Genetic Susceptibility to Triple-Negative Breast Cancer

Kristen N. Stevens¹, Celine M. Vachon¹, and Fergus J. Couch¹,²

Abstract

Triple-negative breast cancers (TNBC), defined by the absence of estrogen receptor, progesterone receptor, and HER-2 expression, account for 12% to 24% of all breast cancers. TNBC is associated with early recurrence of disease and poor outcome. Germline mutations in the BRCA1 and BRCA2 breast cancer susceptibility genes have been associated with up to 15% of TNBC, and TNBC accounts for 70% of breast tumors arising in BRCA1 mutation carriers and 16% to 23% of breast tumors in BRCA2 carriers. Whether germline mutations in other breast cancer susceptibility genes also predispose to TNBC remains to be determined. Common variation in a subset of the 72 known breast cancer susceptibility loci identified through genome-wide association studies and other large-scale genotyping efforts have also been associated with risk of TNBC (TOX3, ESR1, RAD51L1, TERT, 19p13.1, 20q11, MDM4, 2p24.1, and FTO). Furthermore, variation in the 19p13.1 locus and the MDM4 locus has been associated with TNBC, but not other forms of breast cancer, suggesting that these are TNBC-specific loci. Thus, TNBC can be distinguished from other breast cancer subtypes by a unique pattern of common and rare germline predisposition alleles. Additional efforts to combine genetic and epidemiologic data are needed to better understand the etiology of this aggressive form of breast cancer, to identify prevention and therapeutic targets, and to impact clinical practice through the development of risk prediction models. Cancer Res. 73(7): 2025–30. ©2012 AACR.
High-Risk Susceptibility Genes for TNBC

Genetic susceptibility to TNBC has been associated with a high risk of penetrance, germline mutations in the BRCA1 and BRCA2 breast cancer predisposition genes. Approximately 70% of breast tumors develop in women with inherited mutations in BRCA1 exhibit low or absent expression of ER, PR, and HER-2 histologic markers, and morphologic features, recurrence patterns, and death rates (10) are similar to unselected TNBC tumors (1). Consistent with these observations, several studies of unselected triple-negative cases have shown that 9% to 14% overall and approximately 20% of cases diagnosed under the age of 50 years harbor germline BRCA1 mutations (11). Similarly, as many as 34% of triple-negative cases with a family history of breast cancer and 30% of triple-negative cases from women of Ashkenazi Jewish ancestry are associated with germline BRCA1 mutations (12, 13). To a lesser extent, BRCA2 mutations are also associated with TNBC in that 16% to 23% of breast tumors arising in BRCA2 mutation carriers display triple-negative properties (10). While few breast cancer susceptibility genes have been systematically evaluated for mutations in triple-negative cases, it is already clear that up to 15% of unselected triple-negative cases result from inherited mutations in the BRCA1 and BRCA2 high-risk susceptibility genes.

A recent report from The Cancer Genome Atlas (TCGA) Network provides further insight into the distribution of mutations in high-risk genes by breast cancer subtype. There are 49 deleterious variants in 9 genes (ATM, BRCA1, BRCA2, BRIPI, CHEK2, NBN, PTEN, RAD51C, and TP53) were detected in exome-sequencing data from 507 breast tumors (14). Among the 93 basal-like tumors in this group, mutations were identified in BRCA1 (9/13 BRCA1 mutations), BRCA2 (3/14 BRCA2 mutations), RAD51C (1/1 RAD51C mutation), and TP53 (1/2 TP53 mutations). This confirms the known associations with BRCA1 and BRCA2 and suggests that germline RAD51C and TP53 mutations may be found among basal-like breast cancer cases. Interestingly, no mutations in the remaining 5 genes (ATM, BRIPI, CHEK2, NBN, and PTEN) were detected among basal tumors. Large-scale examination of the mutational spectrum of all known breast cancer susceptibility genes (BRCA1, BRCA2, CHEK2, PALB2, BRIPI, TP53, PTEN, STK11, CDH1, ATM, BARD1, RAD51C, RAD51D, NBN, and XRCC2; ref. 15) in women with TNBC, and the individual TNBC subtypes, will be necessary to fully understand the role of these genes in triple-negative risk.

Genetic Risk Factors for Breast Cancer by ER Status

Excluding BRCA1 and BRCA2, relatively little is known about the inherited genetic factors that increase risk for TNBC. The majority of information on genetic susceptibility to this aggressive form of breast cancer has come from investigation of commonly inherited variants with small effects (OR < 1.3) on breast cancer risk. Currently, common variants in 72 loci have been implicated in breast cancer predisposition by genome-wide association studies (GWAS) of breast cancer (16–28), candidate gene studies (29), and a large-scale custom genotyping effort from the Collaborative Oncological Gene-environment Study (COGS; refs. 30, 31; Supplementary Table S1).

Interestingly, the incorporation of ER status into these GWAS and additional follow-up studies has shown that these risk loci are heterogeneous with respect to ER status, with only a subset associated with risk of ER-negative breast cancer. Specifically, 38 of 65 loci identified through GWAS of overall breast cancer have been associated with ER-negative breast cancer as well as ER-positive breast cancer (Fig. 1A and B; Supplementary Table S1; refs. 22, 25, 30–35). In addition, 3 separate meta-analyses of ER-negative breast cancer GWAS, conducted to specifically investigate genetic susceptibility to risk of ER-negative breast cancer, identified variants in 7 loci associated with risk of ER-negative disease. These include TERT (rs10069690 OR = 1.18; P = 1.0 × 10⁻⁶; ref. 26), 20q11 (rs22843378 OR = 1.14; P = 6.0 × 10⁻⁸), 6p14 (rs17530068 OR = 1.15; P = 4.1 × 10⁻⁶; ref. 28), MDM4 (1q32.1; rs41245739 OR = 1.14; P = 2.1 × 10⁻¹²), LG6 (1q32.1; rs6678914 OR = 1.10; P = 1.4 × 10⁻⁷), 2p24.1 (rs12710696 OR = 1.10; P = 4.6 × 10⁻⁸), and FTO (1q42.2; rs11075995 OR = 1.11; P = 4.0 × 10⁻⁷; ref. 31; Fig. 1B). Further study of the TERT locus has identified 3 independent signals that influence the risk of different subtypes of breast and ovarian cancer (36). The rs10069690 variant and an independent variant in the TERT promoter (5-1296255 OR = 0.91; P = 6.15 × 10⁻⁶), accounting for 2 of these TERT loci, have been associated with ER-negative breast cancer. The heterogeneity observed by ER status in these studies supported the investigation of known breast cancer susceptibility loci among breast cancer subtypes defined by all 3 histologic markers (ER, PR, and HER-2).

Common Susceptibility Loci for TNBC

Several large-scale follow-up studies with extensive pathology data have investigated the relevance of common breast cancer risk loci to breast tumor subtypes defined by ER, PR, and HER-2. The first of these studies, from the Breast Cancer Association Consortium (BCAC; ref. 33), found that 5 of 12 variants investigated were associated with TNBC (TOX3 OR = 1.10; P = 1.0 × 10⁻⁶; 2q35 OR = 1.12; P = 0.001; MAP3K1 OR = 1.11; P = 0.016; LSP1 OR = 1.11; P = 0.011; TGFBI OR = 0.011; P = 0.038; Fig. 1C). However, a much larger study by the Triple-Negative Breast Cancer Consortium (TNBCC) involving nearly 3,000 triple-negative cases only confirmed an association for the TOX3 locus (OR = 1.17; P = 3.7 × 10⁻⁵; ref. 37; Fig. 1C). In addition, TNBCC found that single-nucleotide polymorphisms (SNP) from more recently identified risk loci, including...
### Predisposition to Triple-Negative Breast Cancer

#### SNPs and OR Values

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<th>Chr.</th>
<th>Locus</th>
<th>OR</th>
<th>Ref. Cases Controls</th>
<th>OR</th>
<th>Ref. Cases Controls</th>
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**SNP Chr. Locus OR P Ref. Cases Controls**

#### SNP Chr. Locus OR P Ref. Cases Controls

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<th>Locus</th>
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**SNP Chr. Locus OR P Ref. Cases Controls**

#### SNP Chr. Locus OR P Ref. Cases Controls

**Cancer Research Reviews**

**Figure 1.** TNBC susceptibility loci across breast cancer subtypes. Forest plots for 13 TNBC susceptibility variants are shown to provide visual comparison of the strength and direction of association between each SNP and risk of ER-positive breast cancer (A), ER-negative breast cancer (B), TNBC (C), and BRCA1-related breast cancers (D). The 13 SNPs are stratified by strength of evidence for association with TNBC risk (strong vs. marginal). For each breast cancer subtype, estimates (OR) and 95% CIs are shown for each variant from the largest study of each relevant breast cancer subtype. ORs are denoted by black boxes and 95% CIs are denoted by corresponding black lines. Box heights are inversely proportional to precision of the OR estimate as influenced by sample size such that a larger OR box indicates larger sample size and better precision. A vertical gray line is shown at the null value of 1, such that ORs to the left of the null line are less than 1 and ORs to the right of the null line are more than 1. Estimates with confidence intervals that do not overlap the null line indicate significance at \( P < 0.05 \). ^d Denotes ER-positive and ER-negative estimates from a GWAS of Asian women; triple-negative and BRCA1 carrier estimates from studies of women of European ancestry. ^e Denotes the estimate shown for rs12662670 TNBC and for rs9397435 in ER-positives, ER-negatives, and BRCA1 carriers. ^f Denotes the estimate shown for rs10483813/rs999737 in ER-negatives and ER-positives, rs999737 in TNBC, and rs1801320 (HR for 3G vs. 2G) in BRCA1 carriers. ^g Denotes the estimate shown for rs17468277/rs1045485 in ER-negatives and ER-positives, rs17468277 in TNBC, and rs1045485 in BRCA1 carriers. **© 2013 American Association for Cancer Research.**

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rs2046210 and rs12662670 in the ESR1 locus (rs2046210 OR = 1.29; \( P = 4.4 \times 10^{-5} \); rs12662670 OR = 1.33; \( P = 1.1 \times 10^{-4} \)) and rs10483813 in the RAD51L1 locus (OR = 0.86; \( P = 3.0 \times 10^{-4} \)), were strongly associated with TNBC. These RAD51L1 findings were consistent with evidence from a recent BCAC study of TNBC (OR = 0.8; \( P = 0.02 \); ref. 32; Fig. 1C). In contrast, an association between CASP8 and TNBC risk was observed by TNBC (OR = 0.87; \( P = 0.005 \)), but not by BCAC (OR = 0.92; \( P = 0.15 \); ref. 33). Thus, SNPs in the TOX3, ESR1, and RAD51L1 loci, and possibly in 2q35, MAP3K1, LSP1, TGFBI, and CASP8, that influence the risk of both ER-positive and ER-negative breast cancer (Fig. 1A and B) have also been identified as genetic risk factors for TNBC (Fig. 1C).

Several of the loci identified in ER-negative breast cancer studies also seem to influence the risk of TNBC. The ER-negative TERT variant rs10069690 has been associated with an increased risk of TNBC (rs10069690 OR = 1.25; \( P = 9.5 \% \) confidence interval (CI), 1.16–1.34; \( P = 1.1 \times 10^{-5} \); Fig. 1C; ref. 26). In addition, separation of HER-2–positive ER/PR-negative cases (\( n = 376 \); OR = 1.03; \( P = 0.71 \)) from HER-2–negative cases (\( n = 3,707 \); OR = 1.25; \( P = 1.1 \times 10^{-5} \)) has suggested that this variant may be uniquely associated with TNBC (Fig. 1C; ref. 26). However, given the complexity of the associations between variation in this locus and breast cancer risk (36), this variant may be uniquely associated with TNBC (Fig. 1C; ref. 28). Furthermore, of the 4 loci identified by Garcia-Closas and colleagues, MDM4 (OR = 1.17; 95\% CI, 1.09–1.26; \( P = 3.1 \times 10^{-5} \)), 2q24.1 (OR = 1.15; 95\% CI, 1.07–1.23; \( P = 6.7 \times 10^{-5} \)), and FTO (OR = 1.11; 95\% CI, 1.03–1.20; \( P = 0.007 \)) were associated with TNBC in subtype analyses (Fig. 1C; ref. 31). Of these, the MDM4 locus may have a specific association with TNBC (OR = 1.17; \( P = 3.1 \times 10^{-5} \)), as no significant association has been seen with non–triple-negative ER-negative breast cancer (OR = 1.02; 95\% CI, 0.92–1.12; \( P = 0.711 \); pHet = 0.005).

**Common Susceptibility Loci for BRCA1 Mutation Carriers**

Because TNBC and breast cancer in BRCA1 mutation carriers are phenotypically similar, studies of genetic modifiers of breast cancer risk in BRCA1 mutation carriers have provided further insight into the genetic risk factors for TNBC. Specifically, SNPs in the 19p13.1 locus that displayed genome-wide significant associations with breast cancer in a GWAS of BRCA1 mutation carriers (rs81070 HR = 1.26; \( P = 2.3 \times 10^{-7} \); rs8100241 HR = 0.84; \( P = 3.9 \times 10^{-5} \); Fig. 1D; ref. 27) have also been associated with TNBC risk in the general population (rs81070 OR = 1.27; \( P = 2.3 \times 10^{-7} \); rs8100241 OR = 0.84; \( P = 8.7 \times 10^{-7} \); Fig. 1C; ref. 37). In BCAC and TNBC combined, the 19p13.1 locus was associated with TNBC risk (rs81070 OR = 1.25; \( P = 4.2 \times 10^{-13} \); rs8100241 OR = 0.81; \( P = 1.9 \times 10^{-13} \)) but was not associated with the risk of ER-positive or ER-negative non–triple-negative breast cancer (Fig. 1C; ref. 35). Furthermore, these variants seemed to be specifically associated with tumors that were positive for the basal markers CK5/6 or EGFR (OR = 1.27; 95\% CI, 1.07–1.50; \( P = 0.0069 \)), indicating specificity for the basal subtype. In addition, variants in ESR1, PTHLH, TOX3, CASP8, and TERT are also associated with both TNBC and the risk of breast cancer in BRCA1 carriers (Fig. 1C and D; refs. 36, 38–42). Of the known TNBC risk factors, only RAD51L1 was not found to be a modifier of BRCA1-related breast cancer risk (Fig. 1D). Recent data also show that BRCA2 ER-negative tumors have pathologic characteristics similar to BRCA1 ER-negative tumors (10). Thus, further studies of BRCA1 and BRCA2 breast tumors, stratified by ER or triple-negative tumor status, may provide additional valuable insight into genetic susceptibility to TNBC.

Together with studies of overall breast cancer risk loci by ER, PR, and HER-2 subtypes, these findings suggest that TNBC and the other subtypes of breast cancer may have distinct genetic risk factor profiles. Although the 19p13.1 locus and MDM4 seem to be specific to TNBC, it is important to note that these loci were also significantly associated with overall ER-negative breast cancer (Fig. 1B). Whether this overall association is driven by the inclusion of triple-negative or basal tumors or reflects meaningful associations with other non-TNBC ER-negative tumors remains to be determined. On this basis, it will be important to continue to evaluate new breast cancer loci as candidate risk factors for TNBC and other subtypes of breast cancer if a comprehensive understanding of genetic predisposition to breast cancer is to be attained.

**Future Directions and Implications of Understanding TNBC Genetics**

The exact biologic mechanisms underlying TNBC genetic risk loci are currently unknown, and additional fine-mapping, resequencing, and functional studies are necessary to determine whether single or multiple variants at these loci affect triple-negative risk through the dysregulation of nearby genes or though long-range genetic effects. One hypothesis is that causal variants at these loci directly initiate and promote development of a triple-negative tumor through pathways that are specific to this hormone receptor–negative subtype. Interestingly, 3 loci specific to TNBC contain genes (TERT, C19orf62, and MDM4) that encode proteins involved in DNA repair and the preservation of genomic stability. The TERT gene encodes the catalytic subunit of telomerase, which controls telomere maintenance, and has been associated with genomic instability and linked to tumorigenesis (43). MDM4 is a repressor of TP53 and TP73 transcription and is important for cell-cycle regulation and apoptosis in response to DNA damage (44). C19orf62 encodes the MERIT40 protein, which is integral to the localization of the BRCA1-A complex during DNA double-strand break (DSB) repair, through the recruitment and retention of the BRCA1-BARD1 ubiquitin ligase and the BRCC36 deubiquitination enzyme (45). Telomere maintenance, DSB repair, and DNA damage checkpoints have been linked as coordinating factors in genomic integrity, and the disruption of this pathway, resulting in genomic instability, has been implicated in cancer (46, 47). Indeed, one proposed mechanism of spontaneous telomere loss in cancer cells is a deficiency in DSB repair combined with oncogene-mediated DNA replication stress (46). In addition, evidence suggests that DNA damage...
checkpoint and DNA repair proteins have an essential role in telomere maintenance, by controlling the processing of telomeric DNA and through other mechanisms that have yet to be delineated (47). This highlights a potential common biologic pathway that may be specifically associated with the development of TNBC. Focusing on these pathways involved in DNA repair and the preservation of genomic stability, as highlighted by the associations of TNBC with genetic variation in 19p13.1, MDM4, and TERT, may lead to the development of targeted prevention and/or therapeutic agents for patients with TNBC, analogous to PARP inhibitors and the homologous recombination DNA repair pathway in BRCA1- and BRCA2-deficient carriers (48).

An alternative hypothesis is that variants or even combinations of variants in the TNBC-associated risk loci may act to change existing malignant breast lesions to a triple-negative phenotype during the formation of the tumor. This is particularly intriguing considering the relevance of the ESR1 locus, which is directly involved in the estrogen signaling, to ER-negative and triple-negative breast cancer in addition to ER-positive breast cancer. While a particular locus such as ESR1 may predispose breast epithelium to cancer in general, others such as TERT and 19p13.1 may act further downstream after tumorigenesis has begun to direct tumors towards the triple-negative phenotype. Thus, the identification of these TNBC genetic loci offer exciting opportunities to better understand how triple-negative tumors arise.

Beyond gaining insight into the TNBC etiology, accurately defining the spectrum of high-risk mutations in breast cancer susceptibility genes among women with TNBC has the potential to modify clinical practice. A recent study from the United Kingdom showed that up to a third of TNBCs found to carry BRCA1 mutations would not have been clinically tested for these mutations based on traditional risk profiling (11) and would not have benefited from the modified clinical care associated with known cancer-predisposing mutations. By characterizing the association between mutations in all high-risk susceptibility genes and family history of cancer, age of onset of cancer, and other epidemiologic risk factors, improved breast cancer risk prediction models can be developed that more accurately identify women at risk for TNBC.

Similarly, identification of additional common genetic variants associated with the risk of TNBC will likely have use for breast cancer risk prediction. The expectation is that inclusion of all 72 common breast cancer risk loci in the Gail model, in addition to clinical and epidemiologic risk factors, will improve risk model performance (49), and the effectiveness of these models will likely be further improved by tailoring them to specific subtypes of breast cancer, including TNBC. On the basis of the specificity of 19p13.1, TERT, and MDM4 for this subtype, triple-negative–specific risk models may be feasible. Accurate risk prediction models for TNBC that incorporate genetic information from both rare, high-risk and common, low-risk susceptibility loci would argue for screening women for cancer at a younger age and may assist in identifying high-risk women earlier in life.

Although we have made progress in understanding TNBC genetics, it is clear that there is much to learn about the genetic susceptibility to TNBC and that there is a scientific and clinical need to continue this line of work. We must continue to combine high quality genetic, phenotypic, and pathologic data from large breast cancer studies and consortia to better define genetic susceptibility to TNBC, particularly considering that TNBC is a relatively rare subtype of breast cancer. Analyses that attempt to explain the complex biology of human cancers are necessary to make progress in understanding the etiology of TNBC and to impact disease prevention and clinical care.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: C.M. Vachon, F.J. Couch
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.N. Stevens, F.J. Couch
Writing, review, and/or revision of the manuscript: K.N. Stevens, F.J. Couch
Study supervision: F.J. Couch

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