**Supplementary Table 1.** *BRIP1* variants called in SEARCH

| Exon | Nucleotide change | Protein change | dbSNP ID | CASES (n=13,213) | | CONTROLS (n=5242) | | Validated with Sanger?[1] | *In silico* tools | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Het. | Hom. | Het. | Hom. | | CADD | PolyPhen | SIFT |
| Truncating Variants | | | | | | | | | | | |
| 3 | c.133G>T | p.Glu45Ter | | 0 | 0 | 1 | 0 | Y | 37 | - | - |
| | c.380-1G>T | | | 1 | | 0 | | N/D | 17.99 | - | - |
| 5 | c.394dupA | p.Thr132AsnfsTer10 | | 0 | | 1 | | Y | 19.7 | - | - |
| 7 | c.633delT | p.Gly212AlafsTer62 | | 1 | | 0 | | N/D | 16.8 | - | - |
| 7 | c.890delA | p.Lys297SerfsTer6 | | 1 | | 0 | | Y | 32 | - | - |
| 8 | c.1056T>G | p.Tyr352Ter | | 1 | 0 | 0 | 0 | Y | 39 | - | - |
| 9 | c.1315C>T | p.Arg439Ter | | 1 | 0 | 0 | 0 | Y | 40 | - | - |
| 13 | c.1871C>A | p.Ser624Ter | | 1 | 0 | 0 | 0 | Y | 43 | - | - |
| 13 | c.1888dupA | p.Thr630AsnfsTer9 | | 1 | | 1 | | Y | 24.7 | - | - |
| 14 | c.2010dupT | p.Glu671Ter | | 4 | | 1 | | Y | 29.3 | - | - |
| 14 | c.2038_2039dupTT | p.Leu680PhefsTer9 | | 1 | | 0 | | N | 16.54 | - | - |
| 14 | c.2050_2051delTG | p.Cys684ProfsTer32 | | 1 | | 0 | | Y | 23.7 | - | - |
| 19 | c.2684_2687delCCAT | p.Ser895Ter | | 1 | | 1 | | Y | 35 | - | - |
| 19 | c.2715dupT | p.Glu906Ter | | 1 | | 0 | | Y | 16.22 | - | - |
| 19 | c.2765T>G | p.Leu922Ter | | 1 | 0 | 0 | 0 | Y | 37 | - | - |
| | c.2906-2A>C | | | 4 | | 2 | | N/D | 15.83 | - | - |
| 20 | c.2990_2993delCAAA | p.Thr997ArgfsTer61 | | 1 | | 0 | | N/D | 34 | - | - |
| 20 | c.2992_2993delAA | p.Lys998GlufsTer3 | | 1 | | 4 | | Y | 38 | - | - |
| 20 | c.3401delC | p.Pro1134LeufsTer16 | | 2 | | 1 | | N/D | 41 | - | - |
| 20 | c.3525dupT | p.Ile1176TyrfsTer13 | | 1 | | 0 | | Y | 16.33 | - | - |
| 20 | c.3651G>A | p.Trp1217Ter | | 0 | 0 | 1 | 0 | Y | 38 | - | - |
| In-frame deletion | | | | | | | | | | | |
| 20 | c.3374_3376delCAG | p.Ala1125del | | 0 | | 2 | | N/D | 16.11 | | |

| Missense Variants | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | c.139C>G | p.Pro47Ala | rs28903098 | 13 | 0 | 5 | 0 | N/D | 14.21 | prob. damaging | tolerated |
| 3 | c.169C>T | p.Leu57Phe | | 1 | 0 | 0 | 0 | N/D | 12.46 | prob. damaging | deleterious |
| 3 | c.205G>A | p.Gly69Arg | rs372581879 | 0 | 0 | 1 | 0 | N/D | 15.08 | benign | tolerated |
| 4 | c.293A>G | p.Asn98Ser | | 0 | 0 | 1 | 0 | N/D | 0.013 | benign | tolerated |
| 4 | c.316C>T | p.Arg106Cys | | 1 | 0 | 1 | 0 | N/D | 11.58 | benign | tolerated |
| 4 | c.317G>A | p.Arg106His | rs143615668 | 1 | 0 | 0 | 0 | N/D | 8.081 | benign | tolerated |
| 5 | c.413T>C | p.Leu138Ser | | 1 | 0 | 2 | 0 | Y | 23.1 | poss. damaging | deleterious |
| 5 | c.415T>G | p.Ser139Ala | rs202072866 | 1 | 0 | 0 | 0 | Y | 23.9 | poss. damaging | tolerated |
| 5 | c.430G>A | p.Ala144Thr | rs116952709 | 3 | 0 | 1 | 0 | N/D | 18.56 | poss. damaging | tolerated |
| 6 | c.517C>T | p.Arg173Cys | rs4988345 | 121 | 22 | 45 | 6 | Y | 20.8 | Benign | deleterious |
| 6 | c.538G>C | p.Val180Leu | | 0 | 0 | 1 | 0 | N/D | 11.10 | Benign | tolerated |
| 6 | c.543C>A | p.His181Gln | | 1 | 0 | 0 | 0 | N/D | 0.052 | Benign | tolerated |
| 6 | c.550G>T | p.Asp184Tyr | rs201047375 | 6 | 0 | 2 | 0 | N/D | 12.95 | prob. damaging | deleterious |
| 6 | c.577G>A | p.Val193Ile | rs4988346 | 111 | 18 | 42 | 5 | N/D | 0.342 | Benign | tolerated |
| 6 | c.590C>A | p.Ser197Tyr | | 0 | 1 | 1 | 0 | N/D | 9.206 | poss. damaging | tolerated |
| 6 | c.590C>T | p.Ser197Phe | | 0 | 1 | 0 | 0 | N/D | 10.27 | Benign | tolerated |
| 7 | c.668A>G | p.Gln223Arg | | 2 | 0 | 0 | 0 | N/D | 10.71 | Benign | tolerated |
| 7 | c.679C>G | p.Gln227Glu | rs45459799 | 2 | 0 | 1 | 0 | N/D | 0.156 | Benign | tolerated |
| 7 | c.751C>T | p.Arg251Cys | | 1 | 0 | 0 | 0 | Y | 21.6 | prob. damaging | deleterious |
| 7 | c.764A>G | p.Gln255Arg | | 1 | 0 | 0 | 0 | N/D | 19.31 | prob. damaging | deleterious |
| 7 | c.778A>G | p.Thr260Ala | rs138743097 | 3 | 0 | 2 | 0 | N/D | 11.43 | benign | tolerated |
| 7 | c.790C>T | p.Arg264Trp | rs28997569 | 27 | 0 | 19 | 0 | Y | 16.72 | prob. damaging | deleterious |
| 7 | c.797C>T | p.Thr266Met | | 0 | 0 | 1 | 0 | Y | 21.4 | prob. damaging | deleterious |
| 7 | c.841C>A | p.His281Asn | | 1 | 0 | 0 | 0 | N/D | 17.64 | poss. damaging | tolerated |
| 7 | c.856C>T | p.Pro286Ser | | 0 | 0 | 1 | 0 | N/D | 16.49 | prob. damaging | tolerated |
| 7 | c.868G>A | p.Gly290Ser | rs145601931 | 1 | 0 | 0 | 0 | N/D | 5.895 | benign | tolerated |
| 7 | c.888G>C | p.Glu296Asp | | 0 | 0 | 1 | 0 | N/D | 11.59 | poss. damaging | tolerated |
| 7 | c.890A>G | p.Lys297Arg | rs28997570 | 49 | 0 | 25 | 0 | N/D | 8.669 | benign | tolerated |
| 8 | c.931T>C | p.Tyr311His | | 1 | 0 | 0 | 0 | N/D | 9.222 | benign | tolerated |
| 8 | c.941A>G | p.His314Arg | rs112076926 | 2 | 0 | 0 | 0 | N/D | 19.09 | prob. damaging | tolerated |
| 8 | c.1000G>A | p.Ala334Thr | | 2 | 0 | 0 | 0 | Y | 33 | prob. damaging | deleterious |
| 8 | c.1012G>A | p.Glu338Lys | | 1 | 0 | 0 | 0 | Y | 33 | prob. damaging | deleterious |
| 8 | c.1021G>A | p.Val341Ile | | 1 | 0 | 0 | 0 | N/D | 19.25 | benign | deleterious |
| 8 | c.1045G>C | p.Ala349Pro | rs149364097 | 1 | 0 | 1 | 0 | Y | 17.53 | poss. damaging | deleterious |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | c.1054T>C | p.Tyr352His | | 1 | 0 | 1 | 0 | Y | 18.42 | poss. damaging | deleterious |
| 8 | c.1055A>G | p.Tyr352Cys | - | 1 | 0 | 0 | 0 | Y | 20.8 | prob. damaging | deleterious |
| 8 | c.1105T>C | p.Tyr369His | - | 1 | 0 | 0 | 0 | Y | 23.0 | prob. damaging | deleterious |
| 8 | c.1114C>T | p.Leu372Phe | - | 2 | 0 | 0 | 0 | Y | 21.4 | prob. damaging | deleterious |
| 8 | c.1124C>T | p.Ala375Val | - | 1 | 0 | 0 | 0 | N/D | 19.22 | benign | deleterious |
| 9 | c.1207C>T | p.Arg403Trp | rs369631413 | 0 | 0 | 1 | 0 | Y | 19.28 | prob. damaging | deleterious |
| 9 | c.1216G>T | p.Ala406Ser | - | 1 | 0 | 0 | 0 | N/D | 20.6 | poss. damaging | deleterious |
| 9 | c.1255C>T | p.Arg419Trp | rs150624408 | 4 | 0 | 2 | 0 | Y | 20.6 | prob. damaging | deleterious |
| 9 | c.1286A>C | p.Asn429Thr | - | 0 | 0 | 1 | 0 | Y | 19.17 | prob. damaging | tolerated |
| 9 | c.1292G>A | p.Arg431Lys | - | 1 | 0 | 0 | 0 | N/D | 21.5 | poss. damaging | tolerated |
| 12 | c.1637A>G | p.Asp546Gly | - | 1 | 0 | 1 | 0 | N/D | 18.40 | benign | deleterious |
| 12 | c.1652C>T | p.Ala551Val | rs375246789 | 2 | 0 | 0 | 0 | N/D | 23.7 | prob. damaging | tolerated |
| 12 | c.1655T>C | p.Ile552Thr | rs369340666 | 1 | 0 | 1 | 0 | Y | 22.5 | poss. damaging | deleterious |
| 12 | c.1660C>G | p.Gln554Glu | - | 1 | 0 | 0 | 0 | N/D | 16.31 | poss. damaging | deleterious |
| 12 | c.1676C>G | p.Thr559Arg | - | 1 | 0 | 0 | 0 | N/D | 13.04 | poss. damaging | tolerated |
| 12 | c.1684A>G | p.Ile562Val | rs45533636 | 0 | 0 | 1 | 0 | N/D | 3.237 | benign | tolerated |
| 12 | c.1704T>G | p.Asn568Lys | - | 2 | 0 | 0 | 0 | N/D | 5.134 | benign | tolerated |
| 12 | c.1735C>T | p.Arg579Cys | rs28997571 | 2 | 0 | 1 | 0 | N/D | 19.23 | benign | deleterious |
| 12 | c.1759C>G | p.His587Asp | - | 0 | 0 | 2 | 0 | N/D | 13.68 | benign | tolerated |
| 12 | c.1771T>A | p.Phe591Ile | - | 2 | 0 | 0 | 0 | N/D | 26.0 | prob. damaging | tolerated |
| 13 | c.1796C>T | p.Ala599Val | - | 1 | 0 | 0 | 0 | N/D | 21.8 | prob. damaging | tolerated |
| 13 | c.1804G>T | p.Asp602Tyr | - | 1 | 0 | 0 | 0 | Y | 22.0 | prob. damaging | deleterious |
| 13 | c.1871C>T | p.Ser624Leu | | 1 | 0 | 0 | 0 | Y | 32 | prob. damaging | deleterious |
| 13 | c.1899C>G | p.Ile633Met | rs28997572 | 3 | 0 | 1 | 0 | Y | 15.89 | prob. damaging | deleterious |
| 14 | c.1964C>G | p.Pro655Arg | - | 2 | 0 | 0 | 0 | Y | 26.6 | prob. damaging | deleterious |
| 14 | c.2071A>C | p.Ile691Leu | - | 1 | 0 | 0 | 0 | N/D | 14.59 | poss. damaging | deleterious |
| 14 | c.2087C>T | p.Pro696Leu | rs147755155 | 6 | 0 | 0 | 0 | N/D | 15.37 | prob. damaging | deleterious |
| 15 | c.2167G>A | p.Val723Ile | rs145616741 | 1 | 0 | 0 | 0 | N/D | 14.99 | prob. damaging | tolerated |
| 15 | c.2172T>G | p.Ile724Met | - | 1 | 0 | 0 | 0 | N/D | 11.67 | prob. damaging | tolerated |
| 15 | c.2220G>T | p.Gln740His | rs45589637 | 20 | 0 | 6 | 0 | N/D | 10.44 | poss. damaging | deleterious |
| 15 | c.2221G>T | p.Val741Leu | - | 1 | 0 | 1 | 0 | N/D | 11.22 | benign | tolerated |
| 15 | c.2233G>A | p.Ala745Thr | | 2 | 0 | 0 | 0 | N/D | 15.00 | prob. damaging | tolerated |
| 15 | c.2236A>G | p.Ile746Val | rs111536363 | 2 | 0 | 0 | 0 | N/D | 11.46 | benign | tolerated |
| 16 | c.2285G>A | p.Arg762His | rs200960251 | 1 | 0 | 0 | 0 | N/D | 15.93 | prob. damaging | deleterious |
| 16 | c.2330G>A | p.Arg777His | | 2 | 0 | 0 | 0 | N/D | 16.54 | prob. damaging | deleterious |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 | c.2344A>G | p.Ile782Val | rs142806416 | 3 | 0 | 1 | 0 | N/D | 11.36 | benign | tolerated |
| 17 | c.2440C>T | p.Arg814Cys | rs201869624 | 1 | 0 | 0 | 0 | Y | 19.51 | prob. damaging | deleterious |
| 17 | c.2441G>A | p.Arg814His | rs45468199 | 2 | 0 | 0 | 0 | N/D | 15.43 | benign | tolerated |
| 18 | c.2542C>T | p.Arg848Cys | rs45572934 | 0 | 0 | 1 | 0 | Y | 23.6 | prob. damaging | deleterious |
| 18 | c.2561G>A | p.Ser854Asn | - | 1 | 0 | 0 | 0 | N/D | 1.534 | benign | tolerated |
| 18 | c.2564G>A | p.Arg855His | rs200894063 | 1 | 0 | 0 | 0 | Y | 19.48 | poss. damaging | deleterious |
| 19 | c.2623G>C | p.Glu875Gln | - | 0 | 0 | 1 | 0 | N/D | 12.82 | poss. damaging | tolerated |
| 19 | c.2666A>G | p.Gln889Arg | - | 1 | 0 | 0 | 0 | N/D | 10.85 | benign | tolerated |
| 19 | c.2717A>G | p.Glu906Gly | - | 0 | 0 | 1 | 0 | N/D | 5.913 | benign | tolerated |
| 19 | c.2723C>T | p.Thr908Ile | - | 1 | 0 | 0 | 0 | N/D | 1.648 | benign | tolerated |
| 19 | c.2755T>C | p.Ser919Pro | rs4986764 | 6348 | 4816 | 2474 | 1942 | N/D | 4.321 | benign | tolerated |
| 19 | c.2863A>C | p.Asn955His | - | 1 | 0 | 0 | 0 | N/D | 7.268 | benign | tolerated |
| 20 | c.2935A>G | p.Lys979Glu | - | 3 | 0 | 0 | 0 | N/D | 6.269 | benign | tolerated |
| 20 | c.2948T>A | p.Ile983Asn | - | 0 | 0 | 1 | 0 | N/D | 8.314 | benign | tolerated |
| 20 | c.3050C>T | p.Pro1017Leu | - | 3 | 0 | 2 | 0 | N/D | 0.119 | benign | tolerated |
| 20 | c.3064G>A | p.Glu1022Lys | - | 4 | 0 | 7 | 0 | N/D | 1.051 | benign | tolerated |
| 20 | c.3103C>T | p.Arg1035Cys | rs45437094 | 1 | 0 | 0 | 0 | N/D | 7.694 | benign | deleterious |
| 20 | c.3178G>A | p.Val1060Ile | rs149016505 | 1 | 0 | 0 | 0 | N/D | 6.966 | benign | tolerated |
| 20 | c.3236T>C | p.Ile1079Thr | rs150813402 | 1 | 0 | 0 | 0 | N/D | 3.250 | benign | tolerated |
| 20 | c.3275C>T | p.Pro1092Leu | - | 1 | 0 | 0 | 0 | N/D | 0.003 | benign | tolerated |
| 20 | c.3290A>C | p.Glu1097Ala | - | 1 | 0 | 1 | 0 | N/D | 10.58 | benign | deleterious |
| 20 | c.3378A>C | p.Glu1126Asp | rs145855459 | 3 | 0 | 0 | 0 | Y | 13.91 | benign | tolerated |
| 20 | c.3444C>A | p.Asp1148Glu | rs28997573 | 7 | 0 | 10 | 0 | Y | 0.005 | benign | tolerated |
| 20 | c.3448G>C | p.Ala1150Pro | - | 1 | 0 | 0 | 0 | N/D | 5.508 | benign | tolerated |
| 20 | c.3487G>A | p.Asp1163Asn | - | 1 | 0 | 0 | 0 | Y | 0.021 | benign | tolerated |
| 20 | c.3493A>C | p.Ile1165Leu | - | 1 | 0 | 0 | 0 | N/D | 3.169 | benign | tolerated |
| 20 | c.3507C>A | p.Asp1169Glu | rs375741316 | 2 | 0 | 0 | 0 | N/D | 5.323 | benign | tolerated |
| 20 | c.3571A>G | p.Ile1191Val | - | 1 | 0 | 0 | 0 | N/D | 0.234 | benign | tolerated |
| 20 | c.3621T>A | p.Asp1207Glu | - | 1 | 0 | 0 | 0 | N/D | 8.997 | benign | tolerated |

[1]N/D = no validation attempted.

**Supplementary Table 2.** *BRIP1* variants called in BCFR

| Exon | Nucleotide change | Protein change | dbSNP ID | CASES (n=1,313) | CONTROLS (n=1,123) | Validated with Sanger? | CADD | PolyPhen | SIFT |
|---|---|---|---|---|---|---|---|---|---|
| Truncating Variants | | | | | | | | | |
| 14 | c.2008insT | p.Glu671Ter | - | 0 | 1 | Yes | 32 | | |
| 15 | c.2108delAinsTCC | p.Lys703fs | | 1 | 0 | Yes | 16.77 | | |
| 17 | c.2392C>T | **p.Arg798Ter** | rs137852986 | 2 | 1 | Yes | 39 | | |
| 20 | c.2992del4, c.2992_2995del | p.Lys998fs (Lys998Glufs*60) | | 1 | 0 | Yes | 36 | | |
| Missense Variants | | | | | | | | | |
| 2 | c.10A>G | p.Met4Val | rs45512093 | 1 | 0 | Yes | 1.235 | benign | tolerated |
| 3 | c.139C>G | p.Pro47Ala | rs28903098 | 0 | 4 | Yes | 14.21 | prob. damaging | deleterious |
| 4 | c.254C>T | p.Ser85Leu | | 1 | 0 | Yes | 13.95 | poss. damaging | tolerated |
| 4 | c.316C>A | p.Ar106Ser | | 0 | 1 | Yes | 5.990 | benign | tolerated |
| 5 | c.430G>A | p.Ala144Thr | | 8 | 1 | | 18.56 | prob. damaging | tolerated |
| 6 | c.587A>G | p.Asn196Ser | | 3 | 1 | Yes | 0.036 | benign | tolerated |
| 6 | c.590C>T | p.Ser197Phe | | 1 | 0 | Yes | 10.27 | prob. damaging | tolerated |
| 7 | c.689C>T | p.Ser230Leu | | 0 | 1 | Yes | 3.213 | benign | tolerated |
| 7 | c.790C>T | p.Arg264Trp | rs28997569 | 0 | 1 | Yes | 16.72 | prob. damaging | deleterious |
| 7 | c.890A>G | p.Lys297Arg | rs28997570 | 3 | 9 | Yes | 8.669 | poss. damaging | tolerated |
| 8 | c.975A>T | p.Leu325Phe | | 0 | 1 | Yes | 12.60 | benign | deleterious |
| 10 | c.1376G>C | p.Arg459Thr | | 0 | 1 | Yes | 14.03 | benign | tolerated |
| 11 | c.1499A>G | p.Lys500Arg | | 1 | 0 | Yes | 14.65 | prob. damaging | tolerated |
| 12 | c.1735C>T | p.Arg579Cys | rs28997571 | 0 | 1 | Yes | 19.23 | benign | tolerated |
| 15 | c.2220G>T | p.Gln740His | rs45589637 | 0 | 2 | Yes | 10.44 | prob. damaging | tolerated |
| 15 | c.2236A>G | p.Ile746Val | rs111536363 | 1 | 1 | Yes | 11.46 | benign | tolerated |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 15 | c.2254A>C | p.Lys752Gln | | 1 | 0 | Yes | 12.04 | prob. damaging | tolerated |
| 16 | c.2344A>G | p.Ile782Val | rs142806416 | 1 | 0 | Yes | 11.36 | benign | tolerated |
| 19 | c.2594G>A | p.Arg865Gln | - | 0 | 1 | Yes | 28.5 | prob. damaging | deleterious |
| 19 | c.2830C>G | p.Gln944Glu | rs140233356 | 1 | 0 | Yes | 9.684 | poss. damaging | tolerated |
| 20 | c.2915T>G | p.Val972Gly | - | 1 | 0 | Yes | 3.520 | benign | tolerated |
| 20 | c.2948T>A | p.Ile983Asn | - | 1 | 0 | Yes | 8.314 | benign | tolerated |
| 20 | c.3038C>T | p.Thr1013Ile | - | 0 | 1 | Yes | 10.14 | poss. damaging | tolerated |
| 20 | c.3392A>C | p.Tyr1131Ser | - | 0 | 1 | Yes | 13.23 | prob. damaging | tolerated |
| 20 | c.3464G>A | p.Gly1155Glu | rs45603843 | 1 | 0 | Yes | 0.052 | benign | tolerated |
| 20 | c.3559G>A | p.Ala1187Thr | rs367610893 | 1 | 0 | Yes | 7.277 | benign | tolerated |

**Supplementary Table 3.** *BRIP1* variants called in the PeterMac Study

| Exon | Nucleotide change | Protein change | dbSNP ID | CASES (n=1853) | CONTROLS (n=2001) | Validated with Sanger? | CADD | PolyPhen | SIFT |
|---|---|---|---|---|---|---|---|---|---|
| Truncating Variants | | | | | | | | | |
| | c.1850A>T | p.Leu617Ter | | 0 | 1 | yes | 43 | | |
| 13 | c.1871C>A | p.Ser624Ter | | 1 | 0 | yes | 43 | | |
| 17 | c.2392C>T | **p.Arg798Ter** | rs137852986 | 4 | 0 | yes | 39 | | |
| 20 | c.2990_2993delCAAA | p.Thr997ArgfsTer61 | | 0 | 2 | yes | 34 | | |
| 20 | c.2992_2993delAA | p.Lys998GlufsTer3 | | 1 | 1 | yes | 38 | | |
| Missense Variants | | | | | | | | | |
| 3 | c.139C>G | p.Pro47Ala | rs28903098 | 2 | 0 | N/A | 14.21 | prob. damaging | deleterious |
| 4 | c.347C>G | p.Ser116Cys | . | 0 | 1 | yes | 15.54 | prob. damaging | deleterious |
| 5 | c.430G>A | p.Ala144Thr | rs116952709 | 2 | 0 | N/A | 18.56 | prob. damaging | tolerated |
| 6 | c.517C>T | p.Arg173Cys | rs4988345 | 33 | 26 | N/A | 20.80 | prob. damaging | deleterious |
| 6 | c.550G>T | p.Asp184Tyr | rs201047375 | 1 | 0 | N/A | 12.95 | prob. damaging | deleterious |
| 7 | c.790C>T | p.Arg264Trp | rs28997569 | 2 | 4 | N/A | 16.72 | prob. damaging | deleterious |
| 8 | c.1000G>T | p.Ala334Ser | . | 1 | 0 | yes | 20.90 | benign | deleterious |
| 8 | c.1105T>C | p.Tyr369His | . | 0 | 1 | yes | 23.00 | prob. damaging | deleterious |
| 9 | c.1168G>A | p.Val390Ile | . | 0 | 1 | yes | 12.02 | benign | tolerated |
| 9 | c.1255C>T | p.Arg419Trp | rs150624408 | 2 | 0 | N/A | 20.60 | prob. damaging | deleterious |
| 9 | c.1286A>C | p.Asn429Thr | . | 0 | 1 | yes | 19.17 | prob. damaging | tolerated |
| 10 | c.1433A>G | p.His478Arg | rs45501097 | 1 | 0 | yes | 11.00 | benign | tolerated |
| 10 | c.1441G>T | p.Gly481Cys | . | 1 | 0 | yes | 19.52 | prob. damaging | deleterious |
| 10 | c.1444A>G | p.Ile482Val | rs142744352 | 0 | 1 | N/A | 17.96 | prob. damaging | tolerated |
| 11 | c.1610T>A | p.Leu537His | . | 1 | 0 | yes | 20.50 | prob. damaging | deleterious |
| 13 | c.1798T>C | p.Phe600Leu | . | 0 | 1 | yes | 24.70 | prob. damaging | deleterious |
| 14 | c.2056A>G | p.Thr686Ala | . | 1 | 0 | yes | 12.95 | benign | tolerated |
| 14 | c.2087C>T | p.Pro696Leu | rs147755155 | 0 | 1 | N/A | 15.37 | prob. damaging | deleterious |
| 15 | c.2220G>T | p.Gln740His | rs45589637 | 2 | 3 | N/A | 10.44 | poss. damaging | deleterious |
| 16 | c.2330G>A | p.Arg777His | . | 1 | 0 | yes | 16.54 | prob. damaging | deleterious |
| 17 | c.2390A>G | p.Lys797Arg | . | 1 | 0 | yes | 19.53 | prob. damaging | deleterious |
| 17 | c.2411A>G | p.His804Arg | . | 1 | 0 | yes | 20.80 | prob. damaging | tolerated |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 17 | c.2440C>T | p.Arg814Cys | rs201869624 | 1 | 1 | yes | 19.51 | prob. damaging | deleterious |
| 17 | c.2467A>G | p.Arg823Gly | . | 1 | 0 | yes | 20.80 | prob. damaging | deleterious |
| 19 | c.2582C>G | p.Ser861Cys | . | 1 | 0 | N/A | 21.50 | prob. damaging | deleterious |
| 20 | c.3371A>G | p.Glu1124Gly | . | 1 | 0 | N/A | 15.13 | benign | deleterious |
| 21 | c.3505G>T | p.Asp1169Tyr | . | 1 | 0 | yes | 11.40 | poss. damaging | deleterious |

N/A – not applicable because no validation done for known variants

**Supplementary Table 4.** Variants across the *BRIP1* region used to define haplotypes.

| Marker | Name | Position | Minor Allele Frequency | Allele1 | Allele2 |
|---|---|---|---|---|---|
| 1 | rs2188728 | 59676854 | 0.423 | C | A |
| 2 | rs1974491 | 59724501 | 0.350 | A | G |
| 3 | rs7222964 | 59726936 | 0.117 | A | G |
| 4 | rs1858990 | 59735821 | 0.164 | C | A |
| 5 | rs2106664 | 59736794 | 0.468 | A | G |
| 6 | rs7219555 | 59740122 | 0.293 | A | C |
| 7 | rs12603617 | 59745599 | 0.241 | G | A |
| 8 | rs17533380 | 59746759 | 0.239 | G | A |
| 9 | rs4986764 | 59763347 | 0.420 | G | A |
| 10 | rs4986765 | 59763465 | 0.343 | G | A |
| 11 | rs6504063 | 59767501 | 0.421 | A | G |
| 12 | rs11871134 | 59775949 | 0.034 | A | G |
| 13 | rs7214703 | 59785060 | 0.340 | G | A |
| 14 | rs9901948 | 59793232 | 0.0001 | A | G |
| **15** | **p.Arg798Ter** | **59793412** | **0.0002** | **G** | **A** |
| 16 | rs16945572 | 59800001 | 0.079 | A | G |
| 17 | rs6504066 | 59802506 | 0.239 | A | G |
| 18 | rs2159451 | 59812748 | 0.338 | G | A |
| 19 | rs11652980 | 59817082 | 0.050 | G | C |
| 20 | rs2159450 | 59826625 | 0.247 | A | C |
| 21 | rs2109255 | 59826765 | 0.247 | A | G |
| 22 | rs2191247 | 59828023 | 0.248 | A | C |
| 23 | rs2191249 | 59835864 | 0.247 | C | A |
| 24 | rs9902995 | 59841185 | 0.247 | A | G |
| 25 | rs7212172 | 59869081 | 0.246 | A | G |
| 26 | rs1468577 | 59870617 | 0.248 | G | A |
| 27 | rs2191248 | 59876352 | 0.348 | G | A |
| 28 | rs16945638 | 59886310 | 0.078 | A | G |

| | | | | | |
|---|---|---|---|---|---|
| 29 | rs16945643 | 59893990 | 0.078 | A | G |
| 30 | rs7215784 | 59894708 | 0.242 | G | A |
| 31 | rs12453935 | 59897455 | 0.197 | G | A |
| 32 | rs6504074 | 59899790 | 0.261 | C | A |
| 33 | rs16945665 | 59911493 | 0.038 | G | A |
| 34 | rs7222876 | 59911541 | 0.001 | G | A |
| 35 | rs2378908 | 59911765 | 0.138 | G | A |
| 36 | rs7223243 | 59911799 | 0.430 | G | A |

## Supplementary Table 5. Published studies of *BRIP1* mutation screening in breast/ovarian cancer families

| Authors/Title | Source country / Ethnicity | Study design | Mutation detection method | Selection of cases | Number of cases screened for BRIP1 mutations | Number of heterozygous cases | Number of controls screened for BRIP1 mutations | Number of heterozygous controls | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Rutter et al Hum Mutat. 2003 Aug;22(2):121-8. | USA | Candidate gene approach | DHPLC and Sanger sequencing | HBOC families + early onset BC cases (<35 y.o) | 79 | 8 | 30 | 4 | |
| Lewis et al Breast Cancer Res. 2005;7(6):R1005-16. | Australian | Candidate gene approach; mutation screening of familial BC cases and genotyping of 2 specific missense p.P47A and p.M299I. | DHPLC and Sanger sequencing | Multiple-case BC families (KConFab) | 75 families screened for entire coding sequence + 253 index cases screened for exons 3 and 7 | 1 frameshift, 4 missense | (genotyped only for variants found in cases) | 1 missense | |
| Vahteristo et al BMC Cancer. 2006 Jan 24;6:19. | Finnish | Candidate gene approach; mutation screening of familial BC cases and genotyping of 2 specific missense p.Val93Ile and the SNP ser919Pro. | CSGE | BC families negative for *BRCA1/2* | 43 | 1 rare missense (Val93Ile) | 183 (only genotyped for p.Val93Ile) | 0 | p.Val93Ile identified in 1 family then genotyped in 346 additional BC cases and in 183 controls |
| Seal et al Nat Genet. 2006 Nov;38(11):1239-41. | UK | Candidate gene approach with focus on LOF variants; case-control mutation screening study | CSGE | HBOC families | 1,212 | 9 | 2,081 | 2 | RR 2.0 (95%CI 1.2-3.2) |
| Guénard et al . J Hum Genet. 2008;53(7):579-91. | French Canadian | Candidate gene approach; likely deleterious variants subsequently genotyped in 73 controls | Sanger sequencing | HBOC families negative for *BRCA1/2* | 96 | 0 | 0 | N/A | |
| De Nicolo et al Clin Cancer Res. 2008 Jul 15;14(14):4672-80. | Italian | Candidate gene approach in BC families | Sanger sequencing | HBOC families negative for *BRCA1/2* and *CHEK2* 1100delC | 49 | 1 LOF | 0 | N/A | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Kurian et al J Clin Oncol. 2014 Jul 1;32(19):2001-9. | USA | Multi-gene panel testing of 42 genes | Agilent SureSelect, MiSeq | HBOC cases (NCCN guidelines) | 198 HBOC cases including 174 BC cases, of whom 141 tested negative for *BRCA1/2* | 0 LOF, 8 missense | 0 | N/A | |
| Castéra et al Eur J Hum Genet. 2014 Nov;22(11):1305-13. | French | Multi-gene panel testing ; 3 different capture design (16 genes, 21 genes, 27 genes) , all including *BRIP1* | Agilent SureSelect, Illumina GAIIx | Consecutive HBOC cases referred to Cancer Genetics Clinics for *BRCA1/2* testing | 708 | 0 | 0 | N/A | |
| Li et al J Med Genet. 2015 Nov 3. pii: jmedgenet-2015-103452. doi: 10.1136/jmedgenet-2015-103452. | Australian | Multi-gene panel testing of 17 genes; potentially relevant variants genotyped in other family members. | Agilent Target Enrichment kit, Axeq technologies | 660 cases from multiple-case BC families (KConFab) | 660 | 9 LOF, 7 missense | - | - | RR 0.47 (95%CI 0.15-1.18) ; HR>1.56 excluded |
| Aloraifi et al **Cancer Genet.** 2015 Sep;208(9):455-63. | Multi-ethnic: 10 mutation screening studies on BRIP1 ; only 2 studies detected LOF variants. | Meta-analysis on 6 genes performed on studies with high-risk BC cases with matched controls | DHPLC, CSGE, Sanger sequencing | Early onset (<50 yo) or familial BC cases | 1,287 | 10 | 2,174 | 2 | |
| Hirotsu et al Mol Genet Genomic Med. 2015 Sep;3(5):459-66. | Japanese | Multi-gene panel testing of 25 DNA repair genes | Ion AmpliSeq, Ion Proton, Life Technologies | 155 breast or ovarian cancer cases (94% with family history of BC), including 144 cases negative for *BRCA1/2* | 144 | 0 | 0 | N/A | |
| Rajkumar et al Asian Pac J Cancer Prev. 2015;16(13):5211-7. | Indian | Multi-gene panel testing of 30 genes | TruSeq Enrichment kit, Illumina HiScan SQ | Family history of BC or early onset cases (<35 yo) | 91 | 0 | 0 | N/A | |
| Lincoln et al **.** J Mol Diagn. 2015 Sep;17(5):533-44. | USA | Multi-gene panel testing of 29 genes | Agilent SureSelect, MiSeq or HISeq2500 | HBOC cases (NCCN guidelines) | 735 | 1 | 0 | N/A | |
| Aloraifiet al FEBS J. 2015 Sep;282(17):3424-37. | Irish | Multi-gene panel testing of 312 genes. | TruSeq Enrichment kit, Illumina HiSeq | Familal BC cases negative for *BRCA1/2* | 104 | 0 | 101 | 0 | |
| Maxwell et al Genet Med. 2015 Aug;17(8):630-8. | USA | Multi-gene panel testing of 22 genes | Agilent SureSelect, sequencer? | *BRCA1/2* negative patients with early onset BC (<40 yo) | 278 | 1 | 0 | N/A | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cybulski Cet al Clin Genet. 2015 Oct;88(4):366-70. | Polish | Whole exome sequencing and evaluation of 12 genes | Agilent SureSelect human exome kit v4, HiSeq2000 | Familial cases negative for *BRCA1*, *CHEK2* and *NBS1* Polish founder mutation | 144 | 1 | 0 | N/A |
| Tung et al Cancer. 2015 Jan 1;121(1):25-33. | Multi-ethnic, Ashkenazi pop. | Multi-gene panel testing of 25 genes | RainDance Thunderstorm emulsion PCR, HiSeq2500 | Negative *BRCA1/2* cases tested at Myriad | 1781 (multi-ethnic pop) + 377 Ashkenazi Jews | 7 | 0 | N/A |
| Couch et al J Clin Oncol. 2015 Feb 1;33(4):304-11. | 12 studies, population from USA, Germany,UK, Finland, Greece | Multi-gene panel testing of 17 genes | Agilent custom capture, HiSeq | TNBC cases unselected for family history of BC or OC | 1,824 | 8 | 0 | N/A |