**Supplementary Table S1. Description of the BCAC studies contributing to COGS.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study**  **Acronym** | **Study Name** | **Country** | **Genotyped samples** | |
| **Case (n=42,671)** | **Control (n=42,164)** |
| **STUDIES OF WOMEN WITH EUROPEAN ANCESTERY** | | | | |
| ABCFS† | Australian Breast Cancer Family Study([1](#_ENREF_1)) | Australia | 762 | 492 |
| ABCS | Amsterdam Breast Cancer Study([2](#_ENREF_2)) | Netherlands | 1325 | 1422 |
| BBCC | Bavarian Breast Cancer Cases and Controls([3](#_ENREF_3)) | Germany | 564 | 458 |
| BBCS | British Breast Cancer Study([4](#_ENREF_4)) | U.K. | 1529 | 1392 |
| BIGGS | Breast Cancer in Galway Genetic Study([5](#_ENREF_5)) | Ireland | 836 | 719 |
| BSUCH | Breast Cancer Study of the University Clinic Heidelberg([6](#_ENREF_6)) | Germany | 848 | 954 |
| CECILE | CECILE Breast Cancer Study([7](#_ENREF_7)) | France | 1016 | 994 |
| CGPS | Copenhagen General Population Study([8](#_ENREF_8)) | Denmark | 2446 | 4072 |
| CNIO-BCS | Spanish National Cancer Centre Breast Cancer Study([9](#_ENREF_9)) | Spain | 738 | 876 |
| CTS\* | California Teachers Study([10](#_ENREF_10)) | U.S.A. | 51 | 44 |
| ESTHER | ESTHER Breast Cancer Study ([11](#_ENREF_11)) | Germany | 476 | 502 |
| GENICA\* | Gene Environment Interaction & Breast Cancer in Germany([12](#_ENREF_12), [13](#_ENREF_13)) | Germany | 465 | 427 |
| HEBCS | Helsinki Breast Cancer Study([14](#_ENREF_14)) | Finland | 1664 | 1234 |
| HMBCS | Hannover-Minsk Breast Cancer Study([15](#_ENREF_15)) | Belarus | 690 | 130 |
| KARBAC | Karolinska Breast Cancer Study([16](#_ENREF_16)) | Sweden | 718 | 662 |
| KBCP | Kuopio Breast Cancer  Project([17](#_ENREF_17)) | Finland | 445 | 251 |
| kConFab/  AOCS | Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer / Australian Ovarian Cancer Study([18](#_ENREF_18)) | Australia | 589 | 871 |
| LMBC | Leuven Multidisciplinary Breast Centre([19](#_ENREF_19)) | Belgium | 2671 | 1388 |
| MARIE | Mammary Carcinoma Risk Factor Investigation([20](#_ENREF_20)) | Germany | 1816 | 1778 |
| MBCSG | Milan Breast Cancer Study Group([21](#_ENREF_21)) | Italy | 488 | 400 |
| MCBCS | Mayo Clinic Breast  Cancer Study([22](#_ENREF_22)) | U.S.A. | 1862 | 1920 |
| MCCS | Melbourne Collaborative Cohort Study([23](#_ENREF_23)) | Australia | 614 | 511 |
| MEC | Multiethnic Cohort([24](#_ENREF_24)) | U.S.A. | 731 | 741 |
| NBCS\* | Norwegian Breast Cancer Study([25](#_ENREF_25)) | Norway | 22 | 70 |
| NBHS | Nashville Breast Health Study | U.S.A | 126 | 119 |
| OBCS | Oulu Breast Cancer  Study([26](#_ENREF_26)) | Finland | 507 | 414 |
| OFBCR‡ | Ontario Familial Breast Cancer Registry([27](#_ENREF_27)) | Canada | 1118 | 495 |
| ORIGO | Leiden University Medical Centre Breast Cancer Study([28](#_ENREF_28), [29](#_ENREF_29)) | Netherlands | 344 | 327 |
| PBCS | NCI Polish Breast Cancer Study([30](#_ENREF_30)) | Poland | 519 | 424 |
| pKARMA | Karolinska Mammography Project for Risk Prediction of Breast Cancer([31](#_ENREF_31)) | Sweden | 5269 | 5452 |
| RBCS | Rotterdam Breast Cancer Study([32](#_ENREF_32)) | Netherlands | 664 | 699 |
| SASBAC | Singapore and Sweden Breast Cancer Study([33](#_ENREF_33)) | Sweden | 1163 | 1378 |
| SBCS | Sheffield Breast Cancer Study([34](#_ENREF_34)) | U.K. | 841 | 840 |
| SEARCH | Studies of Epidemiology and Risk Factors in  Cancer Heredity([35](#_ENREF_35), [36](#_ENREF_36)) | U.K. | 6645 | 8037 |
| SKKDKFZ\* | Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study([37](#_ENREF_37)) | Germany | 144 | 0 |
| SZBCS | Szczecin Breast Cancer Study([38](#_ENREF_38)) | Poland | 365 | 315 |
| TNBCC\* | Triple Negative Breast Cancer Consortium Study([39](#_ENREF_39)) | Various | 343 | 329 |
| UKBGS | Breakthrough Generations Study([40](#_ENREF_40)) | U.K. | 476 | 470 |
| **STUDIES OF WOMEN WITH ASIAN ANCESTERY** | | | | |
|  |  |  | **Case (n=6,269)** | **Control (n=6,624)** |
| ACP | Asian Cancer Project | Thailand | 423 | 636 |
| HERPACC | Hospital-based Epidemiologic Research Program at Aichi Cancer Center ([41](#_ENREF_41)) | Japan | 694 | 1376 |
| LAABC | Los Angeles County  Asian-American Breast  Cancer Case-Control Study ([42](#_ENREF_42)) | USA | 812 | 990 |
| MYBRCA | Malaysian Breast Cancer  Genetic Study ([43](#_ENREF_43)) | Malaysia | 770 | 610 |
| SBCGS | Shanghai Breast Cancer  Genetic Study ([44](#_ENREF_44)) | China | 848 | 892 |
| SEBCS | Seoul Breast Cancer  Study ([45](#_ENREF_45)) | South Korea | 1162 | 1129 |
| SGBCC | Singapore Breast Cancer Cohort | Singapore | 533 | 502 |
| TBCS | IARC-Thai Breast  Cancer ([46](#_ENREF_46)) | Thailand | 138 | 253 |
| TWBCS | Taiwanese Breast Cancer  Study ([47](#_ENREF_47)) | Taiwan | 889 | 236 |

BCAC, Breast Cancer Association Consortium; COGS, Collaborative Oncological Gene-environment Study; \* CTS, NBCS and SKKDKFZ are studies in BCAC but were genotyped as part of the triple negative consortium (TNBCC). Part of GENICA was also genotyped as part of TNBCC. †Australian site of the Breast Cancer Family Registry; ‡Ontario site of the Breast Cancer Family

**Supplementary Table S2. Predicted effects of *BRCA1* and *BRCA2* variants included in the iCOGS array on protein function**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **HGVS DNAa** | **HGVS Protein** | **Amino acid change** | **SNP rsID** | **IARC classb** | **A-GVGD**  **category** | **MetaLR scorec** | **MetaSVM scored** | **VEST3 scoree** |
| *BRCA1* |  |  |  |  |  |  |  |  |
| c.536A>G | p.Tyr179Cys | Y179C | rs56187033 | Class1 | C35 | 0.94 | 1.06 | 0.93 |
| c.1067A>G | p.Gln356Arg | Q356R | rs1799950 | Class1 | C0 | 0.07 | -0.85 | 0.65 |
| c.1233T>G | p.Asp411Glu | D411E | rs80357024 | Class3 | C0 | 0.03 | -1.02 | 0.60 |
| c.1487G>A | p.Arg496His | R496H | rs28897677 | Class1 | C0 | 0.39 | -0.53 | 0.70 |
| c.2315T>C | p.Val772Ala | V772A | rs80357467 | Class1 | C0 | 0.67 | -0.14 | 0.90 |
| c.2521C>T | p.Arg841Trp | R841W | rs1800709 | Class1 | C15 | 0.15 | -0.86 | 0.61 |
| c.3024G>A | p.Met1008Ile | M1008I | rs1800704 | Class1 | C0 | 0.18 | -0.94 | 0.60 |
| c.3119G>A | p.Ser1040Asn | S1040N | rs4986852 | Class1 | C0 | 0.36 | -0.55 | 0.47 |
| c.4213A>G | p.Ile1405Val | I1405V | rs80357353 | Class3 | C0 | 0.08 | -1.02 | 0.56 |
| c.4327C>T | p.Arg1443Ter | R1443X | [rs41293455](http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/?chr=17&from=41234451&to=41234451&gts=rs41293455&mk=41234451:41234451|rs41293455) | Class5 | - | - | - | - |
| c.4837A>G | p.Ser1613Gly | S1613G | rs1799966 | Class1 | C0 | 0.00 | -1.08 | 0.45 |
| c.4883T>C | p.Met1628Thr | M1628T | rs4986854 | Class1 | C0 | 0.34 | -0.75 | 0.86 |
| c.4956G>T | p.Met1652Ile | M1652I | rs1799967 | Class1 | C0 | 0.25 | -0.78 | 0.68 |
| c.4991T>C | p.Leu1664Pro | L1664P | rs80357314 | Class1 | C0 | 0.52 | -0.32 | 0.72 |
| c.5096G>A | p.Arg1699Gln | R1699Q | rs41293459 | Class3h | C35 | 0.87 | 0.94 | 0.91 |
| c.5123C>A | p.Ala1708Glu | A1708E | rs28897696 | Class5 | C65 | 0.84 | 0.85 | 0.99 |
| c.5207T>C | p.Val1736Ala | V1736A | rs45553935 | Class3f | C65 | 0.84 | 0.85 | 0.93 |
| c.5252G>A | p.Arg1751Gln | R1751Q | rs80357442 | Class1 | C0 | 0.71 | 0.60 | 0.93 |
| c.5348T>C | p.Met1783Thr | M1783T | rs55808233 | Class3g | C45 | 0.58 | 0.22 | 0.81 |
| c.5363G>A | p.Gly1788Asp | G1788D | rs80357069 | Class3f | C65 | 0.95 | 1.07 | 0.98 |
| *BRCA2* |  |  |  |  |  |  |  |  |
| c.125A>G | p.Tyr42Cys | Y42C | rs4987046 | Class1 | C0 | 0.00 | -0.76 | 0.34 |
| c.865A>C | p.Asn289His | N289H | rs766173 | Class1 | C0 | 0.00 | -0.87 | 0.52 |
| c.978C>A | p.Ser326Arg | S326R | rs28897706 | Class1 | C0 | 0.00 | -0.90 | 0.69 |
| c.1151C>T | p.Ser384Phe | S384F | rs41293475 | Class1 | C0 | 0.01 | -0.87 | 0.89 |
| c.1514T>C | p.Ile505Thr | I505T | rs28897708 | Class2 | C0 | 0.00 | -0.86 | 0.90 |
| c.1964C>G | p.Pro655Arg | P655R | rs28897712 | Class1 | C0 | 0.00 | -0.89 | 0.60 |
| c.2971A>G | p.Asn991Asp | N991D | rs1799944 | Class1 | C0 | 0.00 | -1.00 | 0.15 |
| c.3055C>G | p.Leu1019Val | L1019V | rs55638633 | Class1 | C0 | 0.07 | -1.03 | 0.77 |
| c.4258G>T | p.Asp1420Tyr | D1420Y | rs28897727 | Class1 | C0 | 0.00 | -0.91 | 0.63 |
| c.4585G>A | p.Gly1529Arg | G1529R | rs28897728 | Class1 | C65 | 0.76 | 0.60 | 0.91 |
| c.5312G>A | p.Gly1771Asp | G1771D | rs80358755 | Class1 | C0 | 0.00 | -0.93 | 0.50 |
| c.5744C>T | p.Thr1915Met | T1915M | rs4987117 | Class1 | C0 | 0.05 | -1.04 | 0.31 |
| c.6323G>A | p.Arg2108His | R2108H | rs35029074 | Class1 | C0 | 0.00 | -0.89 | 0.87 |
| c.7057G>C | p.Gly2353Arg | G2353R | rs80358935 | Class1 | C0 | 0.50 | -0.46 | 0.60 |
| c.7397C>T | p.Ala2466Val | A2466V | rs169547 | Class2 | C0 | 0.00 | -0.93 | 0.13 |
| c.7469T>C | p.Ile2490Thr | I2490T | rs11571707 | Class3g | C0 | 0.01 | -0.97 | 0.43 |
| c.7522G>A | p.Gly2508Ser | G2508S | rs80358978 | Class3 | C55 | 0.82 | 0.75 | 0.87 |
| c.7534C>T | p.Leu2512Phe | L2512F | rs80358980 | Class2 | C0 | 0.74 | 0.56 | 0.66 |
| c.7544C>T | p.Thr2515Ile | T2515I | rs28897744 | Class1 | C0 | 0.55 | 0.18 | 0.68 |
| c.7928C>G | p.Ala2643Gly | A2643G | rs80359018 | Class3g | C0 | 0.66 | 0.35 | 0.57 |
| c.8149G>T | p.Ala2717Ser | A2717S | rs28897747 | Class1 | C0 | 0.53 | -0.31 | 0.65 |
| c.8167G>C | p.Asp2723His | D2723H | rs41293511 | Class5 | C65 | 0.95 | 1.10 | 0.97 |
| c.8187G>T | p.Lys2729Asn | K2729N | rs80359065 | Class1 | C0 | 0.46 | -0.11 | 0.54 |
| c.8435G>A | p.Gly2812Glu | G2812E | rs80359091 | Class3 | C65 | 0.88 | 0.96 | 0.94 |
| c.8567A>C | p.Glu2856Ala | E2856A | rs11571747 | Class1 | C0 | 0.21 | -0.59 | 0.64 |
| c.8573A>G | p.Gln2858Arg | Q2858R | rs80359114 | Class2 | C0 | 0.41 | -0.21 | 0.72 |
| c.8850G>T | p.Lys2950Asn | K2950N | rs28897754 | Class2 | C35 | 0.32 | -0.35 | 0.56 |
| c.8905G>A | p.Val2969Met | V2969M | rs59004709 | Class1 | C0 | 0.19 | -0.74 | 0.45 |
| c.9104A>C | p.Tyr3035Ser | Y3035S | rs80359165 | Class3g | C55 | 0.57 | 0.18 | 0.78 |
| c.9155G>A | p.Arg3052Gln | R3052Q | rs80359171 | Class2 | C35 | 0.81 | 0.75 | 0.86 |
| c.9154C>T | p.Arg3052Trp | R3052W | rs45580035 | Class5 | C65 | 0.76 | 0.60 | 0.97 |
| c.9242T>C | p.Val3081Ala | V3081A | rs80359189 | Class3g | C25 | 0.71 | 0.80 | 0.74 |
| c.9292T>C | p.Tyr3098His | Y3098H | rs41293521 | Class1 | C0 | 0.15 | -0.95 | 0.77 |

a :Nucleotide numbering reflects cDNA numbering in reference sequence of BRCA1: NM\_007294.3

b :IARC Classification system ([48](#_ENREF_48)), based on multifactorial likelihood model or frequency in the general population

c : Predicted functionally damaging variants (MetaLR score >0.5) ([49](#_ENREF_49))

d : Predicted functionally damaging variants (MetaSVM score >0) ([49](#_ENREF_49))

e : VEST 3.0 score (range 0 to 1). Variants with higher scores are more likely functionally damaging ([50](#_ENREF_50))

f: Defined as pathogenic or likely pathogenic by multiple submitters in ClinVar

g: Defined as benign or Likely Benign by multiple submitters in ClinVar

h: Associated with intermediate penetrance ([51](#_ENREF_51))

**Supplementary Table S3. Frequency of *BRCA1* and *BRCA2* variants from iCOGS in breast cancer cases and controls**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Caucasian** | | | | |  | **Asian** | | | | |
| **HGVS DNAa** | **Amino acid change** | **Cases (n=42,671)** | | **Controls (n=42,164)** | **ORb** | **95% CI** | **P-value** | **Cases (n=5,795)** | | **Controls (n=6,624)** | **ORb** | **95% CIc** | **P-value** |
| *BRCA1* |  |  | |  |  |  |  |  | |  |  |  |  |
| c.536A>G | Y179C | 19 | | 11 | 1.68 | 0.82-3.45 | 0.159 | 0 | | 0 | ND |  | - |
| c.1067A>G | Q356R | 5170 | | 5137 | 0.99 | 0.95-1.03 | 0.499 | 8 | | 5 | 6.74 | 0.76-59.58 | 0.086 |
| c.1233T>G | D411E | 0 | | 0 | ND | - | - | 0 | | 0 | ND | - | - |
| c.1487G>A | R496H | 80 | | 82 | 1.05 | 0.77-1.43 | 0.774 | 0 | | 0 | ND | - | - |
| c.2315T>C | V772A | 17 | | 16 | 1.1 | 0.55-2.17 | 0.791 | 0 | | 0 | ND | - | - |
| c.2521C>T | R841W | 160 | | 207 | 0.81 | 0.66-1.00 | 0.045 | 1 | | 0 | ND | - | - |
| c.3024G>A | M1008I | 32 | | 24 | 0.91 | 0.53-1.57 | 0.73 | 0 | | 0 | ND | - | - |
| c.3119G>A | S1040N | 1538 | | 1652 | 0.95 | 0.89-1.02 | 0.17 | 1 | | 1 | ND | - | - |
| c.4213A>G | I1405V | 1 | | 0 | ND | - | - | 0 | | 0 | ND | - | - |
| c.4327C>T | R1443X | 9 | | 1 | 8.32 | 1.05-15.95 | 0.045 | 1 | | 1 | 1.54 | 0.09-25.75 | 0.764 |
| c.4837A>G | S1613G | 23265 | | 22900 | 1.02 | 0.99-1.04 | 0.163 | 3873 | | 4119 | 0.98 | 0.93-1.03 | 0.45 |
| c.4883T>C | M1628T | 68 | | 44 | 1.17 | 0.80-1.69 | 0.422 | 79 | | 104 | 0.89 | 0.66-1.19 | 0.43 |
| c.4956G>T | M1652I | 1473 | | 1337 | 1.01 | 0.94-1.09 | 0.791 | 20 | | 26 | 1.21 | 0.65- 2.25 | 0.545 |
| c.4991T>C | L1664P | 1 | | 1 | 0.94 | 0.06-15.01 | 0.964 | 0 | | 0 | ND | - | - |
| c.5096G>A | R1699Q | 16 | | 4 | 4.29 | 1.43-12.85 | 0.009 | 0 | | 0 | ND | - | - |
| c.5123C>A | A1708E | 4 | | 0 | ND | - | - | 0 | | 0 | ND | - | - |
| c.5207T>C | V1736A | 2 | | 0 | ND | - | - | 0 | | 0 | ND | - | - |
| c.5252G>A | R1751Q | 5 | | 6 | 0.85 | 0.26-2.77 | 0.781 | 1 | | 0 | ND | - | - |
| c.5348T>C | M1783T | 0 | | 0 | ND | - | - | 0 | | 0 | ND | - |  |
| c.5363G>A | G1788D | 0 | | 1 | ND | - | - | 3 | | 1 | 3.03 | 0.32-29.18 | 0.337 |
| *BRCA2* |  |  | |  |  |  |  |  | |  |  |  |  |
| c.125A>G | Y42C | 158 | | 155 | 1.00 | 0.80 -1.25 | 0.967 | 2 | | 6 | 0.34 | 0.07 - 1.68 | 0.185 |
| c.865A>C | N289H | 2544 | | 2625 | 0.95 | 0.90 -1.00 | 0.069 | 1265 | | 1324 | 1.03 | 0.95 - 1.12 | 0.449 |
| c.978C>A | S326R | 124 | | 100 | 1.20 | 0.92 -1.56 | 0.178 | 1 | | 0 | ND | - | - |
| c.1151C>T | S384F | 89 | | 97 | 0.92 | 0.69 -1.23 | 0.588 | 0 | | 3 | ND | - | - |
| c.1514T>C | I505T | 83 | | 71 | 1.10 | 0.80 -1.52 | 0.55 | 0 | | 0 | ND | - | - |
| c.1964C>G | P655R | 30 | | 11 | 1.25 | 0.62 -2.55 | 0.531 | 0 | | 0 | ND | - | - |
| c.2971A>G | N991D | 2545 | | 2630 | 0.95 | 0.90 -1.00 | 0.061 | 1266 | | 1325 | 1.03 | 0.95 - 1.12 | 0.438 |
| c.3055C>G | L1019V | 20 | | 17 | 1.18 | 0.62 -2.26 | 0.62 | 0 | | 0 | ND | - | - |
| c.4258G>T | D1420Y | 657 | | 749 | 0.86 | 0.77 -0.96 | 0.005 | 6 | | 8 | 1.01 | - | 0.99 |
| c.4585G>A | G1529R | 51 | | 47 | 1.09 | 0.73 -1.63 | 0.66 | 2 | | 0 | ND | - | - |
| c.5312G>A | G1771D | 22 | | 29 | 0.70 | 0.40 -1.23 | 0.219 | 1 | | 0 | ND | - | - |
| c.5744C>T | T1915M | 2353 | | 2409 | 1.00 | 0.94 -1.06 | 0.939 | 4 | | 8 | 0.56 | 0.14 - 2.23 | 0.412 |
| c.6323G>A | R2108H | 64 | | 69 | 0.94 | 0.67 -1.32 | 0.704 | 0 | | 2 | ND | - | - |
| c.7057G>C | G2353R | 8 | | 4 | 1.94 | 0.58 -6.46 | 0.281 | 0 | | 0 | ND | - | - |
| c.7397C>T | A2466V | 17 | | 26 | 0.64 | 0.35 -1.19 | 0.157 | 1 | | 0 | ND | - | - |
| c.7469T>C | I2490T | 9 | | 5 | 1.48 | 0.49 -4.43 | 0.487 | 30 | | 35 | 0.90 | 0.55 - 1.48 | 0.685 |
| c.7522G>A | G2508S | 0 | | 0 | ND | - | - | 31 | | 12 | 2.68 | 1.37 - 5.23 | 0.004 |
| c.7534C>T | L2512F | 1 | | 1 | 0.97 | 0.06 -15.83 | 0.985 | 0 | | 0 | ND | - | - |
| c.7544C>T | T2515I | 67 | | 66 | 0.90 | 0.64 -1.26 | 0.54 | 0 | | 0 | ND | - | - |
| c.7928C>G | A2643G | 0 | | 2 | ND | - | - | 0 | | 0 | ND | - | - |
| c.8149G>T | A2717S | 137 | | 185 | 0.77 | 0.62 -0.96 | 0.02 | 0 | | 0 | ND | - | - |
| c.8167G>C | D2723H | 8 | | 0 | ND | - | - | 0 | | 0 | ND | - | - |
| c.8187G>T | K2729N | 3 | | 1 | 2.84 | 0.29 -27.64 | 0.368 | 164 | | 128 | 1.41 | 1.12 - 1.78 | 0.004 |
| c.8435G>A | G2812E | 1 | | 1 | 1.01 | 0.06 -16.12 | 0.996 | 0 | | 0 | ND | - | - |
| c.8567A>C | E2856A | 210 | | 243 | 0.94 | 0.78 -1.13 | 0.478 | 0 | | 0 | ND | - | - |
| c.8573A>G | Q2858R | 1 | | 1 | 1.01 | 0.06 -16.23 | 0.992 | 0 | | 0 | ND | - | - |
| c.8850G>T | K2950N | 83 | | 88 | 0.97 | 0.72 -1.32 | 0.866 | 0 | | 0 | ND | - | - |
| c.8905G>A | V2969M | 42 | | 46 | 0.88 | 0.58 -1.34 | 0.543 | 0 | | 0 | ND | - | - |
| c.9104A>C | Y3035S | 18 | | 7 | 2.52 | 1.05 -6.05 | 0.038 | 3 | | 0 | ND | - | - |
| c.9155G>A | R3052Q | 4 | | 2 | 1.79 | 0.33 -9.79 | 0.504 | 0 | | 0 | ND | - | - |
| c.9154C>T | R3052W | 5 | | 0 | ND | - | - | 0 | | 0 | ND | - | - |
| c.9242T>C | V3081A | 2 | | 3 | 0.67 | 0.11 -3.99 | 0.656 | 1 | | 1 | 1.14 | 0.07 - 18.23 | 0.928 |
| c.9292T>C | Y3098H | 14 | | 20 | 0.70 | 0.35 -1.38 | 0.304 | 0 | | 0 | ND | - | - |

a :Nucleotide numbering reflects cDNA numbering in reference sequence of BRCA1: NM\_007294.3

b :OR : odds ratio

c :Confidence interval

ND: Not determined

**Supplementary Table S4: Family studies of Y3035S showing scores for each family by constant relative risk and 75% penetrance**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Pedigree** | **Unaffected** | | **Affected** | | **Breast Cancer Risk Ratio** | |
|  | Non-  Carriers | Carriers | Non-Carriers | Carriers | Constant age related risk | 75% risk of BRCA2 pathogenic variant |
| Pedigree H | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree F | 0 | 0 | 0 | 2 | 1.99 | 1.95 |
| Pedigree M | 1 | 0 | 0 | 2 | 3.74 | 3.72 |
| Pedigree I | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree G | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree J | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree O | 1 | 1 | 0 | 1 | 1.06 | 1.30 |
| Pedigree K | 1 | 1 | 0 | 3 | 14.15 | 15.38 |
| Pedigree L | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree R | 1 | 0 | 0 | 2 | 1.87 | 1.85 |
| Pedigree Q | 1 | 1 | 0 | 1 | 1 | 1 |
| Pedigree A | 0 | 1 | 0 | 0 | 1 | 1 |
| Pedigree B | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree C | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree D | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree E | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree S | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree T | 0 | 0 | 0 | 1 | 1 | 1 |
| Pedigree U | 0 | 0 | 0 | 1 | 1 | 1 |

**SUPPLEMENTARY REFERENCES**

1. Dite GS, Jenkins MA, Southey MC, Hocking JS, Giles GG, McCredie MR, et al. Familial risks, early-onset breast cancer, and BRCA1 and BRCA2 germline mutations. J Natl Cancer Inst. 2003;95:448-57.

2. Schmidt MK, Tollenaar RA, de Kemp SR, Broeks A, Cornelisse CJ, Smit VT, et al. Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2\*1100delC germline mutation. J Clin Oncol. 2007;25:64-9.

3. Schrauder M, Frank S, Strissel PL, Lux MP, Bani MR, Rauh C, et al. Single nucleotide polymorphism D1853N of the ATM gene may alter the risk for breast cancer. J Cancer Res Clin Oncol. 2008;134:873-82.

4. Fletcher O, Johnson N, Palles C, dos Santos Silva I, McCormack V, Whittaker J, et al. Inconsistent association between the STK15 F31I genetic polymorphism and breast cancer risk. J Natl Cancer Inst. 2006;98:1014-8.

5. Colleran G, McInerney N, Rowan A, Barclay E, Jones AM, Curran C, et al. The TGFBR1\*6A/9A polymorphism is not associated with differential risk of breast cancer. Breast Cancer Res Treat. 2010;119:437-42.

6. Yang R, Dick M, Marme F, Schneeweiss A, Langheinz A, Hemminki K, et al. Genetic variants within miR-126 and miR-335 are not associated with breast cancer risk. Breast Cancer Research and Treatment. 2011;127:549-54.

7. Villeneuve S, Fevotte J, Anger A, Truong T, Lamkarkach F, Gaye O, et al. Breast cancer risk by occupation and industry: analysis of the CECILE study, a population-based case-control study in France. Am J Ind Med. 2011;54:499-509.

8. Weischer M, Bojesen SE, Tybjaerg-Hansen A, Axelsson CK, Nordestgaard BG. Increased risk of breast cancer associated with CHEK2\*1100delC. J Clin Oncol. 2007;25:57-63.

9. Milne RL, Ribas G, Gonzalez-Neira A, Fagerholm R, Salas A, Gonzalez E, et al. ERCC4 associated with breast cancer risk: a two-stage case-control study using high-throughput genotyping. Cancer research. 2006;66:9420-7.

10. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control. 2002;13:625-35.

11. Widschwendter M, Apostolidou S, Raum E, Rothenbacher D, Fiegl H, Menon U, et al. Epigenotyping in peripheral blood cell DNA and breast cancer risk: a proof of principle study. PloS one. 2008;3:e2656.

12. Pesch B, Ko Y, Brauch H, Hamann U, Harth V, Rabstein S, et al. Factors modifying the association between hormone-replacement therapy and breast cancer risk. Eur J Epidemiol. 2005;20:699-711.

13. Justenhoven C, Pierl CB, Haas S, Fischer HP, Baisch C, Hamann U, et al. The CYP1B1\_1358\_GG genotype is associated with estrogen receptor-negative breast cancer. Breast Cancer Res Treat. 2008;111:171-7.

14. Heikkinen T, Karkkainen H, Aaltonen K, Milne RL, Heikkila P, Aittomaki K, et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res. 2009;15:3214-22.

15. Bogdanova NV, Antonenkova NN, Rogov YI, Karstens JH, Hillemanns P, Dork T. High frequency and allele-specific differences of BRCA1 founder mutations in breast cancer and ovarian cancer patients from Belarus. Clin Genet. 2010;78:364-72.

16. Margolin S, Werelius B, Fornander T, Lindblom A. BRCA1 mutations in a population-based study of breast cancer in Stockholm County. Genet Test. 2004;8:127-32.

17. Hartikainen JM, Tuhkanen H, Kataja V, Dunning AM, Antoniou A, Smith P, et al. An autosome-wide scan for linkage disequilibrium-based association in sporadic breast cancer cases in eastern Finland: three candidate regions found. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14:75-80.

18. Beesley J, Jordan SJ, Spurdle AB, Song H, Ramus SJ, Kjaer SK, et al. Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007;16:2557-65.

19. De Maeyer L, Van Limbergen E, De Nys K, Moerman P, Pochet N, Hendrickx W, et al. Does estrogen receptor negative/progesterone receptor positive breast carcinoma exist? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26:335-6; author reply 6-8.

20. Flesch-Janys D, Slanger T, Mutschelknauss E, Kropp S, Obi N, Vettorazzi E, et al. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. Int J Cancer. 2008;123:933-41.

21. Catucci I, Verderio P, Pizzamiglio S, Manoukian S, Peissel B, Barile M, et al. SNPs in ultraconserved elements and familial breast cancer risk. Carcinogenesis. 2009;30:544-5; author reply 6.

22. Olson JE, Ma CX, Pelleymounter LL, Schaid DJ, Pankratz VS, Vierkant RA, et al. A comprehensive examination of CYP19 variation and breast density. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007;16:623-5.

23. Giles GG, English DR. The Melbourne Collaborative Cohort Study. IARC Sci Publ. 2002;156:69-70.

24. Kolonel LN, Altshuler D, Henderson BE. The multiethnic cohort study: exploring genes, lifestyle and cancer risk. Nat Rev Cancer. 2004;4:519-27.

25. Nordgard SH, Johansen FE, Alnaes GI, Bucher E, Syvanen AC, Naume B, et al. Genome-wide analysis identifies 16q deletion associated with survival, molecular subtypes, mRNA expression, and germline haplotypes in breast cancer patients. Genes Chromosomes Cancer. 2008;47:680-96.

26. Erkko H, Xia B, Nikkila J, Schleutker J, Syrjakoski K, Mannermaa A, et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature. 2007;446:316-9.

27. John EM, Hopper JL, Beck JC, Knight JA, Neuhausen SL, Senie RT, et al. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast cancer research : BCR. 2004;6:R375-89.

28. de Bock GH, Schutte M, Krol-Warmerdam EM, Seynaeve C, Blom J, Brekelmans CT, et al. Tumour characteristics and prognosis of breast cancer patients carrying the germline CHEK2\*1100delC variant. J Med Genet. 2004;41:731-5.

29. Huijts PE, Vreeswijk MP, Kroeze-Jansema KH, Jacobi CE, Seynaeve C, Krol-Warmerdam EM, et al. Clinical correlates of low-risk variants in FGFR2, TNRC9, MAP3K1, LSP1 and 8q24 in a Dutch cohort of incident breast cancer cases. Breast cancer research : BCR. 2007;9:R78.

30. Garcia-Closas M, Brinton LA, Lissowska J, Chatterjee N, Peplonska B, Anderson WF, et al. Established breast cancer risk factors by clinically important tumour characteristics. Br J Cancer. 2006;95:123-9.

31. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nature genetics. 2013;45:353-61.

32. Hollestelle A, Pelletier C, Hooning M, Crepin E, Schutte M, Look M, et al. Prevalence of the variant allele rs61764370 T>G in the 3'UTR of KRAS among Dutch BRCA1, BRCA2 and non-BRCA1/BRCA2 breast cancer families. Breast Cancer Research and Treatment. 2011;128:79-84.

33. Wedren S, Lovmar L, Humphreys K, Magnusson C, Melhus H, Syvanen AC, et al. Oestrogen receptor alpha gene haplotype and postmenopausal breast cancer risk: a case control study. Breast cancer research : BCR. 2004;6:R437-49.

34. MacPherson G, Healey CS, Teare MD, Balasubramanian SP, Reed MW, Pharoah PD, et al. Association of a common variant of the CASP8 gene with reduced risk of breast cancer. J Natl Cancer Inst. 2004;96:1866-9.

35. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007;447:1087-93.

36. Lesueur F, Pharoah PD, Laing S, Ahmed S, Jordan C, Smith PL, et al. Allelic association of the human homologue of the mouse modifier Ptprj with breast cancer. Human molecular genetics. 2005;14:2349-56.

37. Rashid MU, Jakubowska A, Justenhoven C, Harth V, Pesch B, Baisch C, et al. German populations with infrequent CHEK2\*1100delC and minor associations with early-onset and familial breast cancer. Eur J Cancer. 2005;41:2896-903.

38. Jakubowska A, Jaworska K, Cybulski C, Janicka A, Szymanska-Pasternak J, Lener M, et al. Do BRCA1 modifiers also affect the risk of breast cancer in non-carriers? Eur J Cancer. 2009;45:837-42.

39. Stevens KN, Fredericksen Z, Vachon CM, Wang X, Margolin S, Lindblom A, et al. 19p13.1 is a triple-negative-specific breast cancer susceptibility locus. Cancer research. 2012;72:1795-803.

40. Swerdlow AJ, Jones ME, Schoemaker MJ, Hemming J, Thomas D, Williamson J, et al. The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology. Br J Cancer. 2011;105:911-7.

41. Kawase T, Matsuo K, Suzuki T, Hiraki A, Watanabe M, Iwata H, et al. FGFR2 intronic polymorphisms interact with reproductive risk factors of breast cancer: results of a case control study in Japan. International journal of cancer Journal international du cancer. 2009;125:1946-52.

42. Wu AH, Yu MC, Tseng CC, Stanczyk FZ, Pike MC. Dietary patterns and breast cancer risk in Asian American women. Am J Clin Nutr. 2009;89:1145-54.

43. Thirthagiri E, Lee SY, Kang P, Lee DS, Toh GT, Selamat S, et al. Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. Breast cancer research : BCR. 2008;10:R59.

44. Zheng W, Long J, Gao YT, Li C, Zheng Y, Xiang YB, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nature genetics. 2009;41:324-8.

45. Han S, Lee KM, Choi JY, Park SK, Lee JY, Lee JE, et al. CASP8 polymorphisms, estrogen and progesterone receptor status, and breast cancer risk. Breast Cancer Research and Treatment. 2008;110:387-93.

46. Sangrajrang S, Schmezer P, Burkholder I, Waas P, Boffetta P, Brennan P, et al. Polymorphisms in three base excision repair genes and breast cancer risk in Thai women. Breast Cancer Research and Treatment. 2008;111:279-88.

47. Ding SL, Yu JC, Chen ST, Hsu GC, Kuo SJ, Lin YH, et al. Genetic variants of BLM interact with RAD51 to increase breast cancer susceptibility. Carcinogenesis. 2009;30:43-9.

48. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat. 2008;29:1282-91.

49. Dong C, Wei P, Jian X, Gibbs R, Boerwinkle E, Wang K, et al. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. Human molecular genetics. 2015;24:2125-37.

50. Carter H, Douville C, Stenson PD, Cooper DN, Karchin R. Identifying Mendelian disease genes with the variant effect scoring tool. BMC Genomics. 2013;14 Suppl 3:S3.

51. Spurdle AB, Whiley PJ, Thompson B, Feng B, Healey S, Brown MA, et al. BRCA1 R1699Q variant displaying ambiguous functional abrogation confers intermediate breast and ovarian cancer risk. Journal of medical genetics. 2012;49:525-32.