



Collaborative Studies of BRCA1/2 Mutation Carriers: PROSE and MAGIC

February 2008 Newsletter

This has been a productive year for our research collaborations. This newsletter is being sent to update you on our progress and plans for the PROSE and MAGIC research studies.

DATA UPDATE

DATA AND BIOSAMPLE COLLECTION

Our data collection as of October 3, 2007*** is provided in the following table. Please contact Tara (tfriebel@mail.med.upenn.edu) if your center's numbers look incorrect, or if you have additional data/DNA to submit. Also, if you are currently participating in PROSE, and are interested in participating MAGIC as well, please contact us.

Center ID	PI	Study	Data Received *	DNA Received**	Data last updated
Austria	Wagner	PROSE,MAGIC	296	365	3/29/2006
Baylor-Houston	Plon	PROSE,MAGIC	22	0	4/15/2002
Baylor-Dallas	Blum	PROSE,MAGIC	21	15	5/23/2006
Beth Israel	Tung	PROSE,MAGIC	87	56	9/26/2007
City of Hope	Weitzel	PROSE,MAGIC	119	119	3/3/2007
Creighton	Lynch	PROSE,MAGIC	391	338	10/3/2007
Dana Farber	Garber	PROSE,MAGIC	330	171	5/10/2007
Duke	Schildkraut	PROSE,MAGIC	41	0	1/1/2002
Evanston N'western	Rubinstein	PROSE,MAGIC	71	57	9/13/2006
Fox Chase	Daly	PROSE,MAGIC	120	71	4/14/2007
UCLA	Ganz	PROSE,MAGIC	91	85	6/28/2007
Georgetown	Isaacs	PROSE,MAGIC	122	173	8/24/2006
Mayo	Couch/Hartmann	PROSE,MAGIC	118	106	7/6/2006
NKI	Van 't veer	PROSE	127	NA	11/1/2002
Penn	Domchek/Rebbeck	PROSE,MAGIC	452	429	9/4/2007
Marsden	Eeles	PROSE	123	NA	9/7/2007
St. Mary's	Evans	PROSE	313	NA	2/23/2006
UT S'western	Tomlinson	PROSE,MAGIC	93	78	8/5/2004
Chicago	Olopade	PROSE,MAGIC	97	69	4/10/2007
Utah/Irvine	Neuhausen	PROSE,MAGIC	377	265	6/27/2007
Women's Coll.	Narod	PROSE,MAGIC	127	70	6/23/2005
Yale	Matloff	PROSE	170	NA	9/7/2007
Total			3,708	2,467	

*Numbers reflect everyone sent to date for either PROSE and/or Modifiers

**DNA is collected on MAGIC women only.

***Due to Tara's maternity leave, data sent after this date has not been added

MAGIC “INTERACTORS” STUDY

In order to provide a validation data set for the associations that we observe in the MAGIC data set, we have obtained additional data and DNA from a number of collaborators in the CIMBA consortium. The following centers have contributed CIMBA formatted data and DNA in order to validate our MAGIC study results:

Center ID	PI	Study	CIMBA Data	DNA	Data last updated
Israel	Friedman	MAGIC-CIMBA	424	424	3/12/2007
Helinski	Nevanlinna	MAGIC-CIMBA	207	207	7/23/2007
Ontario	Andrulis	MAGIC-CIMBA	418*	418	6/25/2007
EMBRACE	Easton	MAGIC-CIMBA	1525*	1525*	
kConFab	Chenevix-Trench	MAGIC-CIMBA	815	815	10/6/2006
Total (not counting expected)			1446	1864	

*Expected

NEWS

Welcome New Centers: Welcome Guy’s & St Thomas Foundation Trust in London (PI: Gabriella Pichert) as a new PROSE center.

Data Collection Focus: Areas of focus for data collection:

- 1) **Follow-up Data:** We would like to receive follow up data on ALL living participants.
- 2) **Tumor markers:** In order to address the hypothesis of our recently funded grant, we are hoping to collect complete tumor marker data on all breast cancer cases, including ER, PR, and HER2 status. This includes missing tumor marker data on participants already submitted.
- 3) **Data deadline:** Please have all new and updated data submitted by **April 15, 2008**. Data/DNA submitted after this date will not be included in the next round of analysis.

NCI CONSORTIUM

The PROSE/MAGIC group has been designated as an emerging NCI consortium. This allows us to obtain funding for meetings and possibly for research in the future. We are listed on the NCI consortium web site, and will have access to NCI portals for our research: http://epi.grants.cancer.gov/Consortia/table.html#br_ovar

PROSE Studies Update

RECENT PROSE PUBLICATIONS

- Friebel TM, Domchek S, Rebbeck TR for the PROSE Study Group (2007) Utilization of Bilateral Prophylactic Oophorectomy and Mastectomy in a prospective series of unaffected BRCA1 and BRCA2 (B1/2) Mutation Carriers, *Clinical Breast Cancer*, Vol 7, No. 11, 875-822, 2007.

- Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, Isaacs C, Evans G, Lynch HT, Eeles R, Neuhausen S, Daly MB, Matloff E, Blum J, Sabbatini P, Hudis C, Norton L, Barakat RR, Offit K, Rebbeck TR (2007) Risk-Reducing Salpingo-Oophorectomy for the Prevention of *BRCA1* and *BRCA2* Associated Breast and Gynecologic Cancer: A Multi-Center, Prospective Study, *Journal of Clinical Oncology*, In Press.

MAGIC Studies Update

MAGIC WORK IN PROGRESS

- BRCA1/2-INTERACTING GENES (Work being led by Tim Rebbeck at Penn): As you know, the primary hypotheses of the modifiers of Cancer Risk grant are to evaluate genes involved in DNA damage recognition and repair that interact with *BRCA1* or *BRCA2* as modifiers of *BRCA1/2*-associated breast cancer risk. We have generated our candidate gene lists, and simultaneously developing assays for genotyping on all eligible participants. The candidate genes of interest include those that interact with *BRCA1* and/or *BRCA2*, and include: *MRE11*, *Rad50*, *NBS1*, *TopB1*, *BACH1*, *CtIP*, and others such as *MDM2*. At each locus, we have identified haplotype tagged SNPs (htSNPs) as well as candidate functional SNPs. Complete haplotypes are being generated at each of these loci, and associations of these haplotypes with breast and ovarian cancer risk, accounting for other risk factors, are being analyzed. We are now drafting a manuscript of the *MRE11-RAD50-NBS12* complex, and completing analyses of the additional genes in this pathway.
- IGF PATHWAY GENES (Work being led by Susan Neuhausen at UCI): The goal of this project is to identify variants in genes involved in the insulin-like growth factor (IGF) signaling pathway that modify *BRCA1/2*-associated cancer risk. We have completed the genotyping of the Taqman and SNPlex assays for a total of approximately 180 SNPs. The analysis for *IGFBP1*, *IGFBP2*, *IGFBP5*, *IGF1R*, *IRS1*, *SHBG*, and *IGF1* is complete. We are in the process of writing the manuscript which we will send to you all for comments soon. We found significant associations for genetic variants in *IRS1* in both *BRCA1* and *BRCA2* carriers, for *IGFBP1* in *BRCA1* carriers, and for *IGFBP5* in *BRCA2* carriers. We are using the additional carriers that we obtained to try to replicate the results and will be requesting that CIMBA attempt to replicate our results.

CIMBA CONSORTIUM

The “Consortium of Investigators of Modifiers of *BRCA1/2*” (CIMBA) has the goal of finding genetic modifiers of *BRCA1/2*-associated cancer risks. CIMBA has now met four times, most recently in Copenhagen in early May. The next CIMBA meeting is in Barcelona, February 1-2, 2008.

A series of CIMBA research studies has been proposed, including a genome-wide association study and pooled analyses of existing genotype data available for CIMBA members. MAGIC has proposed to lead the CIMBA studies of *BRCA*-interacting proteins and the IGF pathway, which is consistent with the goals of our R01 grants. A new set of SNPs will be determined in this meeting of CIMBA. We will send you the list of those SNPs to see if you are interested in participating. It is

likely that Georgia Chenevix-Trench will again perform genotyping or you can receive reagents and perform your own genotyping.

Finally, MAGIC will lead the pooled analysis of existing data related to BRCA-interacting genes that has been collected by CIMBA centers. This will include analyses of SNPs at BRCA2, NBS1, and other relevant genes.

RECENT MAGIC PUBLICATIONS

1. Couch FJ, Sinilnikova O, Vierkant RA, Pankratz VS, Fredericksen ZS, Stoppa-Lyonnet D, Coupier I, Hughes D, Hardouin A, Berthet P, Peock S, Cook M, Baynes C, Hodgson S, Morrison PJ, Porteous ME, Jakubowska A, Lubinski J, Gronwald J, Spurdle AB; kConFab, Schmutzler R, Vermold B, Engel C, Meindl A, Sutter C, Horst J, Schaefer D, Offit K, Kirchhoff T, Andrulis IL, Ilyushik E, Glendon G, Devilee P, Vreeswijk MP, Vasen HF, Borg A, Backenhorn K, Struewing JP, Greene MH, Neuhausen SL, Rebbeck TR, Nathanson K, Domchek S, Wagner T, Garber JE, Szabo C, Zikan M, Foretova L, Olson JE, Sellers TA, Lindor N, Nevanlinna H, Tommiska J, Aittomaki K, Hamann U, Rashid MU, Torres D, Simard J, Durocher F, Guenard F, Lynch HT, Isaacs C, Weitzel J, Olopade OI, Narod S, Daly MB, Godwin AK, Tomlinson G, Easton DF, Chenevix-Trench G, Antoniou AC; on behalf of the Consortium of Investigators of Modifiers of BRCA1/2. (2007) AURKA F31I Polymorphism and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: A Consortium of Investigators of Modifiers of BRCA1/2 Study. *Cancer Epidemiology, Biomarkers, and Prevention*, 16(7):1416-21.
2. Antoniou AC, Sinilnikova OM, Simard J, Léoné M, Dumont M, Neuhausen SL, Struewing JP, Stoppa Lyonnet D, Barjhoux L, Hughes DJ, Coupier I, Belotti M, Lasset C, Bonadona V, Bignon Y-J, GEMO, Rebbeck TR, Wagner T, Lynch HT, Domchek SM, Nathanson KL, Garber JE, Weitzel J, Narod SA, Tomlinson G, Olopade OI, Godwin A, Isaacs C, Jakubowska A, Lubinski J, Gronwald J, Górski B, Byrski T, Huzarski T, Peock S, Cook M, Baynes C, Murray A, Rogers M, Daly PA, Dorkins H, EMBRACE, Schmutzler R, Vermold B, Engel C, Meindl A, Arnold N, Niederacher D, Deissler H, Spurdle AB, Chen X, Waddell N, Cloonan N, kConFab, Kirchhoff T, Offit K, Friedman E, Kaufmann B, Laitman Y, Galore G, Rennert G, Lejbkowitz F, Raskin L, Andrulis IL, Ilyushik E, Ozcelik H, Devilee P, Vreeswijk MPG, Greene MH, Prindiville SA, Osorio A, Benítez J, Zikan M, Szabo CI, Kilpivaara O, Nevanlinna H, Hamann U, Durocher F, Arason A, Couch FJ, Easton DF, Chenevix-Trench G on behalf of the Consortium of Investigators of Modifiers of BRCA1/2 (2007) RAD51 135G>C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies, *American Journal of Human Genetics*, 81(6):1186-200.
3. Antoniou AC, Spurdle AB, Sinilnikova OM, Healey S, Pooley KA, Schmutzler RK, Vermold B, Engel C, Meindl A, Arnold N, Hofmann W, Sutter C, Niederacher D, Deissler H, Caldes T, Kämpjärvi K, Nevanlinna H, Simard J, Beesley J, Chen X, the Kathleen Cuninghame Consortium for Research into Familial Breast Cancer, Neuhausen SL, Rebbeck TR, Wagner T, Lynch HT, Isaacs C, Weitzel J, Ganz PA, Daly MB, Tomlinson G, Olopade OI, Blum JL, Couch FJ, Peterlongo P, Manoukian S, Barile M, Radice P, Szabo CI, Mateus Pereira LH, Greene MH, Rennert G, Lejbkowitz F, Barnett-Griness O, Andrulis

I, Ozcelik H, OCGN, Gerdes A, Caligo AM, Laitman Y, Kaufmann B, Milgrom R, Friedman E, SWE-BRCA, Domchek SM, Nathanson KL, Osorio A, Llorc G, Milne RL, Benítez J, Hamann U, Hogervorst FBL, Manders P, Ligtenberg MJL, van den Ouweland AMW, The DNA-HEBON collaborators, Peock S, Cook M, Platte R, Evans DG, Eeles R, Pichert G, Chu C, Eccles D, Davidson R, Douglas F, EMBRACE, Godwin AK, Barjhoux L, Mazoyer S, Sobol H, BourdonV, Eisinger F, Chompret A, Capoulade C, Bressac-de-Paillerets B, Lenoir GM, Gauthier-Villars M, Houdayer C, Stoppa-Lyonnet D, GEMO, Chenevix-Trench G, Easton DF on behalf of CIMBA (2008) Common breast cancer predisposition alleles modify breast cancer risk in *BRCA1* and *BRCA2* mutation carriers, American Journal of Human Genetics, in Press.

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