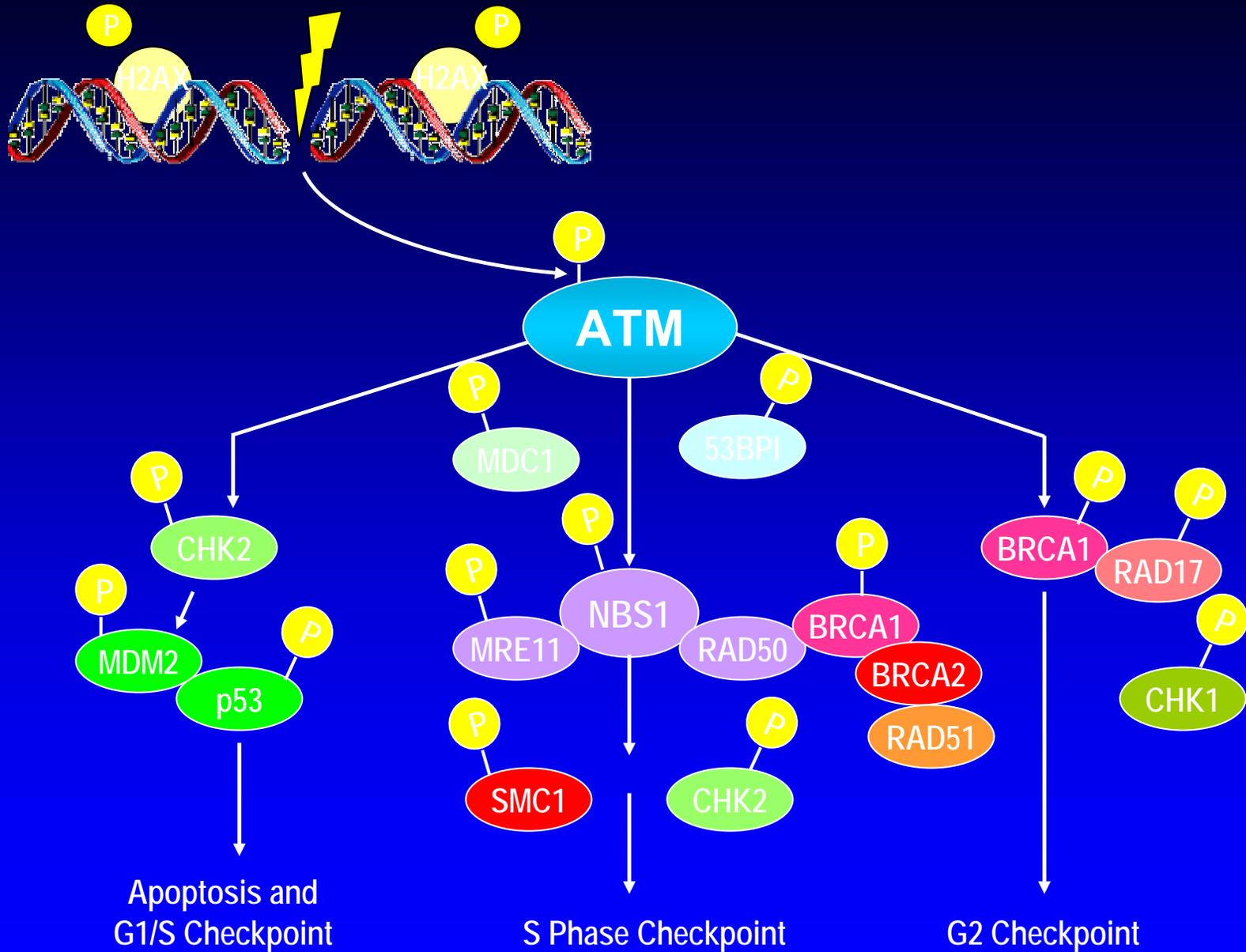
Jonine L. Bernstein, Ph.D.

Overview

- ***“Population-based estimates of breast cancer risks associated with the ATM variants 7271T>G and IVS10-6T>G from the Breast Cancer Family Registry”***
- ***“The CHEK2*1100delC Allelic Variant and Risk of Breast Cancer: Screening Results from the Breast Cancer Family Registry”***

(accepted CEBP, 2005)

Role of ATM and CHEK2 in Cellular DNA Damage Response



“Population-based estimates of breast cancer risks associated with the ATM variants 7271T>G and IVS10-6T>G from the Breast Cancer Family Registry”

Risk of Breast Cancer Associated with ATM Gene Variant 7271T>G: Few Studies, Few Carriers

Design Study	RR	# Carriers
A-T Family-Based		
Stankovic (1998)	12.7 (3.7-45.8)	2/78
Br Ca Family-Based		
Chevenix-Trench (2002)	15.7 (6.4-38.0)	1/525
Szabo (2004) (non-BRCA1/2)	*****	0/961
Population-Based		
Bernstein (2003)	*****	1/1149

ATM Gene Variant IVS10-6T>G: Few Studies, Mixed Results

Design, Study	# Carriers	
	Cases	Controls
Family-Based		
Broeks, 2000	3/82	*****
Dork, 2001	7/1192	3/500
Lei , 2003	2/768	1/557
Chevenix-Trench, 2003	2/262	0/68
Thompson, 2005	4/751	7/775
Population-Based		
Bernstein (2003)	9/1149	*****

Purpose

- To evaluate 7271T>G and IVS10-6T>G *ATM* gene variants and breast cancer risk in a large population-based case-control study;
- To calculate age-specific cumulative risk (penetrance) associated with each variant.

Study Design: Cases (n=3,757)

- BCFR: California, Ontario, Australia
- Incident breast cancer diagnosed 1995-1998
- 2 Stage Sampling
 - California and Ontario:
 - Over-sampled “high-risk” (e.g., age, race, and family hx);
 - High risk + others;
 - Age at dx: California 18-64, Ontario 18-69.
 - Australia: enrolled regardless of family hx
 - all cases diagnosed <40 + a sample 40-59.

All participants in this study answered a questionnaire and provided a blood sample.

Study Design: Controls (n=1,268)

- **No personal history of breast cancer**
- **Recruited from Ontario and Australia**
- **Sampling:**
 - **Ontario: randomly selected residential telephone numbers.**
 - **Australia: electoral rolls**
 - **California: no controls because no DNA at start**

Genotyping 7271T>G and IVS10-6T>G

- **Conducted in 3 labs**

Seattle:

- **Primer extension--AcycloPrime^ä SNP Detection Kit**
- **DHPLC on WAVE platform;**
- **MGB Eclipse[™] Probe System;**

Australia:

- **7271T>G -- Taqman probe using Rotogene 2000;**
- **IVS10-6 – RFLP**

- **Positive findings confirmed by sequencing.**
- **Lab work performed blind to case-control status.**
- **Inter- and intra-lab QC confirm all positive findings.**

Data Analyses

- **Case-Control and Case-only**
 - **Unconditional logistic regression age-adjusted odds ratios and 95% confidence intervals. Sampling weight included in models.**

Risk factors examined: age, family history, reproductive and menstrual history, demographic and lifestyle factors, exogenous hormone use, diagnostic radiation, and tumor characteristics.

Data Analyses

- **Family-Based Analyses**
 - **Penetrance:**
 - Based on modified segregation analyses in first and second degree relatives of carrier cases.
 - **Hazard Ratios (i.e., carrier incidence: general population):**
 - Cumulative risks to age 50 and 70, using SEER age-specific breast cancer incidence rates for 1983-2001.

True carrier status known for Australia family only.

Results: Case-Control Analyses of 7271T>G and IVS10-6T>G

Variant	Case	Control	OR (95% CI)	p-value
7271T>G	7/3751 *	0/1258 ***	****	p=0.1
IVS10-6T>G	13/3752	10/1258**	0.4 (0.2-1.0)	p=0.05

*Includes 1 previously reported Australian carrier case

**Includes 7 previously reported Australian carrier controls

Results: Case-Only Analyses of 7271T>G

Factor	Positive Cases (n)	OR (95%CI)	P-value
<50 yrs. @ Dx	5/7	0.7 (0.2-.9)	ns
Mother with BrCa	3/7	5.5 (1.2-25)	P<0.05
30+ First Pregnancy	3/7	5.1 (1.0-26)	p<0.05
In situ	2/7	6.6 (1.2-37)	(p<0.01)

Results: Penetrance Estimates for 7271T>G

Families	Hazard Ratio (95% CI)	P-value	Risk to Age 50	Risk to Age 70
Austr, Ont, CA (7 carriers)	8.6 (3.9-18.9)	<0.0001	18% (8-35)	52% (28-80)
Ont, CA (6 carriers)	6.2 (1.9-19.5)	<0.002	13% (4-36)	41% (15-81)
All known * (10 carriers)	13.9 (6.2-30.8)	<0.0001	27% (13-50)	69% (41-93)

*Includes 7 CFR families and 3 published pedigrees (Bernstein 2003, Stankovic 1998)

Results: IVS10-6T>G

- **Case-Control and Case-Only Analyses:**
 - No increased risk among carriers for cases versus controls.
 - Carrier status not associated with family history, reproductive factors, or tumor characteristics;
 - Inverse association with age
 - Cases: OR= 0.2 (95%CI=0.1-0.7);
 - Controls: OR=0.2 (95%CI=0.1-0.8).
- **Family-based analyses:**
 - No excess breast cancer risk for relatives of carriers compared to US population (HR=1.6, 95% CI=0.6 – 6.2; $p>0.05$)

Conclusions: 7271T>G and IVS10-6T>G

7271T>G

- **6 carriers identified, doubling # of known carriers.**
- **Rare, highly penetrant breast cancer susceptibility variant.**
- **One of many ATM missense substitutions predicted to have functional consequences. Difficult to assess risk for individual ATM variants, in aggregate, risk for ATM variants could be significant.**

IVS10-6T>G

- **In contrast to earlier studies, no association with breast cancer risk – more common in controls (0.0078%) than cases (0.0035%),**
- **Rare, not associated with family history. Within-family analyses showed no increased risk.**

“The CHEK2*1100delC Allelic Variant and Risk of Breast Cancer: Screening Results from the Breast Cancer Family Registry”

Background: CHEK2*1100delC

- Predicted to result in truncated CHEK2 protein.
 - **CHEK2 Breast Cancer Case/Control Consortium**
 - *Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations*
Nat Genet. 2002 May;31(1):55-9.
 - *CHEK2*1100delC and Susceptibility to Breast Cancer: A Collaborative Analysis Involving 10,860 Breast Cancer Cases and 9,065 Controls from 10 Studies* AJHG (2004), 74: Jun;74(6):1175-82
- 1.9% cases, 0.7% controls carried CHEK2*del1100C
OR= 2.3, 95%CI=1.7-3.2; P=.0000001 (unselected for family history)

Purpose

To examine the association of the CHEK2*1100delC variant and breast cancer risk within a large population-based case-control study, with a special focus on radiation exposure.

Study Design: BCFR Participants

- **Cases and controls from California and Ontario**
- **Cases (n=2,312): Diagnosed between 1995-1998 with incident breast cancer**
- **Controls (n=496): Only from Ontario (ascertained through RDD).**

Study Design: Radiation Data

- **Self reported information on age at exposure and total number of exposures ascertained for diagnostic radiation received to chest and lower abdomen or pelvis.**
- **X-RAY exposure from mammograms or therapeutic radiation were asked separately.**

Characteristics of 2,807 Screened Participants

Registry	Ca/Co*	Race**	CHEK2+	CHEK2-	Weighted carrier frequency
Canada	Case*	Caucasian	18	1121	1.4%
		Non-Caucasian	0	60	****
	Control*	Caucasian	1	475	0.2%
		Non-Caucasian	0	20	*****
California	Case	Caucasian	11	625	0.59
		Non-Caucasian	1	475	0.09

*Case-Control in Ontario:OR=6.7 (95%2.4-18.7)

** Among cases: 1/524 non-Caucasians vs 29/1775 Caucasians (OR=0.12 (0.0-0.9))

Results: Risk of Breast Cancer among Carriers of CHEK2*1100delC (45+ y.o)

Factor	# Positive	OR (95% CI)
Diagnostic X-RAY of Chest (not mammogram)	9/307	3.2 (1.1-9.1)
≥2 Chest X-RAY	7/194	3.6 (1.3-10.5)
≥15yr Interval X-RAYs to Dx	9/233	4.3 (1.5-12.2)
History of BBD	9/294	3.2 (1.2-9.2)

Conclusions: CHEK2*1100delC

- **Our results:**
 - Support hypothesis that CHEK2*1100delC carrier status is associated with increased breast cancer risk;
 - Suggest that this relationship may be modified by other factors, such as radiation exposure.

Caveat: Given ambiguities of measurement and small number of carriers, it is important to replicate these findings in a larger study designed to examine the joint effects of radiation exposure and genetic susceptibility on breast cancer risk and where radiation dose is accurately measured.

Advantages of Using CFR for Large-Scale Screening Studies

- Population already identified, recruited, and interviewed;
- Blood samples drawn and DNA already extracted;
- Defined and available derived variables and data dictionaries from Informatics Center;
- Invested investigators willing to collaborate!

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