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Journal

Journal of Medical Genetics, 53(12)

ISSN

0022-2593

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Publication Date

2016-12-01

DOI

10.1136/jmedgenet-2016-103839

Peer reviewed



Published in final edited form as:

J Med Genet. 2016 December ; 53(12): 800–811. doi:10.1136/jmedgenet-2016-103839.

PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS

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Abstract

Background—The rarity of mutations in *PALB2*, *CHEK2* and *ATM* make it difficult to estimate precisely associated cancer risks. Population-based family studies have provided evidence that at least some of these mutations are associated with breast cancer risk as high as those associated with rare *BRCA2* mutations. We aimed to estimate the relative risks associated with specific rare variants in *PALB2*, *CHEK2* and *ATM* via a multicentre case-control study.

Methods—We genotyped 10 rare mutations using the custom iCOGS array: *PALB2* c.1592delT, c.2816T>G and c.3113G>A, *CHEK2* c.349A>G, c.538C>T, c.715G>A, c.1036C>T, c.1312G>T, and c.1343T>G and *ATM* c.7271T>G. We assessed associations with breast cancer risk (42 671 cases and 42 164 controls), as well as prostate (22 301 cases and 22 320 controls) and ovarian (14 542 cases and 23 491 controls) cancer risk, for each variant.

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Contributors All authors provided DNA samples and/or data and have participated in the Breast Cancer Association Consortium through attendance at regular meetings and planning of the iCOGS experiment. Each author has made substantial contribution through designing and coordinating the studies listed in the supplemental material and therefore have made substantial contributions to the conception or design of this work. Many authors played multiple roles across these activities. Specifically, MCS conceived this study, worked to include the rare variants on the iCOGS and drafted the manuscript. RLM led the statistical analysis and drafted the paper. Members of the PALB2 interest group, MCS, DEG, RW, KP, FC, MT, WF, JD, KM, EJvR, TH, HN, JLH, TD, KC, JR-F, ZLT, PR, IC, PP, HT, FAO, JGD contributed to the inclusion of the PALB2 rare variants on iCOGS. DFE coordinated the BCAC project and contributed to statistical analysis along with DEG. SVT contributed to the selection of CHEK2 rare variants. GC-T contributed to the selection of rare variants in ATM. AD, CL and JD made significant contribution to the data quality related to the calling of the rare genetics variants on iCOGS. MKS, AB, FBH, SV, JC, CC, RJS, PAF, LH, ABE, MWB, JP, IDSS, OF, NJ, MKB, EJS, IT, MJK, NM, FM, BB, RY, PG, TT, FM, MS, SB, SFN, HF, JB, MPZ, JIAP, PM, HAC, SN, AZ, CCD, HB, VA, CS, HB, TB, YDK, TAM, KA, CB, NVB, NNA, AL, SM, AM, VK, V-MK, JMH, AS, EW, DS, BB, GF, JCC, AR, PS, DFJ, JEO, CV, VSP, CM, CAH, BEH, FS, LLM, VK, GGA, WZ, DJH, SL, SEH, PK, IA, JAK, GG, AMM, AJV, MG, SK, PD, RAEMT, CS, AH, MGC, JF, SJC, JL, KC, HD, ME, DME, SR, WJT, SMG, MJH, JWMM, JMC, MTL, PH, JL, JSB, KH, AC, MWRR, CL, CB, AD, UH, DT, HUU, TR, AJ, JL, KJ, KD, SS, AET, CBA, DY, AS, AA, NO, MJ, AGN, GP, MRA, NA, DH, DCT, DV, FB, JS, MD, PS, RE, KM, FW, HG, JS, MW, BGN, RCT, DN, JLD, FCH, KTK, JLS, WJB, ST, DJS, JLK, CM, ASK, CC, LCA, KB, JP, RK, JB, MRT, ZKJ, AAAO, SB, SPR, AH, AH, MR, DL, EVN, IV, SL, JAD, MAR, SN, UE, SWG, KO, LES, GF, GL, JLK, LRW, MTG, IR, PAH, LMP, RB, FM, RPE, RBN, KBM, ADB, FH, PH, SK, BYK, CW, JL, AJ, SKK, EH, BP, BB, LB, ELG, BLF, RAV, JMC, MCL, ZCF, KRK, DL, KHL, MATH, XW, DAL, FD, MB, AB, ESI, JRM, LA, DWC, KLT, ELP, MS, SST, EVB, IO, SHO, LB, HBS, AMVA, KKHA, LAK, LFAGM, TP, YB, ABW, LEK, LSC, NDL, BG, JG, JM, CKH, LL, LN, SAE, ED, JT, IC, IN, JP, NS, RG, ASW, JHR, VG, WS, HC, XOS, RTT, RS, JRM, SAN, CP, ANM, DF, HYL, JPW, TAS, TAC, YYT, ZC, AGM, SAG, SJR, UM, AHW, CLP, DVDB, MCP, ADM, JPH, JMS, JK, PP, HS, IW, GC-T, GGG, SVT, DFE, RLM provided DNA samples and/or phenotypical data. All authors read and approved the final manuscript.

Further information about the financial report received is outlined in the supplementary file online.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This would vary for each study—each study is listed in the supplemental material.

Results—For European women, strong evidence of association with breast cancer risk was observed for *PALB2* c.1592delT OR 3.44 (95% CI 1.39 to 8.52, $p=7.1\times 10^{-5}$), *PALB2* c.3113G>A OR 4.21 (95% CI 1.84 to 9.60, $p=6.9\times 10^{-8}$) and *ATM* c.7271T>G OR 11.0 (95% CI 1.42 to 85.7, $p=0.0012$). We also found evidence of association with breast cancer risk for three variants in *CHEK2*, c.349A>G OR 2.26 (95% CI 1.29 to 3.95), c.1036C>T OR 5.06 (95% CI 1.09 to 23.5) and c.538C>T OR 1.33 (95% CI 1.05 to 1.67) ($p=0.017$). Evidence for prostate cancer risk was observed for *CHEK2* c.1343T>G OR 3.03 (95% CI 1.53 to 6.03, $p=0.0006$) for African men and *CHEK2* c.1312G>T OR 2.21 (95% CI 1.06 to 4.63, $p=0.030$) for European men. No evidence of association with ovarian cancer was found for any of these variants.

Conclusions—This report adds to accumulating evidence that at least some variants in these genes are associated with an increased risk of breast cancer that is clinically important.

INTRODUCTION

The rapid introduction of massive parallel sequencing (MPS) into clinical genetics services is enabling the screening of multiple breast cancer susceptibility genes in one assay at reduced cost for women who are at increased risk of breast (and other) cancer. These gene panels now typically include the so-called ‘moderate-risk’ breast cancer susceptibility genes, including *PALB2*, *CHEK2* and *ATM*.^{1–3} However, mutations in these genes are individually extremely rare and limited data are available with which to accurately estimate the risk of cancer associated with them.

Estimation of the age-specific cumulative risk (penetrance) of breast cancer associated with specific mutations in these three genes has been limited to those that have been observed more frequently, such as *PALB2* c.1592delT (a Finnish founder mutation), *PALB2* c.3113G>A and *ATM* c.7271T>G. These mutations have been estimated to be associated with a 40% (95% CI 17% to 77%), 91% (95% CI 44% to 100%) and 52% (95% CI 28% to 80%) cumulative risk of breast cancer to the age of 70 years, respectively.^{4–7} These findings, based on segregation analyses in families of population-based case series, indicate that at least some mutations in these ‘moderate-risk’ genes are associated with a breast cancer risk comparable to that of the average pathogenic mutation in *BRCA2*: 45% (95% CI 31% to 56%).⁸ However, such estimates are imprecise and, moreover, may be confounded by modifying genetic variants or other familial risk factors.

Case-control studies provide an alternative approach to estimating cancer risks associated with specific variants. This design can estimate the relative risk directly, without making assumptions about the modifying effects of other risk factors. However, because these variants are rare, such studies need to be extremely large to provide precise estimates.

The clearest evidence for association, and the most precise breast cancer risk estimates, for rare variants in *PALB2*, *CHEK2* and *ATM* relate to protein truncating and splice-junction variants.^{9,10} However, studies based on mutation screening in case-control studies, combined with stratification of variants by their evolutionary likelihood suggest that at least some evolutionarily unlikely missense substitutions are associated with a similar risk to those conferred by truncating mutations.^{11–13} For example, Tavtigian *et al*.¹² estimated an OR of 2.85 (95% CI 0.83 to 4.86) for evolutionarily unlikely missense substitutions in the 3′ third

of *ATM*, which is comparable to that for truncating variants. Specifically, *ATM* c.7271C>G has been associated with a more substantial breast cancer risk in several studies.^{7,13} Le Calvez-Kelm *et al*,¹¹ estimated that the ORs associated with rare mutations in *CHEK2* from similarly designed studies were 6.18 (95% CI 1.76 to 21.8) for rare protein-truncating and splice-junction variants and 8.75 (95% CI 1.06 to 72.2) for evolutionarily unlikely missense substitutions.¹¹

It is plausible that monoallelic mutations in *PALB2*, *CHEK2* and *ATM* could be associated with increased risk of cancers other than breast cancer, as has been observed for *BRCA1* and *BRCA2* and both ovarian and prostate cancers.^{14–17} However, with the exception of pancreatic cancer in *PALB2* carriers, there is little evidence to support or refute the existence of such associations, although a few individually striking pedigrees have been observed.^{4,8,18–20}

In this study we selected rare genetic variants on the basis that they had been observed in breast cancer candidate gene case-control screening projects involving *PALB2*, *CHEK2* or *ATM*. These included three rare variants in *PALB2*: the protein truncating variants c.1592delT (p.Leu531Cysfs)⁴ and c.3113 G>A (p.Trp1038*)⁶ and the missense variant c.2816T>G, (p. Leu939Trp), six rare missense variants in *CHEK2*: c.349A>G (p.Arg117Gly) and c.1036C>T (p.Arg346Cys) predicted to be deleterious on the basis of evolutionary conservation,¹¹ c.538C>T (p.Arg180Cys), c.715G>A (p.Glu239Lys), c.1312G>T (p.Asp438Tyr) and c.1343T>G (p.Ile448Ser) and *ATM* c.7271T>G (p.Val2424Gly).⁷ We assessed the association of these variants with breast, ovarian and prostate risk by case-control analyses in three large consortia participating in the Collaborative Oncological Gene-environment Study.^{21,22}

METHODS

Participants

Participants were drawn from studies participating in three consortia as follows:

The *Breast Cancer Association Consortium (BCAC)*, involving a total of 48 studies: 37 of women from populations with predominantly European ancestry (42 671 cases and 42 164 controls), 9 of Asian women (5795 cases and 6624 controls) and 2 of African-American women (1046 cases and 932 controls). All cases had invasive breast cancer. The majority of studies were population-based or hospital-based case-control studies, but some studies of European women oversampled cases with a family history or with bilateral disease (see online supplementary table S1). Overall, 79% of BCAC cases with known Estrogen Receptor (ER) status (23% missing) are ER-positive. The proportion of cases selected by family history that are ER-positive is 78% (38% missing).

The *Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL)* involving a total of 26 studies: 25 included men with European ancestry (22 301 cases and 22 320 controls) and 3 included African-American men (623 cases and 569 controls). The majority of studies were population-based or hospital-based case-control studies (see online supplementary table S2).

The *Ovarian Cancer Association Consortium (OCAC)*, involving a total of 46 studies. Some studies were case-only and their data were combined with case-control studies from the same geographical region (leaving 36 study groupings). Of these groupings, 33 included women from populations with predominantly European ancestry (16 287 cases (14 542 with invasive disease) and 23 491 controls), 25 included Asian women (813 cases (720 with invasive disease) and 1574 controls), 17 included African-American women (186 cases (150 with invasive disease) and 200 controls) and 29 included women of other ethnic origin (893 cases (709 with invasive disease) and 864 controls). The majority of studies were population-based or hospital-based case-control studies (see online supplementary table S3).

Details regarding sample quality control have been published previously.^{22,23} All study participants gave informed consent and all studies were approved by the corresponding local ethics committees (see online supplementary tables S1–S3).

Variant selection

We selected for genotyping 13 rare mutations that had been observed in population-based case-control mutation screening studies. These variants were *PALB2* (c.1592delT, p. Leu531Cysfs;⁴⁵¹⁰ c.2323C>T p.Gln775*;²⁰ c.2816T>G, p. Leu939Trp;²²⁰ c.3113G>A, p.Trp1038*;²⁶²⁰ c.3116delA, p. Asn1039Ilefs;²⁶²⁰ c.3549C>G, p.Tyr1183*²), *CHEK2* (c.349A>G, p.ArgR117Gly; c.538C>T, p.Arg180Cys; c.715G>A p.Glu239Lys; c.1036C>T, p.Arg346Cys; c.1312G>T, p.Asp438Tyr; c.1343T>G, p.Ile448Ser)¹¹ and *ATM* (c.7271T>G, p.Val2424Gly)⁷¹³²⁴ see table 1. A DNA sample carrying each of these variants was included in a plate of control DNAs that was distributed to each genotyping centre to assist with quality control and genotype calling.

Genotyping

Three *PALB2* variants c.2323C>T (p.Gln775*), c.3116delA (p.Asn1039Ilefs) and c.3549C>G (p.Tyr1183*) were unable to be designed for measurement on the custom Illumina iSelect genotyping array and were not considered further (table 1). Genotyping was conducted using a custom Illumina Infinium array (iCOGS) in four centres, as part of a multiconsortia collaboration as described previously.²² Genotypes were called using Illumina's proprietary GenCall algorithm and then, for the data generated from the rare variant probes, manually confirmed with reference to the positive control sample. Two per cent of samples were provided in duplicate by all studies and 270 HapMap2 samples were genotyped in all four genotyping centres. Subjects with an overall call rate <95% were excluded. Plates with call rates <90% were excluded on a variant-by-variant basis. Cluster plots generated for all of the 10 rare variants were manually checked to confirm automated calls (see online supplementary figure S1).

Statistical methods

The association of each variant with breast, prostate and ovarian cancer risk was assessed using unconditional logistic regression to estimate ORs for carriers versus non-carriers, adjusting for study (categorical). p Values were determined by the likelihood ratio test comparing models with and without carrier status as a covariate. We also applied conditional logistic regression, defining risk sets by study, and found that this made no difference to the

OR estimates, CIs or p values to two significant figures; since model convergence was a problem for this latter regression analysis, all subsequent analyses were based on unconditional logistic regression. For the main analyses of breast cancer risk in European women, we also included as covariates the first six principal components, together with a seventh component specific to one study (Leuven Multidisciplinary Breast Centre (LMBC)) for which there was substantial inflation not accounted for by the components derived from the analysis of all studies. Addition of further principal components did not reduce inflation further. Data from all breast cancer studies were included to assess statistical significance. Data from cases selected for inclusion based on personal or family history of breast cancer were excluded in order to obtain unbiased OR estimates for the general population of white European women (leaving 37 039 cases and 38 260 controls from 32 studies). Multiple testing was adjusted for using the Benjamini-Hochberg procedure to control the false discovery rate, with a significance threshold of 0.05.²⁵ Reported p values are unadjusted unless otherwise stated. Reported CIs are all nominal. We included two race-specific principal components in each of the main breast cancer analyses of Asian and African-American women. Similar analyses were conducted using the data from PRACTICAL and OCAC, consistent with those used previously.^{23,26} All analyses were carried out using Stata: Release V.10 (StataCorp, 2008).

RESULTS

PALB2

In BCAC, *PALB2* c.1592delT (Leu531Cysfs) was only observed in 35 cases and 6 controls, all from four studies from Sweden and Finland (Helsinki Breast Cancer Study (HEBCS), Kuopio Breast Cancer Project (KBCP), Oulu Breast Cancer Study (OBCS) and Karolinska Mammography Project for Risk Prediction Breast Cancer (pKARMA); see online supplementary table S1), giving strong evidence of association with breast cancer risk ($p=7.1\times 10^{-5}$); the OR estimate was 4.52 (95% CI 1.90 to 10.8) based on all studies and 3.44 (95% CI 1.39 to 8.52) based on unselected cases and controls (table 2). We also found evidence of heterogeneity by ER status ($p=0.0023$), the association being stronger for ER-negative disease (OR 6.49 (95% CI 2.17 to 19.4) versus 2.24 (95% CI 1.05 to 7.24) for ER-positive disease).

PALB2 c.3113G>A (p.Trp1038*) was identified in 44 cases and 8 controls from nine BCAC studies. Only one carrier of the variant was of non-European origin. Strong evidence of association with breast cancer risk was observed ($p=6.9\times 10^{-8}$), with an estimated OR of 5.93 (95% CI 2.77 to 12.7) based on all studies and 4.21 (95% CI 1.85 to 9.61) based on unselected cases and controls. There was no evidence of a differential association by ER status ($p=0.15$).

Based on unselected cases, the estimated OR associated with carrying either of these *PALB2* variants (c.1592delT or c.3113G>A) was 3.85 (95% CI 2.09 to 7.09).

PALB2 c.2816T>G (p.Leu939Trp) was identified in 150 cases and 145 controls and there was no evidence of association with risk of breast cancer. There was no evidence of

association with risk of prostate or ovarian cancer for any of the three *PALB2* variants (see tables 3 and 4).

CHEK2

CHEK2 c.349A>G (p.Arg117Gly) was identified in 44 cases and 18 controls in studies participating in BCAC; all of these women were of European origin. We found evidence of association with breast cancer (p=0.003), with little change in the OR after excluding selected cases (OR 2.03 (95% CI 1.10 to 3.73)).

CHEK2 c.538C>T (p.Arg180Cys) was identified in 158 breast cancer cases and 142 controls in studies of white Europeans. Evidence of association with breast cancer risk (p=0.016) was observed, with an unbiased OR estimate of 1.34 (95% CI 1.06 to 1.70). A consistent OR estimate was observed for Asian women, based on 45 case and 45 control carriers (OR 1.16 (95% CI 0.75 to 1.76)).

CHEK2 c.715G>A (p.Glu239Lys) mutations were identified in 15 cases and 9 controls, all European women participating in BCAC and no evidence of association with risk of breast cancer was observed (p=0.21).

CHEK2 c.1036C>T (p.Arg346Cys) was identified in nine cases from seven studies and two controls from two different studies in BCAC (neither control carrier was from a study that had case carriers), all of European origin. We found evidence of association with breast cancer risk (p=0.017) with reduced OR estimate of 3.39 (95% CI 0.68 to 16.9) after excluding selected cases.

None of the above four *CHEK2* variants (*CHEK2* c.349A>G (p.Arg117Gly); c.538C>T (p.Arg180Cys); c.715G>A (p.Glu239Lys) and c.1036C>T (p.Arg346Cys)) were found to be associated with an increased risk of prostate or ovarian cancer (tables 3 and 4). *CHEK2* variant c.1312G>T (p.Asp438Tyr) was not associated with risk of breast cancer for European women (p=0.91). Variant c.1343T>G (p.Ile448Ser) was not observed in any breast cancer cases of European or Asian origin. It was detected in 48 cases and 29 controls of African origin, giving weak evidence of association (OR 1.52 (95% CI 0.95 to 2.43, p=0.083)). *CHEK2* c.1312G>T (p.Asp438Tyr) was identified in 23 cases and 11 controls from PRACTICAL, all European, providing evidence of association with prostate cancer risk (OR 2.21 (95% CI 1.06 to 4.63, p=0.030)). *CHEK2* c.1343T>G (p.Ile448Ser) was observed in 35 cases and 11 controls, all African, participating in PRACTICAL and was also associated with an increased risk of prostate cancer (OR 3.03 (95% CI 1.53 to 6.03, p=0.00059)). There was no evidence that these *CHEK2* variants were associated with risk of ovarian cancer (table 4).

ATM

ATM c.7271T>G (p.Val2424Gly) was identified in 12 cases and 1 control in studies participating in BCAC, all of European origin, giving evidence of association with breast cancer risk (p=0.0012). The OR estimate based on unselected studies was 11.0 (95% CI 1.42 to 85.7). There was no evidence of association of this variant with prostate or ovarian cancer risk (see tables 3 and 4).

DISCUSSION

The present report adds to an accumulating body of evidence that at least some *rare variants* in so-called ‘moderate-risk’ genes are associated with an increased risk of breast cancer that is of clinical relevance.

These findings are presented at a time when detailed information about variants in these genes is becoming more readily available via the translation of diagnostic genetic testing from Sanger sequencing-based testing platforms to MPS platforms that test panels of genes in single assays.^{27–29} The vast majority of information about *PALB2*, *CHEK2* and *ATM*, variants generated from these new testing platforms is not being used in clinical genetics services due to lack of reliable estimates of the cancer risk associated with individual variants, or groups of variants, in each gene. Previous analyses have been largely based on selected families, relying on data on the segregation of the variant. The present study is by far the largest to take a case-control approach. Consistent with previous reports,^{5–7,911–13} *PALB2* c.3113G>A (p.Trp1038*), *PALB2* c.1592delT (p.Leu531Cysfs) and *ATM* c.7271T>G (p.Val2424Gly) were found to be associated with substantially increased risk of breast cancer all with associated relative risk estimates of 3.44 or greater.

The estimates for the two loss-of-function *PALB2* variants (c.1592delT and c.3113G<A) were consistent with each other and with estimates based on segregation analysis.⁵⁶⁹ We found no evidence of association with breast cancer for *PALB2* c.2816T>G (p.Leu939Trp), with an upper 95% confidence limit excluding an OR >1.5 which is notable given the Align-Grantham Variation Grantham Deviation (Align-GVGD) score and the observed impact on protein function.³⁰

The estimate for *ATM* c.7271T>G (p.Val2424Gly) was also consistent with that found by segregation analysis.⁷¹³ The substantial increased risk of breast cancer associated with *ATM* c.7271T>G (p.Val2424Gly) could be due to the reduction in kinase activity (with near-normal protein levels) observed for *ATM* p.Val2424Gly,³¹ thus this variant is likely to be acting as a dominant negative mutation.³²

In contrast, we found no evidence of an association with risk of prostate or ovarian cancer with any of these three variants: however, the confidence limits were wide; based on the upper 95% confidence limit we could exclude an OR of >1.4 for prostate cancer for the loss-of-function *PALB2* c.3113G>A and 1.9 for c.1592delT and c.3113G>A combined.

We analysed six rare missense variants in *CHEK2*. Two of these (*CHEK2* c.349A>G (p.Arg117Gly; rs28909982) and c.1036C>T (p.Arg346Cys)) had evidence of a significant impact on the protein based on in silico prediction. We proposed these variants for inclusion in the iCOGS design as they had been identified in 3/1242 cases and 1/1089 controls and 3/1242 cases and 0/1089 controls, respectively, in a population-based case-control mutation screening study of *CHEK2*.¹¹ In that study, Le Calvez-Kelm *et al*, estimated an OR of 8.75 (95% CI 1.06 to 72.2) for variants with an Align-GVGD score C65 (based on nine cases and one control). The current analysis provides confirmatory evidence of this association in a much larger sample (OR 2.18 (95% CI 1.23 to 3.85)) including 40 unselected case and 18 control carriers. The evidence that *CHEK2* is a breast cancer susceptibility gene is largely

based on studies of protein truncating variants, in particular *CHEK2* 1100delC.³³ Reports of the association of the missense variant I157T, (C15) and breast cancer risk have been conflicting but a large meta-analysis involving 15 985 breast cancer cases and 18 609 controls estimated a modest OR of 1.58 (95% CI 1.42 to 1.75).³⁴ We also found evidence ($p=0.015$) of an association for c.538C>T (Align-GVGD C25); OR 1.34 (95% CI 1.06 to 1.70), a risk comparable to I157T.

The p values reported above have not been adjusted for multiple testing. This was not considered appropriate for the associations with breast cancer risk of *PALB2* c.1592delT, c.3113G>A and *ATM* c.7271T>G because these associations had previously been reported; our aim was to more precisely estimate the associated relative risks. All three associations with breast cancer risk reported for *CHEK2* variants remained statistically significant after adjusting for the other tests conducted in relation to breast cancer risk, but not after correcting for all tests for all cancers. Nevertheless, the findings for *CHEK2* c.349A>G and c.1036C>T confirmed those reported previously, although collectively. The association observed with *CHEK2* c.538C>T requires independent replication.

Do this approach and new data have an impact on clinical recommendations for women and families carrying these rare genetic variants? Although age-specific cumulative risks for cancer are more informative for genetic counselling and clinical management of carriers, our study provides information that is relevant to clinical recommendations. As discussed in Easton *et al.*,³⁵ a relative risk of 4 will place a woman in a 'high-risk' category (in the absence of any other risk factor) and a relative risk between 2 and 4 will place a woman in this category if other risk factors are present. Thus, several of the variants included in this report (*PALB2* c.1592delT; c.3113G>A *ATM* c.7271T>G) would place the carrier in a high-risk group, especially if other risk factors, such as a family history, are present. The high level of breast cancer risk associated with *PALB2* c.1592delT and c.3113G>A reported here is consistent with the penetrance estimate reported for a group of loss-of-function mutations in *PALB2*⁹ and has an advantage in terms of clinical utility that the estimates in this study have been made at a mutation-specific level. Therefore, this work provides important information for risk reduction recommendations (such as prophylactic mastectomy and potentially salpingo-oophorectomy) for carriers of these variants. However, further prospective research is required to characterise these risks and to understand the potential of other risk-reducing strategies such as salpingo-oophorectomy and chemoprevention.

The consistency of the relative risk estimates with those derived through family based studies supports the hypothesis that these variants combine multiplicatively with other genetic loci and familial risk factors; this information is critical for deriving comprehensive risk models. Even with very large sample sizes such as those studied here, however, it is still only possible to derive individual risk estimates for a limited set of variants, and even for these variants the estimates are still imprecise. This internationally collaborative approach also has limited capacity to improve risk estimates for rare variants that are only observed in specific populations. Inevitably, therefore, risk models will depend on combining data across multiple variants, using improved in silico predictions and potentially biochemical/functional evidence to synthesise these estimates efficiently. It will also be necessary

develop counselling and patient management strategies that can accommodate a multifactorial approach to variant classification.

Supplementary Material

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Acknowledgments

The authors thank the following for their contributions to this study: Qin Wang (BCAC), Lesley McGuffog, and Ken Offit (CIMBA), Andrew Lee, and Ed Dicks and the staff of the Centre for Genetic Epidemiology Laboratory, staff of the CNIO genotyping unit, Sylvie LaBoissière and Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre, staff of the Copenhagen DNA laboratory, and Sharon A Windebank, Christopher A Hilker, Jeffrey Meyer and the staff of Mayo Clinic Genotyping Core Facility. The authors also thank UM1 CA167552 (Willett) Cancer Epidemiology Cohort in Male Health Professionals, P01 CA87969 (Stampfer) Dietary and Hormonal Determinants of Cancer in Women, UM1 CA186107 (Stampfer) Long term multidisciplinary study of cancer in women: The Nurses' Health Study, R01CA141298 (Stampfer) Growth Factors and Lethal Prostate Cancer Signature, NCI: K07-CA80668 DAMD17-02-1-0669 NIH/National Center for Research Resources/General Clinical Research Center grant MO1-RR000056, R01CA095023, P50-CA159981, NCI CCSG award P30-CA008748 (Memorial Sloan Kettering Cancer Center), Department of Defense (W81XWH-07-0449), National Health and Medical Research Council of Australia APP1029974 and APP1061177, Deutsche Krebshilfe (Maier), Wellcome Trust Centre for Human Genetics from the Wellcome Trust (090532/Z/09/Z). The authors thank the National Institute of Health Research for their support to The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK.

Funding Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C5047/A8384, C5047/A15007, C5047/A10692, CRUK C8197/A10123), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (No. 1 U19 CA 148537—the GAME-ON initiative), the Department of Defense (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, the Ovarian Cancer Research Fund and Susan G Komen (WF).

REFERENCES

1. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. *Nat Genet.* 2008; 40:17–22. [PubMed: 18163131]
2. Rahman N, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, Reid S, Spanova K, Barfoot R, Chagtai T, Jayatilake H, McGuffog L, Hanks S, Evans DG, Eccles D. Breast Cancer Susceptibility Collaboration (UK), Easton DF, Stratton MR. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet.* 2007; 39:165–167. [PubMed: 17200668]
3. Southey MC, Teo ZL, Winship I. PALB2 and breast cancer: ready for clinical translation! *Appl Clin Genet.* 2013; 6:43–52. [PubMed: 23935381]
4. Erkkö H, Xia B, Nikkilä J, Schleutker J, Syrjäkoski K, Mannermaa A, Kallioniemi A, Pykäs K, Karpainen SM, Rapakko K, Miron A, Sheng Q, Li G, Mattila H, Bell DW, Haber DA, Grip M, Reiman M, Jukkola-Vuorinen A, Mustonen A, Kere J, Aaltonen LA, Kosma VM, Kataja V, Soini Y, Drapkin RI, Livingston DM, Winqvist R. A recurrent mutation in PALB2 in Finnish cancer families. *Nature.* 2007; 446:316–319. [PubMed: 17287723]

5. Erkkö H, Dowty JG, Nikkilä J, Syrjäkoski K, Mannermaa A, Pylkäs K, Southey MC, Holli K, Kallioniemi A, Jukkola-Vuorinen A, Kataja V, Kosma VM, Xia B, Livingston DM, Winqvist R, Hopper JL. Penetrance analysis of the PALB2 c.1592delT founder mutation. *Clin Cancer Res.* 2008; 14:4667–4671. [PubMed: 18628482]
6. Southey MC, Teo ZL, Dowty JG, Odefrey FA, Park DJ, Tischkowitz M, Sabbaghian N, Apicella C, Byrnes GB, Winship I, Baglietto L, Giles GG, Goldgar DE, Foulkes WD, Hopper JL, kConFab for the Beast Cancer Family Registry. A PALB2 mutation associated with high risk of breast cancer. *Breast Cancer Res.* 2010; 12:R109. [PubMed: 21182766]
7. Bernstein JL, Teraoka S, Southey MC, Jenkins MA, Andrulis IL, Knight JA, John EM, Lapinski R, Wolitzer AL, Whittemore AS, West D, Seminara D, Olson ER, Spurdle AB, Chenevix-Trench G, Giles GG, Hopper JL, Concannon P. Population-based estimates of breast cancer risks associated with ATM gene variants c.7271T>G and c.1066-6T>G (IVS10-6T>G) from the Breast Cancer Family Registry. *Hum Mutat.* 2006; 27:1122–1128. [PubMed: 16958054]
8. Antoniou AC, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003; 72:1117–1130. [PubMed: 12677558]
9. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, Lee A, Subramanian D, De Leeneer K, Fostira F, Tomiak E, Neuhausen SL, Teo ZL, Khan S, Aittomäki K, Moilanen JS, Turnbull C, Seal S, Mannermaa A, Kallioniemi A, Lindeman GJ, Buys SS, Andrulis IL, Radice P, Tondini C, Manoukian S, Toland AE, Miron P, Weitzel JN, Domchek SM, Poppe B, Claes KB, Yannoukakos D, Concannon P, Bernstein JL, James PA, Easton DF, Goldgar DE, Hopper JL, Rahman N, Peterlongo P, Nevanlinna H, King MC, Couch FJ, Southey MC, Winqvist R, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med.* 2014; 371:497–506. [PubMed: 25099575]
10. Heikkinen T, Kärkkäinen H, Aaltonen K, Milne RL, Heikkilä P, Aittomäki K, Blomqvist C, Nevanlinna H. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. *Clin Cancer Res.* 2009; 15:3214–3222. [PubMed: 19383810]
11. Le Calvez-Kelm F, Lesueur F, Damiola F, Vallée M, Voegelé C, Babikyan D, Durand G, Forey N, McKay-Chopin S, Robinot N, Nguyen-Dumont T, Thomas A, Byrnes GB, Breast Cancer Family Registry. Hopper JL, Southey MC, Andrulis IL, John EM, Tavtigian SV. Rare, evolutionarily unlikely missense substitutions in CHEK2 contribute to breast cancer susceptibility: results from a breast cancer family registry case-control mutation-screening study. *Breast Cancer Res.* 2011; 13:R6. [PubMed: 21244692]
12. Tavtigian SV, Oefner PJ, Babikyan D, Hartmann A, Healey S, Le Calvez-Kelm F, Lesueur F, Byrnes GB, Chuang SC, Forey N, Feuchtinger C, Gioia L, Hall J, Hashibe M, Herte B, McKay-Chopin S, Thomas A, Vallée MP, Voegelé C, Webb PM, Whiteman DC, Australian Cancer Study; Breast Cancer Family Registries (BCFR); Kathleen Cuningham Foundation Consortium for Research into Familial Aspects of Breast Cancer (kConFab). Sangrajrang S, Hopper JL, Southey MC, Andrulis IL, John EM, Chenevix-Trench G. Rare, evolutionarily unlikely missense substitutions in ATM confer increased risk of breast cancer. *Am J Hum Genet.* 2009; 85:427–446. [PubMed: 19781682]
13. Goldgar DE, Healey S, Dowty JG, Da Silva L, Chen X, Spurdle AB, Terry MB, Daly MJ, Buys SM, Southey MC, Andrulis I, John EM, BCFR; kConFab. Khanna KK, Hopper JL, Oefner PJ, Lakhani S, Chenevix-Trench G. Rare variants in the ATM gene and risk of breast cancer. *Breast Cancer Res.* 2011; 13:R73. [PubMed: 21787400]
14. Thompson D, Easton DF. Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst.* 2002; 94:1358–1365. [PubMed: 12237281]
15. Edwards SM, Kote-Jarai Z, Meitz J, Hamoudi R, Hope Q, Osin P, Jackson R, Southgate C, Singh R, Falconer A, Dearnaley DP, Ardern-Jones A, Murkin A, Dowe A, Kelly J, Williams S, Oram R, Stevens M, Teare DM, Ponder BA, Gayther SA, Easton DF, Eeles RA. Cancer Research UK/ British Prostate Group UK Familial Prostate Cancer Study Collaborators; British Association of Urological Surgeons Section of Oncology. Two percent of men with early-onset prostate cancer

- harbor germline mutations in the BRCA2 gene. *Am J Hum Genet.* 2003; 72:1–12. [PubMed: 12474142]
16. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst.* 1999; 91:1310–1316. [PubMed: 10433620]
 17. Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E, Goh C, Govindasami K, Guy M, O'Brien L, Sawyer E, Hall A, Wilkinson R, Easton D, UKGPCS, Collaborators Goldgar D, Eeles R, Kote-Jarai Z. Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer.* 2012; 106:1697–1701. [PubMed: 22516946]
 18. Tischkowitz M, Sabbaghian N, Ray AM, Lange EM, Foulkes WD, Cooney KA. Analysis of the gene coding for the BRCA2-interacting protein PALB2 in hereditary prostate cancer. *Prostate.* 2008; 68:675–678. [PubMed: 18288683]
 19. Dansonka-Mieszkowska A, Kluska A, Moes J, Dabrowska M, Nowakowska D, Niwinska A, Derlatka P, Cendrowski K, Kupryjanczyk J. A novel germline PALB2 deletion in Polish breast and ovarian cancer patients. *BMC Med Genet.* 2010; 11:20. [PubMed: 20122277]
 20. Teo ZL, Park DJ, Provenzano E, Chatfield CA, Odefrey FA, Nguyen-Dumont T, kConFab. Dowty JG, Hopper JL, Winship I, Goldgar DE, Southey MC. Prevalence of PALB2 mutations in Australasian multiple-case breast cancer families. *Breast Cancer Res.* 2013; 15:R17. [PubMed: 23448497]
 21. Sakoda LC, Jorgenson E, Witte JS. Turning of COGS moves forward findings for hormonally mediated cancers. *Nat Genet.* 2013; 45:345–348. [PubMed: 23535722]
 22. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, Schmidt MK, Chang-Claude J, Bojesen SE, Bolla MK, Wang Q, Dicks E, Lee A, Turnbull C, Rahman N, Breast and Ovarian Cancer Susceptibility Collaboration; Fletcher O, Peto J, Gibson L, Dos Santos Silva I, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Czene K, Irwanto A, Liu J, Waisfisz Q, Meijers-Heijboer H, Adank M, Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON); van der Luijt RB, Hein R, Dahmen N, Beckman L, Meindl A, Schmutzler RK, Müller-Myhsok B, Lichtner P, Hopper JL, Southey MC, Makalic E, Schmidt DF, Uitterlinden AG, Hofman A, Hunter DJ, Chanock SJ, Vincent D, Bacot F, Tessier DC, Canisius S, Wessels LF, Haiman CA, Shah M, Luben R, Brown J, Luccarini C, Schoof N, Humphreys K, Li J, Nordestgaard BG, Nielsen SF, Flyger H, Couch FJ, Wang X, Vachon C, Stevens KN, Lambrechts D, Moisse M, Paridaens R, Christiaens MR, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer LJ, van der Schoot CE, Guénel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JI, Pita G, Alonso MR, Cox A, Brock IW, Cross SS, Reed MW, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Henderson BE, Schumacher F, Le Marchand L, Andrulis IL, Knight JA, Glendon G, Mulligan AM, kConFab Investigators, Australian Ovarian Cancer Study Group; Lindblom A, Margolin S, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Bui QM, Stone J, Dite GS, Apicella C, Tsimiklis H, Giles GG, Severi G, Baglietto L, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Müller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labrèche F, Dumont M, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Brüning T, GENICA (Gene Environment Interaction and Breast Cancer in Germany) Network/. Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RA, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Durda K, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dörk T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo KY, Noh DY, Matsuo K, Ito H, Iwata H, Sueta A, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Shu XO, Lu W, Gao YT, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng JH, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsana P, Shen CY, Hsiung CN, Wu PE, Ding SL, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Blot WJ, Signorello LB, Cai Q, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Simard J, Garcia-Closas M, Pharoah PD, Chenevix-Trench G, Dunning AM, Benitez J, Easton DF. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet.* 2013; 45:353–361. [PubMed: 23535729]
 23. Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, Buckley M, Fridley BL, Tyrer JP, Shen H, Weber R, Karevan R, Larson MC, Song H, Tessier DC, Bacot F, Vincent D, Cunningham JM, Dennis J, Dicks E, Australian Cancer Study, Australian Ovarian Cancer Study

- Group. Aben KK, Anton-Culver H, Antonenkova N, Armasu SM, Baglietto L, Bandera EV, Beckmann MW, Birrer MJ, Bloom G, Bogdanova N, Brenton JD, Brinton LA, Brooks-Wilson A, Brown R, Butzow R, Campbell I, Carney ME, Carvalho RS, Chang-Claude J, Chen YA, Chen Z, Chow WH, Cicek MS, Coetzee G, Cook LS, Cramer DW, Cybulski C, Dansonka-Mieszkowska A, Despierre E, Doherty JA, Dörk T, du Bois A, Dürst M, Eccles D, Edwards R, Ekici AB, Fasching PA, Fenstermacher D, Flanagan J, Gao YT, Garcia-Closas M, Gentry-Maharaj A, Giles G, Gjyshi A, Gore M, Gronwald J, Guo Q, Halle MK, Harter P, Hein A, Heitz F, Hillemanns P, Hoatlin M, Høgdall E, Høgdall CK, Hosono S, Jakubowska A, Jensen A, Kalli KR, Karlan BY, Kelemen LE, Kiemeny LA, Kjaer SK, Konecny GE, Krakstad C, Kupryjanczyk J, Lambrechts D, Lambrechts S, Le ND, Lee N, Lee J, Leminen A, Lim BK, Lissowska J, Lubinski J, Lundvall L, Lurie G, Massuger LF, Matsuo K, McGuire V, McLaughlin JR, Menon U, Modugno F, Moysich KB, Nakanishi T, Narod SA, Ness RB, Nevanlinna H, Nickels S, Noushmehr H, Odunsi K, Olson S, Orlow I, Paul J, Pejovic T, Pelttari LM, Permut-Wey J, Pike MC, Poole EM, Qu X, Risch HA, Rodriguez-Rodriguez L, Rossing MA, Rudolph A, Runnebaum I, Rzepecka IK, Salvesen HB, Schwaab I, Severi G, Shen H, Shridhar V, Shu XO, Sieh W, Southey MC, Spellman P, Tajima K, Teo SH, Terry KL, Thompson PJ, Timorek A, Tworoger SS, van Altena AM, van den Berg D, Vergote I, Vierkant RA, Vitonis AF, Wang-Gohrke S, Wentzensen N, Whittemore AS, Wik E, Winterhoff B, Woo YL, Wu AH, Yang HP, Zheng W, Ziogas A, Zulkifli F, Goodman MT, Hall P, Easton DF, Pearce CL, Berchuck A, Chenevix-Trench G, Iversen E, Monteiro AN, Gayther SA, Schildkraut JM, Sellers TA. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat Genet.* 2013; 45:362–370. [PubMed: 23535730]
24. Chenevix-Trench G, Spurdle AB, Gatei M, Kelly H, Marsh A, Chen X, Donn K, Cummings M, Nyholt D, Jenkins MA, Scott C, Pupo GM, Dörk T, Bendix R, Kirk J, Tucker K, McCredie MR, Hopper JL, Sambrook J, Mann GJ, Khanna KK. Dominant negative ATM mutations in breast cancer families. *J Natl Cancer Inst.* 2002; 94:205–215. [PubMed: 11830610]
25. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B.* 1995; 57:289–300.
26. Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, Ghousaini M, Luccarini C, Dennis J, Jugurnauth-Little S, Dadaev T, Neal DE, Hamdy FC, Donovan JL, Muir K, Giles GG, Severi G, Wiklund F, Gronberg H, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Lindstrom S, Kraft P, Hunter DJ, Gapstur S, Chanock SJ, Berndt SI, Albanes D, Andriole G, Schleutker J, Weischer M, Canzian F, Riboli E, Key TJ, Travis RC, Campa D, Ingles SA, John EM, Hayes RB, Pharoah PD, Pashayan N, Khaw KT, Stanford JL, Ostrander EA, Signorello LB, Thibodeau SN, Schaid D, Maier C, Vogel W, Kibel AS, Cybulski C, Lubinski J, Cannon-Albright L, Brenner H, Park JY, Kaneva R, Batra J, Spurdle AB, Clements JA, Teixeira MR, Dicks E, Lee A, Dunning AM, Baynes C, Conroy D, Maranian MJ, Ahmed S, Govindasami K, Guy M, Wilkinson RA, Sawyer EJ, Morgan A, Dearnaley DP, Horwich A, Huddart RA, Khoo VS, Parker CC, Van As NJ, Woodhouse CJ, Thompson A, Dudderidge T, Ogden C, Cooper CS, Lophatananon A, Cox A, Southey MC, Hopper JL, English DR, Aly M, Adolfsson J, Xu J, Zheng SL, Yeager M, Kaaks R, Diver WR, Gaudet MM, Stern MC, Corral R, Joshi AD, Shahabi A, Wahlfors T, Tammela TL, Auvinen A, Virtamo J, Klarskov P, Nordestgaard BG, Røder MA, Nielsen SF, Bojesen SE, Siddiq A, Fitzgerald LM, Kolb S, Kwon EM, Karyadi DM, Blot WJ, Zheng W, Cai Q, McDonnell SK, Rinckleb AE, Drake B, Colditz G, Wokolorczyk D, Stephenson RA, Teerlink C, Muller H, Rothenbacher D, Sellers TA, Lin HY, Slavov C, Mitev V, Lose F, Srinivasan S, Maia S, Paulo P, Lange E, Cooney KA, Antoniou AC, Vincent D, Bacot F, Tessier DC. COGS–Cancer Research UK GWAS–ELLIPSE (part of GAME-ON) Initiative, Australian Prostate Cancer Bioresource, UK Genetic Prostate Cancer Study Collaborators/British Association of Urological Surgeons’ Section of Oncology, UK ProtecT (Prostate testing for cancer and Treatment) Study Collaborators, PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium, Kote-Jarai Z, Easton DF. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet.* 2013; 45:385–391. [PubMed: 23535732]
27. Glusman G. Clinical applications of sequencing take center stage. *Genome Biol.* 2013; 14:303. [PubMed: 23651925]
28. Sikkema-Raddatz B, Johansson LF, de Boer EN, Almomani R, Boven LG, van den Berg MP, van Spaendonck-Zwarts KY, van Tintelen JP, Sijmons RH, Jongbloed JD, Sinke RJ. Targeted Next-

- Generation Sequencing can Replace Sanger Sequencing in Clinical Diagnostics. *Hum Mutat.* 2013; 34:1035–1042. [PubMed: 23568810]
29. Rattenberry E, Vialard L, Yeung A, Bair H, McKay K, Jafri M, Canham N, Cole TR, Denes J, Hodgson SV, Irving R, Izatt L, Korbonits M, Kumar AV, Lalloo F, Morrison PJ, Woodward ER, Macdonald F, Wallis Y, Maher ER. A comprehensive next generation sequencing based genetic testing strategy to improve diagnosis of inherited pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab.* 2013; 98:E1248–E1256. [PubMed: 23666964]
 30. Park JY, Singh TR, Nassar N, Zhang F, Freund M, Hanenberg H, Meetei AR, Andreassen PR. Breast cancer-associated missense mutants of the PALB2 WD40 domain, which directly binds RAD51C, RAD51 and BRCA2, disrupt DNA repair. *Oncogene.* 2014; 33:4803–4812. [PubMed: 24141787]
 31. Taylor AM, Lam Z, Last JI, Byrd PJ. Ataxia telangiectasia: more variation at clinical and cellular levels. *Clin Genet.* 2015 Mar.87:199–208. [PubMed: 25040471]
 32. Waddell N, Jonnalagadda J, Marsh A, Grist S, Jenkins M, Hobson K, Taylor M, Lindeman GJ, Tavtigian SV, Suthers G, Goldgar D, Oefner PJ, kConFab Investigators. Taylor D, Grimmond S, Khanna KK, Chenevix-Trench G. Characterization of the breast cancer associated ATM 7271T<G (V2424G) mutation by gene expression profiling. *Genes Chromosomes Cancer.* 2006; 45:1169–1181. [PubMed: 17001622]
 33. Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. *J Clin Oncol.* 2008; 26:542–548. [PubMed: 18172190]
 34. Han FF, Guo CL, Liu LH. The effect of CHEK2 variant I157T on cancer susceptibility: evidence from a meta-analysis. *DNA Cell Biol.* 2013; 32:329–335. [PubMed: 23713947]
 35. Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, Devilee P, Meindl A, Couch FJ, Southey M, Goldgar DE, Evans DG, Chenevix-Trench G, Rahman N, Robson M, Domchek SM, Foulkes WD. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med.* 2015; 372:2243–2257. [PubMed: 26014596]

Table 1

Rare genetic variants included in the iCOGS array.

Breast cancer risk estimates									
Gene	Variant*	Amino acid*	dbSNP rs	OR (95% CI)	Penetrance [†] (95% CI)	Align-GVGD	Reference(s)	Designed [‡]	Genotyped
PALB2	c.1592delT	p.Leu531Cysfs	rs180177102	3.94 (1.5–12.1), [§]	40% (17–77)	na	4, 5, 10	Yes	Yes
	c.2323C>T	p.Gln775*	rs180177111			na	25, 26	No	No
	c.2816T>G	p.Leu939Trp	rs45478192			C55	20	Yes	Yes
	c.3113G>A	p.Trp1038*	rs180177132		95% (44–100)	na	2, 6, 20	Yes	Yes
	c.3116delA	p.Asn1039Ilefs	rs180177133			na	2	No	No
CHEK2	c.3549C>G	p.Tyr1183*	rs118203998			na	2	No	No
	c.349A>G	p.Arg117Gly	rs28909982	8.75 (1.06–72.2), [¶]		C65	11	Yes	Yes
	c.538C>T	p.Arg180Cys	rs77130927	2.47 (0.45–13.49), ^{**}		C25	11	Yes	Yes
	c.715G>A	p.Glu239Lys	rs121908702	1.82 (0.62–5.34), ^{††}		C15	11	Yes	Yes
	c.1036C>T	p.Arg346Cys	na	8.75 (1.06–72.2), [¶]		C65	11	Yes	Yes
	c.1312G>T	p.Asp438Tyr	na	2.47 (0.45–13.49), ^{**}		C25	11	Yes	Yes
	c.1343T>G	p.Ile448Ser	rs17886163	1.82 (0.62–5.34), ^{††}		C15	11	Yes	Yes
	c.7271T>G	p.Val2424Gly	rs28904921		52% (28–80)	C65	7, 13, 23, 27	Yes	Yes

* Human Genome Variation Society (HGVS); reference sequences PALB2, NM_024675.3, NP_078951.2; CHEK2, NM_007194.3, NP_009125.1; ATM, NM_000051.3, NP_000042.3.

[†] Age-specific cumulative risk of breast cancer to age 70 years.^{5–7}

[‡] Able to be designed for measurement on the custom Illumina iSelect genotyping array.^{21,22}

[§] Breast cancer cases unselected for family history of breast cancer.⁴

[¶] OR estimated in a combined group of C65 CHEK2 variants.¹¹

^{*} OR estimated in a combined group of C25 CHEK2 variants.¹¹

^{††} OR estimated in a combined group of C15 CHEK2 variants.¹¹

na, not available.

Summary results from Breast Cancer Association Consortium studies of white Europeans (42 671 invasive breast cancer cases and 42 164 controls)

Table 2

Variant	Frequency* Controls	Frequency* Cases	OR (95% CI)	LRT p Value	OR† (95% CI)	LRT p Value‡
<i>PALB2</i> [§]						
c.1592delT (p.Leu531Cysfs)	0.00014	0.00082	4.52 (1.90 to 10.8)	7.1×10 ⁻⁵	3.44 (1.39 to 8.52)	0.003
c.2816T>G (p.Leu939Trp)	0.00342	0.00352	1.05 (0.83 to 1.32)	0.70	1.03 (0.80 to 1.32)	0.82
c.3113G>A (p.Trp1038*)	0.00019	0.00101	5.93 (2.77 to 12.7)	6.9×10 ⁻⁸	4.21 (1.84 to 9.60)	1.2×10 ⁻⁴
<i>CHEK2</i>						
c.349A>G (p.Arg117Gly)	0.00043	0.00103	2.26 (1.29 to 3.95)	0.003	2.03 (1.10 to 3.73)	0.020
c.538C>T (p.Arg180Cys)	0.00337	0.00370	1.33 (1.05 to 1.67)	0.016	1.34 (1.06 to 1.70)	0.015
c.715G>A (p.Glu239Lys)	0.00021	0.00035	1.70 (0.73 to 3.93)	0.210	1.47 (0.60 to 3.64)	0.40
c.1036C>T (p.Arg346Cys)	0.00005	0.00021	5.06 (1.09 to 23.5)	0.017	3.39 (0.68 to 16.9)	0.11
c.1312G>T (p.Asp438Tyr)	0.00078	0.00082	1.03 (0.62 to 1.71)	0.910	0.87 (0.49 to 1.52)	0.62
c.1343T>G (p.Ile448Ser) [‡]	0.00002	0	–	–	–	–
<i>ATM</i>						
c.727T>G (p.Val2424Gly)	0.00002	0.00028	11.6 (1.50 to 89.9)	0.0012	11.0 (1.42 to 85.7)	0.0019

* Proportion of subjects carrying the variant.

† Excluding women from five studies that selected all cases based on family history or bilateral disease and the subset of selected cases from other studies (based on 34 488 unselected cases and 34 059 controls).

‡ *CHEK2* c.1343T>G (p.Ile448Ser) was only observed in one control and no cases of white European origin.

§ *PALB2* c.3113G>A (p.Trp1038*) only observed in the UK, Australia, the USA and Canada. *PALB2* c.1592delT (p.Leu531Cysfs) only observed in Finland and Sweden.

LRT, likelihood ratio test; OR, OR for carriers of the variant versus common-allele homozygotes, adjusted for study and seven principal components.

Table 3

Summary results from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome studies for white European men* (22 301 prostate cancer cases and 22 320 controls)

Variant	Frequency [†] Controls	Frequency [†] Cases	OR (95% CI)	LRT p Value
<i>PALB2</i>				
c.1592delT (p.Leu531Cysfs)	0.00018	0.00031	2.06 (0.59 to 7.11)	0.24
c.2816T>G (p.Leu939Trp)	0.00354	0.00381	0.95 (0.69 to 1.29)	0.73
c.3113G>A (p.Trp1038*)	0.00045	0.00027	0.49 (0.18 to 1.36)	0.16
<i>CHEK2</i> [‡]				
c.349A>G (p.Arg117Gly)	0.00063	0.00081	1.46 (0.71 to 3.02)	0.30
c.538C>T (p.Arg180Cys)	0.00341	0.00296	1.02 (0.73 to 1.44)	0.90
c.715G>A (p.Glu239Lys)	0.00018	0.00027	1.47 (0.41 to 5.35)	0.55
c.1036C>T (p.Arg346Cys)	0.00018	0.00022	1.07 (0.28 to 4.07)	0.93
c.1312G>T (p.Asp438Tyr)	0.00049	0.00103	2.21 (1.06 to 4.63)	0.03
c.1343T>G (p.Ile448Ser)	0	0.00009	–	–
c.1343T>G (Africans [§])	0.019	0.057	3.03 (1.53 to 6.03)	0.001
ATM				
c.7271T>G (p.Val2424Gly)	0.00004	0.00027	4.37 (0.52 to 36.4)	0.17

* For white European men, unless otherwise indicated.

[†] Proportion of subjects carrying the variant.

[‡] *CHEK2* c.1343T>G (p.Ile448Ser) was the only *CHEK2* variant observed in African men and was identified in two cases and no controls of white European origin.

[§] Based on data from 623 and 569 African-American cases and controls, respectively.

LRT, likelihood ratio test; OR, OR for carriers of the variant versus common-allele homozygotes, adjusted for study and seven principal components.

Table 4

Summary results from the Ovarian Cancer Association Consortium studies for white European women (14 542 invasive ovarian cancer cases and 23 491 controls)

Variant	Frequency* Controls	Frequency* Cases	OR (95% CI)	LRT p Value
<i>PALB2</i>				
c.1592delT (p.Leu531Cysfs)	0.00004	0.00012	2.50 (0.21 to 29.1)	0.45
c.2816T>G (p.Leu939Trp)	0.00413	0.00399	0.96 (0.69 to 1.34)	0.81
c.3113G>A (p.Trp1038*)	0.00034	0.00031	1.34 (0.36 to 4.97)	0.66
<i>CHEK2</i>				
c.349A>G (p.Arg117Gly)	0.00038	0.00031	1.07 (0.32 to 3.60)	0.92
c.538C>T (p.Arg180Cys)	0.00128	0.00160	1.49 (0.83 to 2.67)	0.18
c.715G>A (p.Glu239Lys)	0.00021	0.00037	1.47 (0.42 to 5.22)	0.54
c.1036C>T (p.Arg346Cys) [‡]	0	0	–	–
c.1312G>T (p.Asp438Tyr)	0.00081	0.00074	0.92 (0.42 to 1.99)	0.83
c.1343T>G (p.Ile448Ser)	0.00009	0	–	–
<i>ATM</i>				
c.7271T>G (p.Val2424Gly)	0	0.00012	–	–

* Proportion of subjects carrying the variant.

[‡]c.1036C>T (p.Arg346Cys) was not observed in any sample.

LRT, likelihood ratio test; OR, OR for carriers of the variant versus common-allele homozygotes, adjusted for study and seven principal components.

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