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BRIEF REPORT

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Rs867228 in FPR1 accelerates the manifestation of luminal B breast cancer

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ABSTRACT

Formyl peptide receptor-1 (FPR1) is a pathogen recognition receptor involved in the detection of bacteria, in the control of inflammation, as well as in cancer immunosurveillance. A single nucleotide polymorphism in *FPR1*, rs867228, provokes a loss-of-function phenotype. In a bioinformatic study performed on The Cancer Genome Atlas (TCGA), we observed that homo-or heterozygosity for rs867228 in *FPR1* (which affects approximately one-third of the population across continents) accelerates age at diagnosis of specific carcinomas including luminal B breast cancer by 4.9 years. To validate this finding, we genotyped 215 patients with metastatic luminal B mammary carcinomas from the SNPs To Risk of Metastasis (SToRM) cohort. The first diagnosis of luminal B breast cancer occurred at an age of 49.2 years for individuals bearing the dysfunctional TT or TG alleles ($n = 73$) and 55.5 years for patients the functional GG alleles ($n = 141$), meaning that rs867228 accelerated the age of diagnosis by 6.3 years (p=0.0077, Mann & Whitney). These results confirm our original observation in an independent validation cohort. We speculate that it may be useful to include the detection of rs867228 in breast cancer screening campaigns for selectively increasing the frequency and stringency of examinations starting at a relatively young age.

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Introduction

Epidemiological studies suggest that over the past few decades some cancer type tend to manifest relatively early, posing a new challenge for disease detection and management.[1] Back in 2015 we published a study in which we screened single nucleotide polymorphisms (SNPs) in immune-relevant genes for their impact on breast cancer prognosis, finding rs867228 in *FPR1*, the gene coding for formyl peptide receptor-1, to be associated with poor responses to anthracycline-based adjuvant chemotherapy in two distinct cohorts of patients.[2–4] This finding was later confirmed for locally advanced rectal cancer, in which rs867228 was associated with poor responses to neoadjuvant chemoradiotherapy.[5,6]

The knockout of the human *FPR1* orthologue in mice, *Fpr1*, revealed a major defect in chemotherapy-induced immunosurveillance, meaning that mice lacking one or two alleles of *Fpr1* were unable to control tumor growth upon chemotherapy with anthracyclines (such as mitoxantrone) alone or combination with cyclophosphamide.[3,7] Exhaustive phenotyping of the tumor microenvironment, responding to chemotherapy in the context of *Fpr1*-proficient or -deficient immune systems, revealed that FPR1 is required for the function of dendritic cells (DCs), allowing them to approach dying cancer cells that release the FPR1 ligand annexin A1 (ANXA1) and then to engage in the cross-presentation of tumor-associated antigens.[3,8] *In vitro* experiments on peripheral blood mononuclear cells from human volunteers bearing rs867228 confirmed a similar loss-of-function phenotype in both heterozygosity and (more so) in homozygosity.[3,9] Murine adoptive transfer experiments corroborated that the cell type critical for FPR1-dependent immunosurveillance are indeed DCs, likely of the conventional cDC1 phenotype.[8] Altogether, these experiments established that FPR1 plays a cardinal role in the perception of immunogenic cell death, as it occurs in the context of anticancer chemotherapies.[10,11]

In an additional twist, we observed that, in a murine model of hormone-induced breast oncogenesis (which is based on the implantation of capsules releasing the progesterone analogue medroxyprogesterone acetate, MPA, plus six oral gavages with the DNA-damaging agent 7,12-dimethylbenz[a]anthracene, DMBA), the knockout of *Fpr1* accelerated oncogenesis.[8] These results suggest a pivotal function for FPR1 in breast cancer immunosurveillance, which has a major impact on the age at which the disease manifests, as well as on prognosis.[12,13] Indeed, individuals heterozygous or homozygous for rs867228 developed breast cancer earlier than patients lacking rs867228, as determined by a bioinformatic analysis of TCGA.[8] Thus, individuals with

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any kind of breast cancer (irrespective of the molecular subtype) bearing rs867228 in hetero- or homozygosity were diagnosed at 57.5 years old, whereas patients lacking rs867228 were at 55.7 years old (difference: 2.0 years, $p = 0.028$). Subgroup analysis revealed an even stronger effect for patients bearing luminal B breast cancers, in which rs867228 in hetero- or homozygosity was associated with diagnosis at 55.2 years, *i.e.*, 7.7 years earlier ($p = 0.0086$) than in patients lacking rs867228, in which luminal B breast cancer was diagnosed at 62.9 years.[8,14]

Based on these observations, we decided to examine the impact of rs867228 on age at diagnosis of luminal B breast cancer patients in an independent French cohort. Here, we report the validation of our initial observation, confirming that rs867228 has a real impact on the development of luminal B breast cancer.

Materials and methods

Patients and study design

SToRM (NCT01460186) is a prospective clinical observational cohort of 1483 metastatic breast cancer patients from multiple hospitals in France. This study's inclusion criteria were: women/men aged 18 years or older, with a histologically diagnosed breast cancer that was diagnosed as metastatic for less than one year, and with an immunohistological classification of the primary tumor (based on estrogen receptor (ER), progesterone receptor (PR) and HER2). The threshold for ER and PR positivity was ≥10% staining (locally assessed in each hospital).[14,15] Exclusion criteria were the simultaneous existence of another cancer, or the presence of another cancer diagnosed within the previous 5 years, as well the inability to undergo medical fellow-up.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice standards and the Declaration of Helsinki. Patients provided written informed consent; the study was approved by the relevant institutional review board (South-East IV Patient Protection Committee, 26 October 2011, No.: 11/089).

Genotyping

A genome wide association study was carried out in patients with sufficient DNA, using Illumina humaCore Exome Chip set. This chip set is composed of over 250,000 variants designed to capture common variation across the genome, as well as over 200,000 variants focused on coding regions. Patients are followed prospectively with respect to their metastatic diagnosis through direct contact with their oncology time. The quality of the genotyping data was controlled with PLINK software: SNPs and individuals with high levels of missingness (>2%) were deleted. Samples with sex discrepancy, unusual heterozygosity rate (>3sd from the mean), parent-offspring relations were removed. SNPs that are not in Hardy–Weinberg equilibrium ($p < 1e\text{-}10$) have also been removed. Missing genotypes were then imputed against the 1000 genome dataset using shapeit2 and minimac4 software.

Statistical analyses

The SToRM database was analyzed for the *FPR1* SNP rs867228 (chr19:52249211T>G). We performed Mann & Whitney tests for each SNP group, for time at diagnosis, at metastasis and at death as well as overall and progression-free survival.

Results

To validate our initial observation obtained in TCGA, we took advantage of the StoRM cohort, which is a French multicentric, prospective cohort study of metastatic breast cancer patients, for which the inclusion criteria were: women/men aged 18 years or older, with a histologically diagnosed breast cancer that was metastatic for less than one year, and with an immunohistological classification of the primary tumor (based on estrogen receptor (ER), progesterone receptor (PR) and HER2). Patients were recruited between March 2011 and May 2014.[15,16] Demographics and clinical characteristics of the complete study population are presented in Table S1.

Note that the type of breast cancer, the stage at diagnosis as well as the treatment modalities were equally distributed among different genotypes, as indicated by the absence of statistically significant alterations calculated with Fischer's exact test.

We plotted the age of diagnosis for each of the genotypes. For the entire breast cancer cohort, irrespective of the molecular subtype, we found a non-significant trend ($p = 0.09$, Mann & Whitney test) in favor of an early diagnosis for patients bearing at least one of the two loss-of-function alleles (TT or TG, $n = 192$) of rs867228 (52.85[42.45–62.5]) as compared to individuals bearing two functional alleles (GG, $n = 338$) of rs867228 (55.25 [46.825–63.3]) (Table 1, Figure S1a). Subsequent subgroup analyses (Table 1 , Figures 1 and S1a-d) revealed statistically significant ($p < 0.05$) effects for the rs867228 genotype only for luminal B-like hormone receptor-positive (*i.e.*, ER+, PR+, HER2- breast cancers (Figure 1a). When applying a dominant model, the first diagnosis of luminal B HER2- breast cancer occurred at an average age of 49.2 years for patients bearing the dysfunctional TT or TG alleles ($n = 73$) and at 55.6 years for individuals bearing the functional GG allele ($n = 142$). Thus, for this patient subgroup rs867228 present in hetero- or homozygosity accelerated the age of diagnosis by 6.3 years ($p = 0.0067$). In contrast, no significant differences were found for age at diagnosis among the genotypes within luminal B HER2+ (Figure 1c), luminal A-like cancers (Figure 1b), HER2+ cancers (Figure S1c) or triple-negative breast cancers (Figure S1d). Hence, early diagnosis induced by the presence of at least one loss-of-function allele (TT or TG) of *FPR1* rs867228 appears to be a specific feature of luminal B breast cancer. Indeed, the aggregate of luminal B breast cancers (irrespective of HER2 status) exhibited a significantly ($p = 0.036$) earlier diagnosis for patients bearing at least one of the two loss-of-function alleles (TT or TG, $n = 93$) of rs867228 (51.1 [41.4–61]) as compared to individuals bearing two functional alleles (GG, $n = 183$) of rs867228 (55.3 [46.65–63.4]) (Figure 1a).

Additionally, hetero- or homozygosity significantly anticipated the age at metastasis by 6.35 years ($p = 0.038$) and age at

Table 1. Correlation between *FPR1* rs867228 mutational status and age at diagnosis in StoRM patients. Significant *p*-values are indicated in italic. *P*-values lower than 0.01 are highlighted using a color graded score, ranging from pale orange to orange. Abbreviations: HER2, human epidermal growth factor receptor 2 and IQR, interquartile range.

Age at diagnosis	All Median age (IQR), number	Luminal A Median age (IQR), number	Luminal B HER2$^-$ Median age (IQR), number	Luminal B HER2$^+$ Median age (IQR), number	Luminal B Median age (IQR), number	Triple negative Median age (IQR), number	HER2$^+$ Median age (IQR), number
n	530	117	215	61	276	87	50
G/G	55.25 (46.825-63.3), n=338	56.1 (47.3-63.3), n=75	55.6 (47.475-63.3), n=142	52.8 (42.3-63.6), n=41	55.3 (46.65-63.4), n=183	54.75 (44.25-63.35), n=50	53.25 (49.2-57.7), n=30
T/G	52.8 (42.3-62.5), n=177	54.5 (46.6-62.5), n=37	47.2 (41.125-60.65), n=66	56.45 (46.2-66.25), n=20	50.85 (41.25-61), n=86	51.5 (40.65-62.2), n=35	58 (45.85-66.5), n=19
T/T	53.3 (46.4-61.1), n=15	53.3 (47-65.6), n=5	55.3 (47.1-62.6), n=7	NA	55.3 (47.1-62.6), n=7	50.15 (48.525-51.775), n=2	35.1 (35.1-35.1), n=1
T/G & G/G	54.9 (46.825-62.9), n=515	55.1 (47.3-62.825), n=112	54.45 (47.475-62.8), n=208	54.7 (42.3-64.8), n=61	54.6 (46.65-62.8), n=269	52.9 (44.25-63.2), n=85	55.3 (49.2-62.9), n=49
T/T & T/G	52.85 (42.45-62.5), n=192	54.3 (46.7-62.725), n=42	49.2 (41.2-60.7), n=73	56.45 (46.2-66.25), n=20	51.1 (41.4-61), n=93	51.5 (41.3-62.1), n=37	57.8 (42.9-66.05), n=20
G/G *vs* T/G *p* value	0.1047	0.7736	**0.0047**	0.6783	**0.0313**	0.7512	0.5725
G/G *vs* T/T *p* value	0.5383	0.8192	0.7878	NA	0.8363	0.5842	0.1049
T/G *vs* T/T *p* value	0.9575	0.7921	0.5426	NA	0.6888	0.8666	0.1652
T/G & G/G *vs* T/T *p* value	0.6985	0.7979	0.9901	NA	0.9943	0.6813	0.1110
G/G *vs* T/T & T/G *p* value	0.0936	0.8446	**0.0067**	0.6783	**0.0364**	0.6834	0.8045

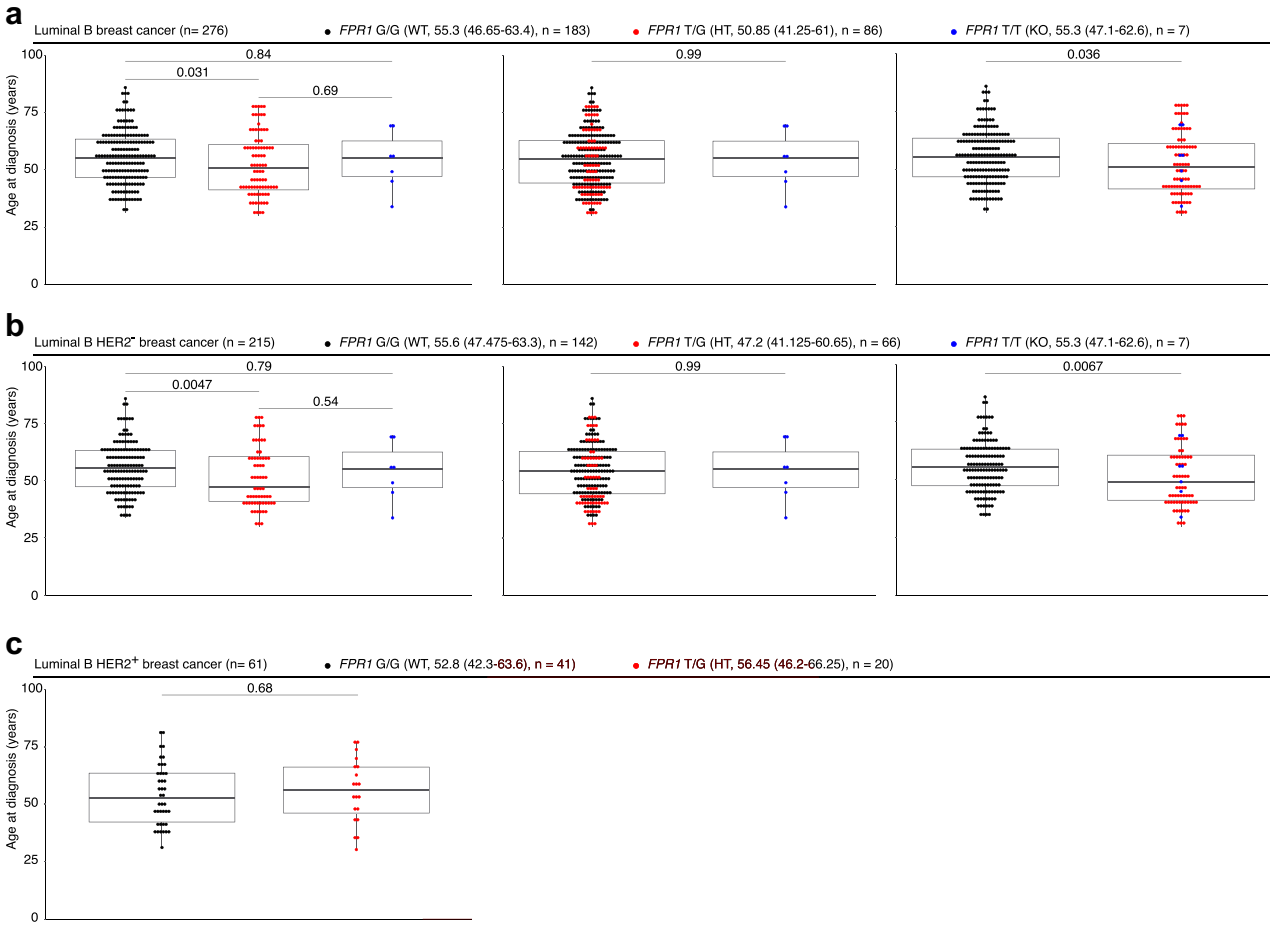

Figure 1. Correlation between *FPR1* polymorphism and age at diagnosis in luminal B breast cancer subcategories. Age at diagnosis according to *FPR1* genotype for luminal B (A), luminal B HER2- (B) and luminal B HER2+ (C) patients.

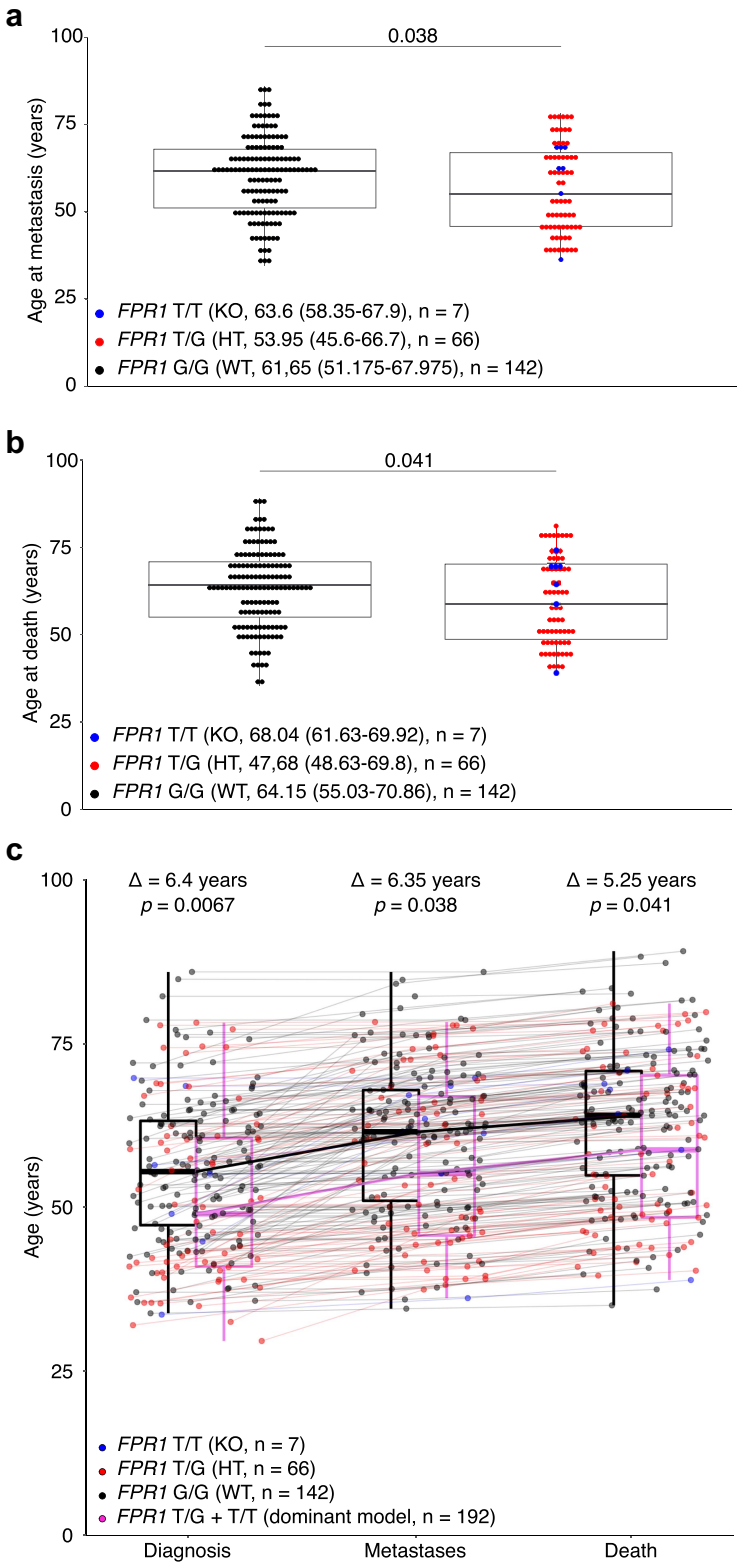

Figure 2. Impact of *FPR1* polymorphism for luminal B HER2 -breast cancer patients. Age at metastasis (a) and death (b) according to *FPR1* genotype are depicted for luminal B HER2- breast cancer patients. (c) Individual trajectories from diagnosis to metastases and death.

death by 5.25 years ($p = 0.041$) of luminal B HER2-breast patients (Figure 2).

Of note, there was no difference in the time to progression free survival or overall survival for any of the rs867228 genotypes among any of the breast cancer subtypes (Figure S2 and S3). Hence, rs867228 influences age of diagnosis but has no significant impact on subsequent disease outcomes.

Discussion

The present paper provides an independent validation for the observation that luminal B breast cancer manifests earlier in individuals bearing rs867228 in homo-or heterozygosity (T/T or T/G) as opposed to patients lacking rs867228 (G/G). In our original report based on the TCGA, the diagnosis-accelerating effect of rs867228 was estimated as 4.9 years.[8,14] In the validation cohort reported here, this effect was estimated to be 6.3 years (49.2 [41.2–60.7] for T/T and T/G *vs* 55.6 [47.475–63.3] for G/G), which is in the same range, hence confirming our initial observation.

At the theoretical level, the question arises why a SNP like rs867228 that apparently accelerates cancer diagnosis would be that frequent among humans. Obviously, there is no genetic selection against cancer development as cancer usually manifests at a post-reproductive age.[17] Why would a loss-of-function SNP affecting *FPR1* be useful in the context of other, nonmalignant challenges? To respond to this question, it may be useful to remember that, at the population level, immune diversity constitutes a benefit. For instance, it has been amply documented that the diversity of major histocompatibility complexes (MHC), confers an advantage to at least some individuals in mounting protective immune responses against infectious pathogens.[18] Similarly, it may be an advantage to conserve loss-of-function variations of pattern recognition receptors in the population.[19] Of course, loss of FPR1 confers susceptibility to infectious diseases caused by *Listeria monocytogenes*,[20] *Staphylococcus aureus*,[21] *Streptococcus pneumoniae* [22] and *Escherichia coli*.[23] However, FPR1 is also the receptor for the causative agent of plague, *Yersinia pestis*, suggesting that its absence may confer protection against specific types of communicable disease.[24] Moreover, FPR1 is involved in the modulation of inflammatory response that can be advantageous or deleterious.[25] Thus, *Fpr1*$^{-/-}$ mice are susceptible to sterile skin wounds[26] and lipopolysaccharide-induced liver damage.[27] In sharp contrast, knockout of *Fpr1* causes resistance to aerosolized lipopolysaccharide,[28] cigarette smoke-induced airway inflammation and emphysema,[29,30] hydrochloric acid-induced sterile lung injury,[31] bleomycin-induced lung fibrosis,[32] primary graft dysfunction of the lung,[33] as well as bronchiolitis obliterans syndrome developing after chronic lung allograft rejection.[34] Beyond these protective effects on the lung, knockout of *Fpr1* also confers resistance to surgically induced endometriosis,[35] cuprizone-induced demyelination of the corpus callosum,[36] dinitrobenzene sulfonic acid-induced colitis,[37] high-fat diet induced glucose intolerance,[38] as well as age-associated cataracts.[39] In some pathologies, FPR1 plays a dual role. Indeed, traumatic brain injury is attenuated in *Fpr1*$^{-/-}$ mice during the acute phase (24 hours) while aggravated in the long-term (4 weeks).[40] In humans, elevation of circulating mitochondrion-derived formylated peptides correlates with disease severity in intracerebral hemorrhage,[41] rheumatoid arthritis,[42] systemic sclerosis,[43] autoantibody-associated vasculitis and large-vessel vasculitis,[44] as well as in septic shock.[45] In sum, FPR1 plays a pleiotropic disease-modulatory role, meaning that the presence of individuals lacking functional FPR1 may confer an advantage to populations challenged by environmental stressors.

In more practical terms, the question arises whether the luminal B breast cancer-accelerating effect of rs867228 can be harnessed to ameliorate current strategies for cancer prevention or interception. It appears that the apparent capacity of rs867228 to anticipate the manifestation of luminal B breast cancer by 5 to 6 years in close-to one third of women might be taken advantage of to design specific strategies dedicated to women at high risk of developing this type of mammary carcinomas such as individuals who manifested major weight gain since age 18 or who developed diabetes.[46,47] As polygenic risk scores are developing as a matter of identifying women at higher risk of breast cancer and proposing adapted risk-based strategies, the incorporation of rs867228 in individual risk communication could help refine the personalized, age-adapted screening strategy.[48,49] Increasing the frequency and stringency of screening examinations for a high-risk population (affected by rs867228 and diabetes or obesity) could help diagnose luminal B breast cancer at a relatively earlier stage for curative interventions with improved chances of long-term success.

As a limitation, this study focused exclusively on rs867228 without including any information on pathogenic variants in genes that increase breast cancer risk such as BRCA1 and BRCA2 (and with a lower penetrance) ATM, BARD1, CHEK2, PALB2, RAD51C and RAD51D, that together build the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, BOADICEA.[48,50] Future multivariate analyses must evaluate the interaction between rs867228 and BOADICEA as well as with more extended polygenic risk scores that are being developed based on genome-wide association studies.[51] As a possibility, known breast cancer risk genes (which increase the probability of women to develop cancer during their lifetime) might preferentially act in a cancer cell-autonomous manner, for instance by debilitating DNA repair and cell cycle checkpoints. In contrast, immunogenetic alterations exemplified by rs867228 apparently do not modulate the lifelong breast cancer risk, but – in speculative terms – rather accelerate the transition from subclinical lesions that are still under immunosurveillance to manifest luminal B cancers that have escaped from immune control, hence leading to precocious diagnosis of the disease. However, this hypothetical interaction between risk-determining genes with cell-autonomous pro-malignant effects and immunogenetic aberrations with merely disease-accelerating effects must be explored in larger retrospective and (ideally) prospective studies.

In sum, it appears that patients with luminal B breast cancer bearing rs867228 in heterozygosity are diagnosed with their disease several years earlier than women lacking rs867228. Future studies should evaluate how rs867228 interacts with other environmental and (poly)genetic risk factors for breast cancer development and whether knowledge on rs867228 may

be advantageously incorporated into early detection campaigns.

Conflicts of interest

GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sotio, Tollys, Vascage and Vasculox/Tioma. GK has been consulting for Reithera. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. FA has grants and advisory roles (compensated to the hospital) for Daiichi Sankyo, Pfizer, Novartis, Astra Zeneca, Lilly, Roche. SD reports grants and non-financial support from Pfizer, grants from Novartis, grants and non-financial support from AstraZeneca, grants and non-financial support from Roche Genentech, grants from Lilly, grants from Puma, grants from Myriad, grants from Orion, grants from Amgen, grants from Sanofi, grants from Genomic Health, grants from GE, grants from Servier, grants from MSD, grants from BMS, grants from Pierre Fabre, grants from Seagen, grants from Exact Sciences, grants from Rappta, grants from Besins, grants from European Commission, grants from French government grants, grants from Fondation ARC, outside the submitted work. Dr Bachelot reports personal fees from Seagen, grants from Seagen to institution, personal fees from Pfizer, grants from Pfizer to institution, personal fees from AstraZeneca/Daiichi, grants from AstraZeneca/Daiichi to institution, personal fees from Novartis, grants from Novartis to institution, personal fees from Lilly, and non-financial support from Pfizer, all outside the submitted work. The funders had no role in the design of the study; in the writing of the manuscript, or in the decision to publish the results.

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Abbreviations

ANXA1, annexin A1; ER, estrogen receptor; FPR1, formyl peptide receptor-1; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TCGA, The Cancer Genome Atlas; SNP, single nucleotide polymorphisms; SToRM, SNPs To Risk of Metastasis.

Disclosure statement

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