**SUPPLEMENTARY DATA**

**Supplementary Table 1**: Targeted Sequencing Panel

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Transcript** | **Length in bp** | **Total amplicons in gene** | **Exons** | **Amplicons** | **Coverage** |
| *CDH1* | NM\_004360 | 2,649 | 36 | 16 | 36 | Full |
| *BRCA2* | NM\_000059 | 10,257 | 126 | 28 | 126 | Full |
| *BRCA1* | NM\_007300 | 5,552 | 68 | 24 | 68 | Full |
| *CHEK2* | NM\_007194 | 1,761 | 28 | 22 | 28 | Full |
| *PALB2* | NM\_024675 | 3,561 | 48 | 15 | 48 | Full |
| *TP53* | NM\_000546.4 | 1,146 | 15 | 10 | 15 | Full |

**Supplementary Table 2**: Definition of variants

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|  |  |  |
| --- | --- | --- |
| **Variant class** | **Variant type** | **Description** |
| Missense/ non-synonymous | Protein altering | A single nucleotide substitution that leads to an amino-acid substitution |
| Stop-gain | Protein truncating | A single nucleotide substitution that leads to the introduction of a premature stop codon |
| Stop-loss | Protein truncating | A single nucleotide substitution that leads to the loss of the wild type stop codon |
| Frameshift indel | Protein truncating | An insertion or deletion of a number of nucleotides that leads to a frame-shift of the amino-acid sequence |
| Non-frameshift indel | Protein altering | An insertion or deletion of a number of nucleotides that leads to the addition or deletion of a number of amino-acids |
| Splicing | Protein truncating | A single nucleotide substitution in the essential splice site 1 or 2 nucleotides adjacent to the splice site |
| Synonymous | Silent | A single nucleotide substitution that leads to the same amino-acid being encoded |

**Supplementary Table 3**: Age of controls and cases by histological subtype.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Pathology** | **Number of samples** | **Bilateral Cancer**  **(includes any subtype of invasive or in situ disease in contralateral breast)** | **Bilateral**  **Lobular**  **Cancer**  **(pathology of contralateral disease)** | **Median Age**  **(Interquartile range)** |
| ILC with concurrent LCIS | 1102 | 64 | 26 (pure LCIS)  5 (ILC only)  9 (ILC+LCIS) | 51 (47-56) |
| ILC no LCIS | 317 | 16 | 6 (ILC no LCIS)  1 (pure LCIS) | 53 (47-57) |
| ILC unknown LCIS | 15 | 0 | 0 | 52 (49-55) |
| Pure LCIS | 368 | 28 | 14 (pure LCIS) | 51 (48-53) |
| Controls | 1,611 | NA | NA | 52 (47-59) |

**Supplementary Table 4**: Amplicons that failed to amplify consistently

|  |  |  |
| --- | --- | --- |
| **Amplicon ID** | **Exonic region** | **% of samples with <10 reads for 90% of the amplicon** |
| BRCA1\_t6\_5 | chr17:41251782-41251907 | 10.2% |
| CDH1\_t1\_1 | chr16:68771309-68771376 | 30.3% |
| CDH1\_t12\_1 | chr16:68855894-68856138 | 3.6% |
| CHEK2\_t1\_1 | chr22:29130381-29130719 | 18.3% |
| CHEK2\_t1\_3 | chr22:29121221-29121365 | 0.2% |
| PALB2\_t13\_3 | chr16:23614770-23615000 | 0.1% |
| PALB2\_t4\_21 | chr16:23646173-23647665 | 0.2% |

**Supplementary Table 6**: BRCA2 mutations in cases (\* = variants in last exon)

|  |  |  |  |
| --- | --- | --- | --- |
| **Type\_of mutation** | **Details** | **ID** | **Pathology of cancer** |
| frameshift deletion | BRCA2:NM\_000059:exon2:c.26delC:p.P9fs, | . | ILC no information on LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon2:c.26delC:p.P9fs, | . | ILC+LCIS |
| frameshift insertion | BRCA2:NM\_000059:exon2:c.36dupT:p.F12fs, | . | ILC+LCIS |
| splicing | BRCA2:NM\_000059:exon7:c.517-2A>G | rs81002858 (6 in Clinvar) | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon8:c.658\_659del:p.V220fs, | . | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon8:c.662\_663del:p.F221fs, | . | ILC+LCIS |
| splicing | BRCA2:NM\_000059:exon8:c.681+2->T | . | LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon9:c.755\_758del:p.D252fs, | . | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon9:c.755\_758del:p.D252fs, | . | Bilateral  ILC+LCIS and IDC/ILC+DCIS |
| frameshift deletion | BRCA2:NM\_000059:exon10:c.1257delT:p.C419fs, | rs80359272 (4 in Clinvar) | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon10:c.1309\_1312del:p.K437fs, | . | ILC |
| frameshift deletion | BRCA2:NM\_000059:exon10:c.1389\_1390del:p.T463fs, | . | ILC |
| frameshift deletion | BRCA2:NM\_000059:exon11:c.3598\_3599del:p.C1200fs, | NOVEL | ILC |
| frameshift deletion | BRCA2:NM\_000059:exon11:c.3680\_3681del:p.L1227fs, | NOVEL | ILC+LCIS |
| stopgain | BRCA2:NM\_000059:exon11:c.C5645A:p.S1882X, | rs80358785 (7 in Clinvar) | ILC+LCIS |
| frameshift insertion | BRCA2:NM\_000059:exon11:c.5835dupA:p.I1945fs, | . | Bilateral  ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon11:c.5946delT:p.S1982fs, | rs80359550 (1290 in Clinvar) | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon11:c.5946delT:p.S1982fs, | rs80359550 (1290 in Clinvar) | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon11:c.6068delA:p.D2023fs, | NOVEL | ILC+LCIS |
| stopgain | BRCA2:NM\_000059:exon16:c.G7757A:p.W2586X, | rs80359003 (9 in Clinvar) | ILC+LCIS |
| nonsynonymous SNV | BRCA2:NM\_000059:exon18:c.A7988T:p.E2663V, | rs80359031 (16 in Clinvar) | ILC+LCIS |
| nonsynonymous SNV | BRCA2:NM\_000059:exon18:c.G8167C:p.D2723H, | rs41293511 (60 in Clinvar) | ILC |
| nonsynonymous SNV | BRCA2:NM\_000059:exon18:c.G8167C:p.D2723H, | rs41293511 (60 in Clinvar) | ILC+LCIS |
| frameshift deletion | BRCA2:NM\_000059:exon22:c.8945\_8946del:p.K2982fs, | NOVEL | ILC+LCIS+DCIS |
| stopgain | BRCA2:NM\_000059:exon25:c.C9294G:p.Y3098X, | rs80359200 (2 in Clinvar) | ILC |
| stopgain | BRCA2:NM\_000059:exon25:c.C9294G:p.Y3098X, | rs80359200 | Bilateral  LCIS Rt breast DCIS left breast |
| stopgain | BRCA2:NM\_000059:exon25:c.C9382T:p.R3128X, | RS80359212 (78 in Clinvar) | ILC no information on LCIS |
| frameshift deletion | \*BRCA2:NM\_000059:exon27:c.9720delT:p.V3240fs, | NOVEL | IDC+DCIS followed 8 years later by ILC+LCIS+DCIS |
| frameshift deletion | \*BRCA2:NM\_000059:exon27:c.10043delA:p.N3348fs, | NOVEL | ILC+LCIS |

**Supplementary Table 7:** CHEK2 mutation in cases

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type of mutation** | **Details (CHEK2:NM\_007194)** | **ID** | **No of ILC no LCIS** | **No of ILC+LCIS cases** | **No of pure LCIS cases** |
| stopgain | exon2:c.C283T:p.R95X | RS587781269 |  | 2 | 1 |
| nonsynonymous SNV | exon3:c.A349G:p.R117G | RS28909982 | 1  (bilateral - IDC contralateral breast - metachronous) | 1 (  bilateral – LCIS contralateral breast - synchronous) |  |
| frameshift deletion | exon11:c.1100delC:p.T367fs | RS555607708 | 1 | 12 | 8 (1 bilateral LCIS) |
| frameshift insertion | exon2:c.188\_189insC:p.L63fs | NOVEL |  |  | 1 |
| stopgain | exon6:c.G697T:p.E233X, | NOVEL |  |  | 1 |
| frameshift deletion | exon12:c.1262delT:p.L421fs | NOVEL |  | 2 |  |

**Supplementary Table 8**: PALB2 mutations in cases

|  |  |  |  |
| --- | --- | --- | --- |
| **Type\_of mutation** | **Details** | **ID** | **Pathology of cancer** |
| frameshift deletion | PALB2:NM\_024675:exon4:c.1035\_1039del:p.L345fs, | NOVEL | ILC+LCIS |
| frameshift deletion | PALB2:NM\_024675:exon4:c.1172delC:p.A391fs, | NOVEL | ILC only (pleomorphic) |
| frameshift deletion | PALB2:NM\_024675:exon4:c.1315delG:p.G439fs, | NOVEL | ILC+LCIS |
| stopgain | PALB2:NM\_024675:exon4:c.G412T:p.E138X, | NOVEL | ILC only |
| frameshift deletion | PALB2:NM\_024675:exon5:c.2167\_2168del:p.M723fs, | NOVEL | ILC only |
| frameshift deletion | PALB2:NM\_024675:exon5:c.2487delG:p.Q829fs | NOVEL | ILC only |
| stopgain | PALB2:NM\_024675:exon7:c.G2718A:p.W906X, | RS180177122 | ILC only |
| splicing | PALB2:NM\_024675:exon8:c.2748+1G>A | NOVEL\* | ILC only |
| stopgain | PALB2:NM\_024675:exon10:c.G3113A:p.W1038X | RS180177132 | ILC only |
| stopgain | PALB2:NM\_024675:exon10:c.G3113A:p.W1038X | RS180177132 | LCIS only |
| stopgain | PALB2:NM\_024675:exon12:c.C3256T:p.R1086X, | . | ILC+LCIS |
| stopgain | PALB2:NM\_024675:exon12:c.C3256T:p.R1086X, | . | ILC+LCIS |

\*Did not validate with Sanger sequencing due to lack of sample material

**Supplementary Table 9**: CDH1 mutations in cases (\* = variant in last exon)

|  |  |  |  |
| --- | --- | --- | --- |
| **Type\_of mutation** | **Details** | **ID** | **Pathology of cancer** |
| splicing | CDH1:NM\_004360:exon1:c.48+1G>A | . | Bilateral LCIS, Bilateral ILC |
| stopgain | CDH1:NM\_004360:exon2:c.G59A:p.W20X, | RS121964875 | Unilateral  LCIS |
| frameshift insertion | CDH1:NM\_004360:exon10:c.1466dupC:p.P489fs, | . | Bilateral LCIS, Unilateral ILC |
| stopgain | CDH1:NM\_004360:exon13:c.G1942T:p.E648X, | . | Bilateral LCIS, Unilateral ILC |
| frameshift deletion | CDH1:NM\_004360:exon15:c.2398delC:p.R800fs, | . | Bilateral LCIS, Unilateral ILC |
| frameshift deletion | CDH1:NM\_004360:exon16:c.2596delG:p.G866fs\* | NOVEL | Unilateral ILC |

**Supplementary Table 10**: Frequency of Variants of Unknown Significance and ILC in women =/< 60 years of age by gene

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene** | **Carriers in Cases** | **Carriers in Controls** | **OR (95% CI)** | **P** |
| BRCA2 | 52 | 46 | 1.28 (0.86-1.92) | 0.258 |
| CHEK2 | 30 | 27 | 1.25 (0.74-2.12) | 0.424 |
| PALB2 | 29 | 37 | 0.88 (0.54-1.44) | 0.620 |
| CDH1 | 12 | 11 | 1.23 (0.54-2.79) | 0.678 |
| BRCA1 | 23 | 15 | 1.73 (0.90-3.34) | 0.104 |
| TP53 | 5 | 5 | 1.12 (0.32-3.89) | 1 |

**Supplementary Figure 1.**

Example of Sanger sequencing confirming *CHEK2 c.1100delC* variant

