
Supplementary information

Genetic insights into biological mechanisms governing human ovarian ageing

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Supplementary Information

Contents:

Supplementary Results

Non-additive effects

Menopause associated genes act across the life-course

Supplementary References

Supplementary Notes

- 1) Acknowledgments and sources of funding for studies included in the genome-wide association analyses
- 2) Acknowledgments and sources of funding for studies included in Breast Cancer Association Consortium
- 3) Further acknowledgments and sources of funding
- 4) Individual study disclosures
- 5) Consortium membership

Supplementary Results

Non-additive effects

Given that additive models can identify variants that exhibit stronger dominant or recessive effects¹, we tested all the identified signals for departure from an additive model. We identified three variants exhibiting non-additive effects (**Supplementary Table 3 and Extended Data Fig. 4 a-d**). For a common variant in *PIWIL1* (rs28416520, MAF=46%, $P=2\times 10^{-14}$) a recessive model was the best fit (**Extended Data Fig. 4 c**). Deletion of *Piwil1* in mice results in sterility in males, but not females, and its role in human oogenesis is uncertain. It is however expressed as a dense paranuclear granule in human primordial follicle oocytes². A low-frequency missense variant in *HELB* (rs75770066, MAF=3%, $P=7\times 10^{-16}$) appeared to exhibit a heterozygous advantage effect (**Extended Data Fig. 4 d**), with higher mean ANM in the heterozygous group (95% CI 51.37-51.58 years) than the common (50.24-50.30) and rare homozygote (48.58-50.16) groups. Further fine-mapping and experimental work will be required to understand the complex biological mechanism(s) at this locus.

Menopause associated genes act across the life-course

Previous large-scale genetic analyses highlighted a clear involvement of homologous recombination and the *BRCA1-A* complex in the regulation of ovarian ageing. Our current study supports much broader DDR involvement, providing increased resolution of these pathways and informing when in the life-course they might act.

Our identified genes and pathway analyses strongly implicate repair pathways associated with replication stress, in particular removal of interstrand crosslinks, which covalently join both strands of the DNA helix, as well as DNA-protein crosslinks and R loops (DNA:RNA hybrids). All of these lesions stall DNA replication and prevent transcription (**Extended Data Fig. 6**). This observation is supported by recent work demonstrating the role of the interstrand crosslink pathway *in utero* for resolving DNA damage in pre-meiotic, primordial germ cells³. This process begins with replication fork remodelling at interstrand crosslinks by *FANCM*⁴⁻⁶, where we identify two independent ANM-associated missense variants (**Supplementary Table 4**). This subsequently leads to recruitment of the core Fanconi Anaemia (FA) complex to signal DNA damage, where we map missense variants in two of the eight genes – *FANCA* and *FANCB*. Furthermore we identify variants mapping key genes in the downstream repair systems coordinated by the FA pathway, including homologous recombination (e.g *RAD51*, *BRCA1*, *BRCA2*) as well as translesion synthesis (e.g *REV1*, *REV3L* and *RAD18*)⁷.

Several DDR genes highlighted by our study have critical meiotic functions in fetal oocytes where at least 500 programmed double-strand breaks (DSBs) initiate recombination⁸. We implicate key recombination and synaptonemal complex genes with functions in meiotic prophase (*STAG3*, *SMC1B*, *EXO1*, *RAD51*, *DMC1*, *HELQ*, *RAD52*, *MSH5*). Mouse models of these genes show defective repair of meiotic recombination and subsequent apoptosis of fetal oocytes resulting in decreased primordial follicles from birth and infertility⁹⁻¹⁷. We note that several of our ANM-associated variants overlap those recently reported for recombination rate¹⁸, however, despite more nominally significant associations than expected by chance, there was no clear relationship between the direction of effect on menopause and recombination rate across the 290 ANM loci (**Supplementary Table 26**).

A range of factors likely contribute to the rate at which follicles are recruited and the follicular reserve depleted. Our data implicate key genes in the mTOR complex 1 (mTORC1) in ANM, including *STK11* and *DEPTOR*. The mTOR protein kinase that controls cell growth by regulating protein and

nucleotide synthesis and is activated by the PI3K pathway. Oocyte-specific deletion of *Pten* in mice removes the inhibiting effect of the PI3K pathway on primordial follicle activation, leading to premature recruitment and exhaustion of the entire primordial follicle pool¹⁹. Other ANM-implicated genes include *FSHB*, *NOBOX*, *INHBB*, *INHBC*, *LHCGR*, *IGF1*, *IGFBP1*, *PPARG* and *BMPRI1B*, highlighting broader endocrine and metabolic mechanisms governing ANM. We also identified common variants in *FTO* associated with ANM (**Supplementary Table 2**) which are distinct from the well-established body weight association in this region (r^2 with lead BMI variant rs1558902 = 0.0002).

Finally, the majority of known genes causing POI implicate aberrant DNA damage or the inability to repair it, with limited evidence in humans that defects in the downstream cell-death signaling pathways impact variation in reproductive ageing. In contrast, our study identifies more than 58 genes implicated in regulation of apoptosis associated with ANM (**Supplementary Table 19**), providing evidence that variation in cell death following DDR is an important mechanism. This includes components and interactors of the central, conserved DDR checkpoint kinases ATR-CHEK1 (single stranded DNA) and ATM-CHEK2 (double strand breaks), that integrate and determine repair and cellular response from a broad variety of DNA repair pathways (**Extended Data Fig. 6**).

Whilst the breadth of DDR pathways identified suggests our identified loci may exert their effect at different stages across the life-course, we sought to evaluate this by assessing patterns of germ cell gene expression across different developmental stages. The individual expression profiles of our 283 consensus genes (**Supplementary Table 2**) were assessed in human fetal primordial germ cells from 5 to 26 weeks gestation, in addition to oocyte and granulosa expression in adult follicles at different stages of growth (**Extended Data Fig. 7** and **Supplementary Table 20**). Collectively these data identified distinct clusters of genes that were active at different stages of life and follicle growth. The majority of our identified genes appeared most active in fetal primordial germ cells and fetal oocytes, however distinct expression profiles were evident across all developmental stages and between oocytes and granulosa cells (**Extended Data Fig. 7**). In many cases the pattern of expression was consistent with the known biological roles of those genes, for example Fanconi anemia genes were predominantly expressed in the fetal germ cells as well as the oocytes of the growing follicles, with less pronounced expression in granulosa cells (**Supplementary Table 20**). In contrast, genes such as *POLG* and *TP63* were predominantly expressed during follicular stages, consistent with apoptotic inducing activity in response to DNA damage observed in growing oocytes in mouse^{20–23}. Further studies will be required to build on our observations and confirm the mechanism underlying the genetic associations.

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Supplementary Notes

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23andMe	23andMe	We would like to thank the research participants and employees of 23andMe for making this work possible. The following members of the 23andMe Research Team contributed to this study: Michelle Agee, Stella Aslibekyan, Adam Auton, Elizabeth Babalola, Robert K. Bell, Jessica Bielenberg, Katarzyna Bryc, Emily Bullis, Briana Cameron, Daniella Coker, Gabriel Cuellar Partida, Devika Dhamija, Sayantan Das, Sarah L. Elson, Teresa Filshtein, Kipper Fletez-Brant, Will Freyman, Pooja M. Gandhi, Karl Heilbron, Barry Hicks, David A. Hinds, Karen E. Huber, Ethan M. Jewett, Yunxuan Jiang, Aaron Kleinman, Katelyn Kukar, Vanessa Lane, Keng-Han Lin, Maya Lowe, Marie K. Luff, Jennifer C. McCreight, Matthew H. McIntyre, Kimberly F. McManus, Steven J. Micheletti, Meghan E. Moreno, Joanna L. Mountain, Sahar V. Mozaffari, Priyanka Nandakumar, Elizabeth S. Noblin, Jared O'Connell, Aaron A. Petrakovitz, G. David Poznik, Morgan Schumacher, Anjali J. Shastri, Janie F. Shelton, Jingchunzi Shi, Suyash Shringarpure, Chao Tian, Vinh Tran, Joyce Y. Tung, Xin Wang, Wei Wang, Catherine H. Weldon, Peter Wilton
AGES	Age, Gene/Environment Susceptibility-Reykjavik Study	This study has been funded by NIH contracts N01-AG-1-2100 and 271201200022C, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.
ALSPAC	Avon Longitudinal Study of Parents and Children	We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. GWAS data for ALSPAC mothers was funded by the Wellcome Trust (WT088806) and phenotype data by the British Heart Foundation (SP/07/008/24066), Wellcome Trust (WT092830M) and MRC (G1001357). GWAS data for ALSPAC offspring was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. DAL, NJT, SMR and GDS work in a Unit that receives support from the University of Bristol and MRC (MC_UU_00011/1 and MC_UU_00011/6).
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BCAC/ iCOGs	Breast Cancer Association Consortium/ iCOGs	See separate section below for details of individual studies.
CARL	INGI-CARLANTINO	We would like to thank all the participants in the study for their contribution and support The study was supported through the Italian Ministry of Health
CHS	Cardiovascular Health Study	This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, U01HL130114 and 75N92021D00006 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
CILENTO	CILENTO	We thank the populations of Cilento for their participation in the study. This work was supported by grants from the Italian Ministry of Universities (FIRB-RBNE08NKH7, INTEROMICS Flagship Project), the Assessoreto Ricerca Regione Campania, the Fondazione con il SUD (2011-PDR-13) and the Istituto Banco di Napoli - Fondazione to MC.
COLAUS	CoLaus (Etude Cohorte Lausannoise)	The CoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 33CSO-122661, 33CS30-139468, 33CS30-148401 and 33CS30_177535/1).
CROATIA Korcula	CROATIA Korcula	We would like to acknowledge the contributions of the recruitment team in Korcula, the administrative teams in Croatia and Edinburgh and the people of Korcula. The SNP genotyping for the KORCULA cohort was performed in Helmholtz Zentrum München, Neuherberg, Germany. Medical Research Council UK and the Ministry of Science, Education and Sport in the Republic of Croatia (number 108-1080315-0302).
CROATIA Vis	CROATIA Vis	We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools, Institute for Anthropological Research in Zagreb and Croatian Institute for Public Health. Medical Research Council UK and the Ministry of Science, Education and Sport in the Republic of Croatia (number 108-1080315-0302).
EGCUT-370 and OmniX	Estonian Genome Center, University of Tartu	This study was supported by EU H2020 grants 692145, 676550, 654248, Estonian Research Council Grant IUT20-60, NIASC, and EU through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012 GENTRANSMED).
EPIC-Norfolk	The EPIC-Norfolk Study	The EPIC-Norfolk study (DOI 10.22025/2019.10.105.00004) has received funding from the Medical Research Council (MR/N003284/1 MC-UU_12015/1 and MC_UU_00006/1) and Cancer Research UK (C864/A14136). The genetics work in the EPIC-Norfolk study was funded by the Medical Research Council (MC_PC_13048). We are grateful to all the participants who have been part of the project and to the many members of the study teams at the University of

		Cambridge who have enabled this research.
FHS	Framingham Heart Study	The authors thank the Framingham Heart Study participants and staff. The Framingham Heart Study phenotype-genotype analyses were supported by NIA R01AG29451 JMM, KLL). The Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study Contract No. N01-HC-25195 and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). Analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. A portion of this research was conducted using the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Framingham Heart Study Contract No. N01-HC-25195, HHSN268201500001 The authors are pleased to acknowledge that the computational work reported on in this paper was performed on the Shared Computing Cluster which is administered by Boston University's Research Computing Services. URL: www.bu.edu/tech/support/research/. The authors thank the participants for their dedication to the study.
FVG	INGI- FRIULI VENEZIA GIULIA	We would like to thank all the participants in the study for their contribution and support The study was supported by Regione FVG (L.26.2008) and Italian Ministry of Health
GS	Generation Scotland: Scottish Family Health Study	We are grateful to all the families who took part, the general practitioners and the Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants and nurses. Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorates [CZD/16/6] and the Scottish Funding Council [HR03006] and is currently supported by the Wellcome Trust [216767/Z/19/Z]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Edinburgh Clinical Research Facility, University of Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratifying Resilience and Depression Longitudinally" (STRADL) Reference 104036/Z/14/Z).
HANDLS		
Health ABC	The Health, Aging, and Body Composition Study	This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, Md. (http://biowulf.nih.gov). The Health ABC Study was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106 and, in part, by the NIA Intramural Research Program. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C.

HRS	Health and Retirement Study	HRS is supported by the National Institute on Aging (NIA U01AG009740). The genotyping was funded separately by the National Institute on Aging (RC2 AG036495, RC4 AG039029). Our genotyping was conducted by the NIH Center for Inherited Disease Research (CIDR) at Johns Hopkins University. Genotyping quality control and final preparation of the data were performed by the Genetics Coordinating Center at the University of Washington.
INCHIANTI	Invecchiare in Chianti	The INCHIANTI study baseline (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).
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ORCADES	Orkney Complex Disease Study	DNA extractions were performed at the Genetics Core Laboratory at the Edinburgh Clinical Research Facility, University of Edinburgh, Scotland. We would like to acknowledge the invaluable contributions of the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney. ORCADES was supported by the Chief Scientist Office of the Scottish Government (CZB/4/276, CZB/4/710), the Royal Society, the MRC Human Genetics Unit, Arthritis Research UK and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947).

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RSI / RSII / RSIII	Rotterdam Study I, 2 and 3	The Rotterdam Study (PMID: 32367290) is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists. The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters, MSc, and Carolina Medina-Gomez, MSc, for their help in creating the GWAS database, and Karol Estrada, PhD, Yurii Aulchenko, PhD, and Carolina Medina-Gomez, MSc, for the creation and analysis of imputed data. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.
SARDINIA	Sardinia	We thank all the volunteers who generously participated in this study and made this research possible. This research was supported by the Intramural Research Program of the NIH, National Institute on Aging, with contracts N01-AG-1-2109 and HHSN271201100005C; by PB05 InterOmics MIUR Flagship Project and by grant FaReBio2011 "Farmaci e Reti Biotecnologiche di Qualità".
SASBAC cases / controls		This work was supported by grants from NIH (RO1-CA58427) and the Agency for Science, Technology and Research (A *STAR; Singapore).

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SHIP-Trend	Study of Health in Pomerania - Trend	SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems GmbH.
TWINGENE	TwinGene	TwinGene is part of the Swedish Twin Registry which is managed by Karolinska Institutet and receives funding through the Swedish Research Council under the grant no 2017-00641. The Ministry for Higher Education; The Swedish Research Council (M-2005-1112); GenomEUtwin (EU/QLRT-2001-01254; QLG2-CT-2002-01254); NIH DK U01-066134; The Swedish Foundation for Strategic Research (SSF); Heart and Lung foundation no. 20070481
TWINSUK	TwinsUK	TwinsUK is funded by the Wellcome Trust, Medical Research Council, European Union, Chronic Disease Research Foundation (CDRF), Zoe Global Ltd and the National Institute for Health Research (NIHR)-funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London.
UK Biobank	UK Biobank	This research has been conducted using the UK Biobank resource under application numbers 871 (Exeter) and 9797 (Cambridge).
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WHI GARNET / WHIMS	Women's Health Initiative	The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: https://s3-us-west-2.amazonaws.com/www-whi-org/wp-content/uploads/WHI-Investigator-Long-List.pdf
China Kadoorie Biobank	China Kadoorie Biobank	The chief acknowledgment is to the participants, the project staff, and the China National Centre for Disease Control and Prevention (CDC) and its regional offices for assisting with the fieldwork. China's National Health Insurance provides electronic linkage to all hospital treatments. We thank Judith Mackay in Hong Kong; Yu Wang, Gonghuan Yang, Zhengfu Qiang, Lin Feng, Maigeng Zhou, Wenhua Zhao, Yan Zhang and Zheng Bian in China CDC; Lingzhi Kong, Xiucheng Yu, and Kun Li in the Chinese Ministry of Health; and Garry Lancaster, Sarah Clark, Martin Radley, Mike Hill, Hongchao Pan, and Jill Boreham in the CTSU, Oxford, for assisting with the design,

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Study acronym	Full study name	Acknowledgments and sources of funding
BCAC	Breast Cancer Association Consortium	We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out. BCAC is funded by the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), and PERSPECTIVE I&I, funded by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Ministère de l'Économie et de l'Innovation du Québec through Genome Québec, the Quebec Breast Cancer Foundation. The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report. Additional funding for BCAC is provided via the Confluence project which is funded with intramural funds from the National Cancer Institute Intramural Research Program, National Institutes of Health. The breast cancer genome-wide association analyses were supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the 'Ministère de l'Économie, de la Science et de l'Innovation du Québec' through Genome Québec and grant PSR-SIIRI-701, The National Institutes of Health (U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710) and the European Union (HEALTH-F2-2009-223175 and H2020 633784 and 634935). All studies and funders are listed in Michailidou et al (2017).
ABCFS	Australian Breast Cancer Family Study	ABCFS thank Maggie Angelakos, Judi Maskiell, Gillian Dite. The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. J.L.H. is a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellow. M.C.S. is a NHMRC Senior Research Fellow.
ABCS		ABCS thanks the Blood bank Sanquin, The Netherlands. The ABCS study was supported by the Dutch Cancer Society [grants NKI 2007-3839; 2009 4363].

BBCC		The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen.
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CBCS	Canadian Breast Cancer Study	CBCS thanks study participants, co-investigators, collaborators and staff of the Canadian Breast Cancer Study, and project coordinators Agnes Lai and Celine Morissette. CBCS is funded by the Canadian Cancer Society (grant # 313404) and the Canadian Institutes of Health Research.
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CECILE		The CECILE study was supported by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Agence Nationale de Sécurité Sanitaire, de l'Alimentation, de l'Environnement et du Travail (ANSES), Agence Nationale de la Recherche (ANR).
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MCBCS		The MCBCS was supported by the NIH grants CA192393, CA116167, CA176785 an NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer [CA116201], and the Breast Cancer Research Foundation and a generous gift from the David F. and Margaret T. Grohne Family Foundation.
MCCS	Melbourne Collaborative Cohort Study	The MCCS was made possible by the contribution of many people, including the original investigators, the teams that recruited the participants and continue working on follow-up, and the many thousands of Melbourne residents who continue to participate in the study. The Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and

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NC-BCFR & OFBCR	Northern California Breast Cancer Family Registry (NC-BCFR) and Ontario Familial Breast Cancer Registry (OFBCR)	The Northern California Breast Cancer Family Registry (NC-BCFR) and Ontario Familial Breast Cancer Registry (OFBCR) were supported by grants U01CA164920 and U01CA167551 from the USA National Cancer Institute of the National Institutes of Health. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR) or the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR or CCFR.
NCBCS	Carolina Breast Cancer Study (NCBCS)	The Carolina Breast Cancer Study (NCBCS) was funded by Komen Foundation, the National Cancer Institute (P50 CA058223, U54 CA156733, U01 CA179715), and the North Carolina University Cancer Research Fund.
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Pierre Fontanillas is employed by and hold stock or stock options in 23andMe, Inc.

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5) Consortium membership

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