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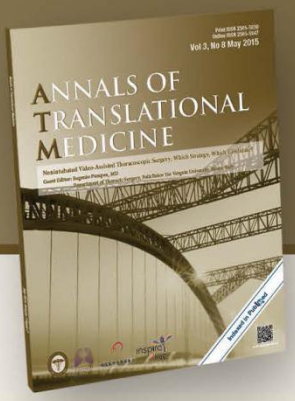

Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-2999

Reviewer: #1(Remarks to the Author)

Comment 1: The authors stresses that patients can "benefit from multigene testing" but do not specify it except "a (general) better understanding on the genetic background". Could the authors confer more direct and specific relevance to the discovered mutations, from the perspective of diagnosis, prognosis or even treatment?

Reply 1: We appreciate the reviewer's insightful comments. As you kindly suggested, we collected more information and analyzed the association between the discovered mutations and breast cancer diagnosis as well as prognosis, and discussed promising treatment strategies.

The association between the discovered mutations and breast cancer diagnosis was presented as follows.

In our study, the average age at diagnosis of breast cancer was similar between patients with and without germline mutations in these *BRCA*-negative cases (42 versus 39, $P = 0.431$; Table 3). However, we found the average age at diagnosis of breast cancer was significantly older for patients with deleterious *RET* mutations than the patients without germline mutations (49 versus 39, $P = 0.028$; Table 3). We further evaluated whether patients with mutations in the 30 predisposition genes were associated with a stronger family history of breast or ovarian cancers than non-mutated patients. In particular, all patients with *RET* mutations were enriched for a family history of breast cancer (100% versus 49%, $P = 0.014$; Table 3). However, no carriers had a family history of ovarian cancer.

We also evaluated associations between mutation status of single predisposition gene and clinical stages (Table 4) as well as tumor pathology (Table 5). Overall, carriers and non-carriers had similar tumor stages (Table 4). When each receptor was examined alone, we observed *PALB2* mutation carriers were more likely to be ER-positive than non-carriers (80% versus 28%, $P = 0.027$; Table 4). Notably, *TP53*-mutated breast cancers were significantly more likely to be ER-, PR- and HER2-positive (100% versus 28%, $P = 0.024$ for ER; 100% versus 27%, $P = 0.020$ for PR; 100% versus 9%, $P = 0.001$ for HER2; Table 5).

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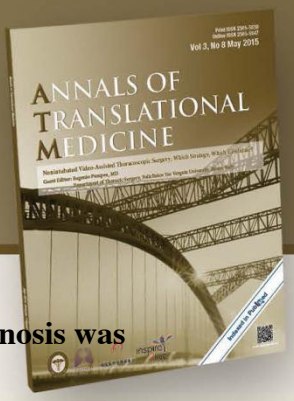

The association between the discovered mutations and breast cancer prognosis was presented as follows.

According to the reviewer's insightful suggestion, we further complement the information of the clinical follow-up and survival for the whole cohort. The median follow-up was 35 months (interquartile range: 24-50 months). There were no significant differences in disease-free survival (DFS) (Log-rank $P = 0.487$; Figure R1A in the response letter) or overall survival (OS) (Log-rank $P = 0.487$; Figure R1B in the response letter) between the germline mutation carriers and non-carriers. We further divided the patients into specific subgroups to determine if the mutation status impacted DFS and OS. No significant results were observed in the survival analysis among the triple-negative breast cancer (TNBC) (DFS, Log-rank $P = 0.752$; OS, Log-rank $P = 0.442$; Figure R1C and R1D in the response letter) and early-age onset breast cancer (DFS, Log-rank $P = 0.640$; OS, Log-rank $P = 0.912$; Figure R1E and R1F in the response letter) patients. **The survival estimates are not integrated in our manuscript but we discuss some previous studies regarding panel testing and prognosis as well as treatment in breast cancer as follows.**

We also explored whether the mutation status could impact the survival in the *BRCA*-negative breast cancer (data not showed), but no significant results were observed in comparing disease-free survival (DFS) or overall survival between the germline mutation carriers and non-carriers. Previous studies came to inconsistent conclusions about *BRCA* mutation status as a prognostic factor in breast cancer(1-6). Among other predisposition genes, *CHEK2* 1100delC was demonstrated to be associated with increased risk of second breast cancer and a worse long-term recurrence-free survival rate(7). Another study indicated *CHEK2* H371Y mutation carriers were more likely to respond to neoadjuvant chemotherapy than non-carriers(8). However, we failed to identify these two mutations in our cohort. Moreover, breast cancer patients with *PALB2* mutations were considered to be at a higher risk of death from breast cancer compared with non-carriers(9). A more recent study involved 16 DNA-repair genes including *ATM*, *BLM*, *CHEK2*, *FANCC*, *MER11A*, *MLH1*, *MSH2*, *MSH6*, *MUTHY*, *NBN*, *PALB2*, *PMS2*, *RAD50*, *RAD51C*, *RAD51D* and *TP53*(10), where most genes were also comprised in our study. The study concluded that 3.4% of *BRCA*-negative breast cancer patients carried germline mutations in the 16 DNA-repair genes, and the DNA-repair gene mutation carriers exhibited an aggressive phenotype and had poor survival compared with noncarriers. By virtue of the germline mutations, breast cancers harboring these mutations had unique mechanisms that could be rationally targeted for therapeutic opportunities. Increasing evidences demonstrated mutations in non-*BRCA1/2* DNA-repair genes contributed to sensitivity to PARP inhibitors, which suggested carriers of mutated DNA-repair genes could undergo treatment with PARP inhibitors(11). Besides PARP, there were other key components, like *PTEN(12-14)*, *ATM(15)*, *MSH2(16,17)* and *APC(18)*, showing potentials for targeted therapy.

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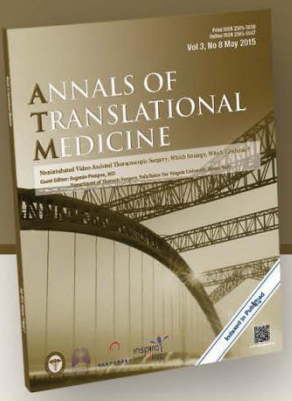


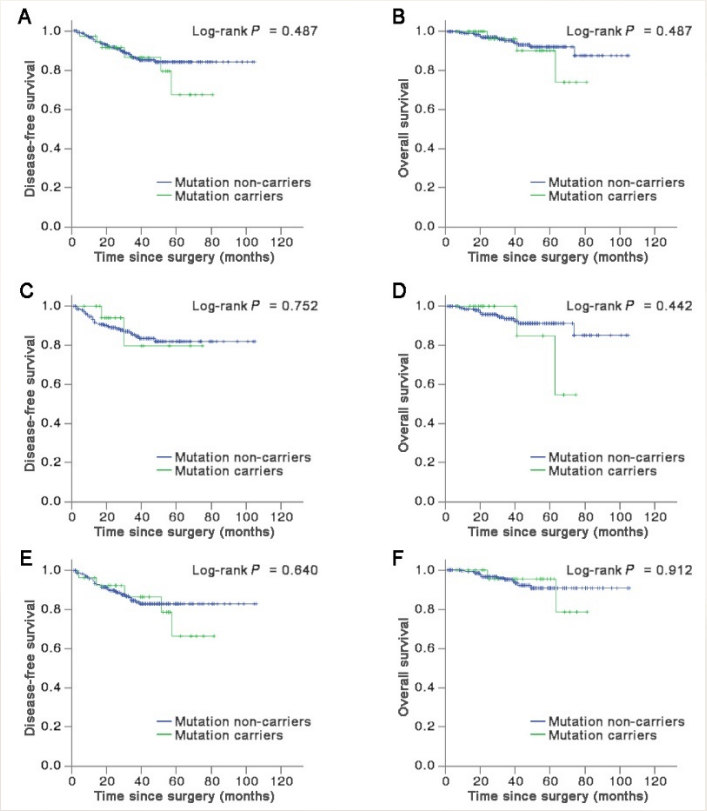


Figure R1. Kaplan–Meier estimates of disease-free survival (DFS) and overall survival (OS). A, DFS by mutation status in all breast cancer patients in our cohort. **B**, OS by mutation status in all breast cancer patients in our cohort. **C**, DFS by mutation status in triple-negative breast cancer (TNBC) patients. **D**, OS by mutation status in TNBC patients. **E**, DFS by mutation status in early-age onset breast cancer patients. **F**, OS by mutation status in early-age onset breast cancer patients.

Changes in the text: We added the data regarding the association between the discovered mutations and breast cancer diagnosis, please find them on **Page 15-16, line 271-288**. We supplemented some discussion about mutations' relationship with prognosis and treatment in breast cancer, please see **Page 22-23, line 394-418**.

Comment 2: The authors mentioned that, "Despite the fact that breast cancer susceptible genes have been extensively studied and multiple genes testing have been widely performed in Caucasians, Ashkenazi Jewish and African Americans, insufficient data supports the knowledge of hereditary background in Chinese breast cancer patients." This raises an expectation that the authors shall compare (at least briefly) the Chinese breast cancer patients with the others, which will definitely further elevate the novelty and significance of this manuscript.

Reply 2: We completely agree with the reviewer's comment and we have reviewed the literature comprehensively to stress the differences of breast cancer patients in Chinese populations comparing with other ethnics. We detailed the according interpretation as follows.

Many retrospective studies proved that clinicopathologic features and outcomes of breast cancer varied between Chinese and Caucasian population. Chinese patients had a younger age at diagnosis of breast cancer, whose peak age onset was between 45 and 55 years old, compared to an average of between 60 and 70 years old in Caucasian breast cancer patients(19). Besides, Chinese patients had a lower rate of incidence of invasive lobular breast cancer. Genomic profiling studies also demonstrated disparities between breast cancers of different ethics. One study compared gene expression and microRNA profiles between Chinese and Italian breast cancers and found lower prevalence of Luminal A subtype among Chinese breast cancers(20). A more recent study revealed a higher mutational prevalence for *TP53* and *AKT1* in Chinese patients(21).

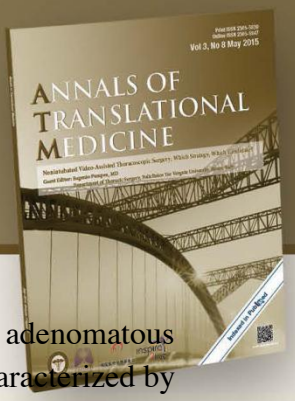
Changes in the text: We have modified our manuscript as advised, please find them on **Page 7-8, line 113-123**.

Comment 3: The presentation in the manuscript, albeit objective, is way too descriptive and in short of biological and clinical interpretation. The authors are encouraged to provide essential genetic/biological background on the genes studied; and establish stronger rationale to employ these genetic mutations for clinical translation.

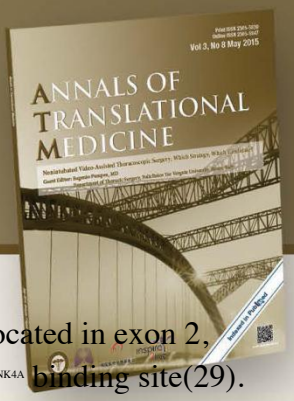
Reply 3: We are most grateful for pointing out the weakness and we raised the genetic/biological background on the genes we studied in the revised manuscript. We have clarified the corresponding point in column of in the "**Genetic and biological background**" the **Table 1**.

Table 1. The multigene panel of 30 breast cancer susceptibility genes.

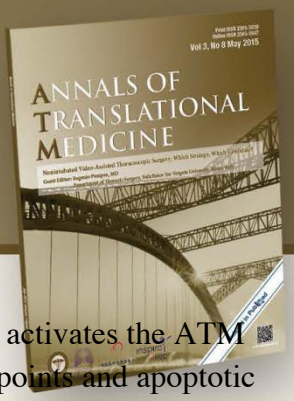
Breast cancer susceptibility genes	Reference sequence	Breast cancer relative risk or selection criterion	Genetic and biological background
APC	NM_001127511	Familial adenomatous polyposis	*APC* encodes a multi-domain protein that has been implicated in many cellular functions including cellular proliferation, differentiation, cytoskeleton regulation, migration and apoptosis. Inactivating *APC*



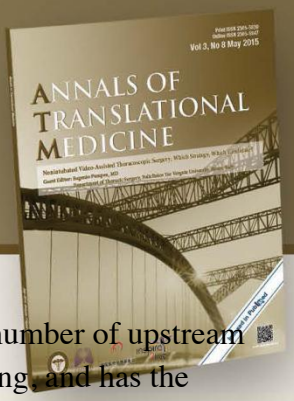
			mutations cause familial adenomatous polyposis, classically characterized by hundreds to thousands of adenomatous colorectal polyps and cancer(22,23).
ATM	NM_000051	2.2–3.7	*ATM* encodes a PI3K-related serine/threonine protein kinase that helps maintain genomic integrity and plays a central role in the repair of DNA double-strand breaks. Germline mutations of *ATM* result in the well-characterized ataxia telangiectasia syndrome(24).
BARD1	NM_000465	Breast cancer association reported	*BARD1* encodes a BRCA1-interacting protein, and heterodimerization of BARD1–BRCA1 via the RING domain is crucial in the homologous recombination repair and transcriptional regulation functions of BRCA1(25).
BMPR1A	NM_004329	Breast cancer association reported	*BMPR1A* encodes a receptor involved in the bone morphogenetic protein signaling pathway, and is found in the germline of patients with Cowden Syndrome(26).
BRIP1	NM_032043	1.2–3.2	*BRIP1* encodes a helicase-like protein that was identified via its direct binding to the BRCA1 BRCT domains, and is known to contribute to DNA repair via homologous recombination(27).
CDH1	NM_004360	2.2–19.9	*CDH1* encodes E-cadherin, a cell–cell adhesion glycoprotein that acts as a critical invasion suppressor. Loss-of-function germline mutations in the CDH1 tumour-suppressor gene is the cause of hereditary diffuse gastric cancer syndrome(28).
CDK4	NM_000075	Breast cancer association reported	*CDK4* is a potential oncogene, which acts early in the cell cycle and is involved in the transition from G to S phase. All *CDK4*



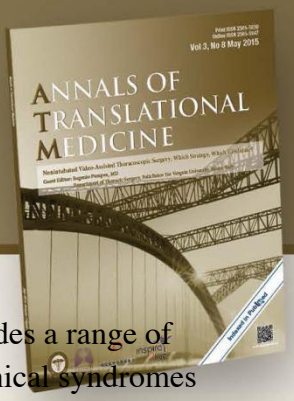
			reported mutations are located in exon 2, which codes for the $p16^{INK4A}$ binding site(29).
CDKN2A	NM_000077	1.1-1.7	*CDKNA* encodes the cyclin-dependent kinase inhibitor $p16^{INK4a}$ and the p53 activator $p14^{ARF}$ which are both involved in the negative control of cell proliferation(30).
CHEK2	NM_001005735	2.6-3.5	*CHEK2* encodes a kinase that, when activated, blocks cell-cycle progression in response to DNA damage, and prevents cell transformation and carcinogenesis. The mostly prevalent recurrent mutation in CHEK2 is 1100delC(31).
EPCAM	NM_002354	Breast cancer association reported	*EPCAM* encodes a membrane-bound protein that is localized to the basolateral membrane of epithelial cells and is overexpressed in some tumors. Monoallelic deletions of the 3' end of EPCAM that silence the downstream gene, MSH2, cause a form of Lynch syndrome(32).
MEN1	NM_000244	Breast cancer association reported	*MEN1* encodes a610–amino acid protein referred to as menin. Menin is predominantly a nuclear protein that has roles in transcriptional regulation, genome stability, cell division, and proliferation(33).
MLH1	NM_000249	0.2-2.0	*MLH1* is a tumor suppressor gene involved in DNA mismatch repair. Germline mutations in this gene are known to cause Lynch syndrome. The most common malignancies in Lynch syndrome are colorectal and endometrial carcinomas(34).
MRE11A	NM_005590	Breast cancer association reported	*MRE11A* encodes the part of the tri-molecular MRE11A/RAND50/NBS1 complex, functions as an exonuclease and endonuclease, contributes to single- and double-strand break repair, processes



			damaged DNA ends and activates the ATM protein, cell cycle checkpoints and apoptotic responses(35).
MSH2	NM_000251	1.2-3.7	*MSH2* encodes the component of post-replicative DNA mismatch repair system which forms two different heterodimers: MutS alpha (MSH2-MSH6 heterodimer) and MutS beta (MSH2-MSH3 heterodimer) which binds to DNA mismatches thereby initiating DNA repair(36).
MSH6	NM_000179	0-13.0	*MSH6* encodes the component of post-replicative DNA mismatch repair system which heterodimerizes with MSH2 to form MutS alpha, which binds to DNA mismatches thereby initiating DNA repair(37).
MUTYH	NM_001048171	1.0-3.4	*MUTYH* encodes for a base excision repair DNA glycosylase. Mutations in this gene cause the *MUTYH*-associated polyposis syndrome, an autosomal recessive inherited condition commonly characterized by the presence of few to hundreds of colonic adenomatous polyps and an increased colorectal cancer risk at young age(38).
NBN	NM_002485	1.9-3.7	*NBN* encodes the part of the genome surveillance complex responsible for DNA damage repair. Homozygous carriers of *NBN* mutations are diagnosed with the Nijmegen Breakage Syndrome, which features immunodeficiency, chromosomal instability, microcephaly as well as a predisposition to various cancers(39).
NF1	NM_000267	2.1-3.2	*NF1* encodes a cytoplasmic protein, termed neurofibromin, which is a large protein containing three alternatively spliced exons (9a, 23a and 48a). The Neurofibromin



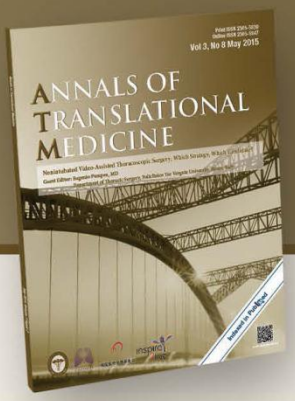
			protein interacts with a number of upstream regulators of Ras signaling, and has the potential to play multiple roles within neurons as part of various intracellular pathways(40).
PALB2	NM_024675	3.0-9.4	*PALB2* encodes for the partner and localizer of BRCA2, which is identified as a BRCA2-interacting protein that is crucial for key BRCA2 genome caretaker functions; it is also shown to interact with BRCA1. Biallelic germline loss-of-function mutations in *PALB2* cause Fanconi's anemia(41).
PALLD	NM_001166108	Breast cancer association reported	*PALLD* encodes a cytoskeletal protein that is required for organizing the actin cytoskeleton. The protein is a component of actin-containing microfilaments, and it is involved in the control of cell shape, adhesion, and contraction(42).
PMS2	NM_000535	Lynch syndrome	*PMS2* encodes for a key component of the mismatch repair system that functions to correct DNA mismatches and small insertions and deletions that can occur during DNA replication and homologous recombination(43,44).
PTCH1	NM_000264	Breast cancer association reported	*PTCH1* encodes a 1447-amino acid transmembrane glycoprotein, which is part of the hedgehog (Hh) pathway. The Hh pathway is a key regulator in embryonic development and tumorigenesis controlling cell differentiation, tissue polarity, and cell proliferation(45).
PTEN	NM_000314	2.0-5.0	*PTEN* encodes a dual-specificity phosphatase that can dephosphorylate both protein and phospholipid substrates. Germline *PTEN* mutations underpin the PTEN Hamartoma-Tumor Syndrome, an



			umbrella term that includes a range of autosomal-dominant clinical syndromes mainly including Cowden syndrome, presenting in adulthood, and Bannayan-Riley-Ruvalcaba syndrome in children(46).
RAD50	NM_005732	Breast cancer association reported	*RAD50* encodes the RAD50 protein. It plays key roles in DNA double strand breaks repairs, which are crucial to safeguarding genome integrity and sustaining tumor suppression(47).
RAD51C	NM_002876	1.5-7.8	*RAD51C* encodes a crucial protein in homologous recombination, which is involved in loading Rad51 at sites of DNA double-stranded breaks, mediating strand exchange and homologous pairing of DNA sequences. A bi-allelic missense mutation in *RAD51C* causes a Fanconi Anemia-like phenotype(48).
RAD51D	NM_001142571	Breast cancer association reported	*RAD51D* encodes a member of the RAD51 protein family and a constituent of DNA repair mechanism by homologous recombination through the BCDX2 complex formation, which binds to single-stranded DNA after damage and provides homology detection between the damaged and wild-type strand in the repair process(49).
RET	NM_020630	Breast cancer association reported	*RET* encodes a transmembrane receptor and member of the tyrosine protein kinase family of proteins. Binding of ligands such as glial cell-line derived neurotrophic factor and other related proteins to the encoded receptor stimulates receptor dimerization and activation of downstream signaling pathways that play a role in cell differentiation, growth, migration and survival(50).

STK11	NM_000455	2.0-4.0	*STK11* encodes a serine/threonine kinase involved in the regulation of cell growth, polarity and motility. Its inactivation has been initially described in human tumors associated with Peutz-Jeghers hereditary syndrome(51).
TP53	NM_001126115	62.0-165.0	*TP53*, which encodes p53, is a tumor suppressor gene that is frequently mutated in sporadic cancers. The tumor suppressor p53 is a key player in stress responses that preserve genomic stability, responding to a variety of insults including DNA damage, hypoxia, metabolic stress and oncogene activation(52).
VHL	NM_000551	Breast cancer association reported	*VHL* encodes a multifunctional protein that shuttles between the nucleus and cytoplasm whose function links to the pathogenesis of von Hippel-Lindau disease(53).

Changes in the text: We have modified our manuscript as you kindly suggested, please find them on in the **Table 1** in our uploaded files.



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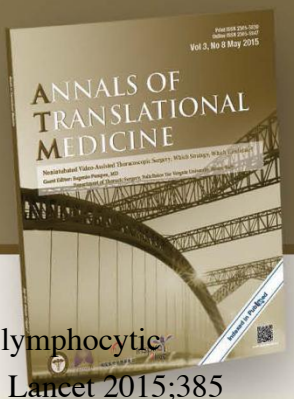

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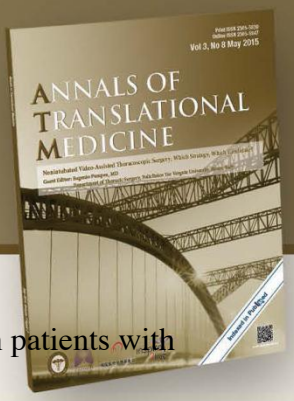

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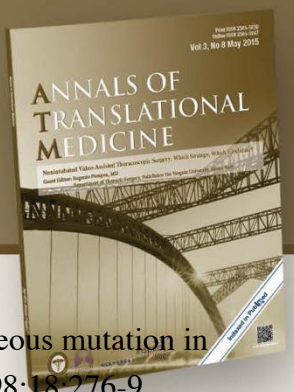

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