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EDITORIAL

A major genetic accelerator of cancer diagnosis: rs867228 in FPR1

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Over the last two decades, it has become clear that cancer is not a purely cell-autonomous disorder and that chronic inflammation as well as failure of immunosurveillance may have a decisive impact on the manifestation and clinical course of malignant disease.[1] Nonetheless, genetic studies have mostly focused on cancer (stem) cell-intrinsic genetic and epigenetic alterations to discover the contribution of oncogenes and tumor suppressor genes to carcinogenesis. The occurrence of malignancies in families as well as the development of several tumors in the same individual spurred the discovery of hereditary cancer susceptibility genes many of which are involved in the maintenance of genomic stability as exemplified by APC regulator of WNT signaling pathway *(APC)*, ATM serine/threonine kinase *(ATM)*, BRCA1 DNA repair associated *(BRCA1)*, BRCA2 DNA repair associated *(BRCA2)*, mutL homolog 1 (*MLH1)*, mutS homolog 2 (*MSH2)*, retinoblastoma (*RB)* and tumor protein p53 (*TP53)*.[2] Thus far, no immune genes that have a broad clinical impact in several types of cancer have been precisely identified, contrasting with the fact that polymorphisms affecting loci linked to immune-related genes are present in certain polygenic scores associated with cancer risk.[3,4]

Formyl peptide receptor 1 (FPR1) is a pathogen recognition receptor that is activated by a promiscuous array of ligands from bacterial origin (such as formyl peptides) to ligands liberated by stressed cells such as annexin A1 (ANXA1), a ubiquitous cytosolic protein.[5] When cancer cells die, for instance in the context of chemotherapies, they leak annexin A1 into the extracellular space.[6] Here, ANXA1 acts on FPR1, a seven-transmembrane G protein-coupled receptor to guide the chemotactic movement of myeloid cells (granulocytes, macrophages and dendritic cells) toward the source of ANXA1. For this reason, in preclinical studies, chemotherapy becomes unable to induce a therapeutically relevant anticancer immune response when cancer cells are deficient in ANXA1 or when the immune system lacks functional FPR1.[6] Indeed, in both cases, dying tumor cells fail to physically interact with dendritic cells (DCs), the professional antigen-presenting cells that are required to prime cytotoxic T lymphocytes for subsequent recognition and lysis of neoplastic cells.[6] Moreover, FPR1-deficient DCs become unable to present major histocompatibility complex (MHC) class I-restricted antigens to $CD8^+$ T lymphocytes. This defect in antigen presentation can be overcome by provision of the Toll-like receptor-3 (TLR3) ligand polyinosinic:polycytidylic acid (poly I:C) both *in vitro* and *in vivo*, in $Fpr1^{-/-}$ mice. Thus, chemotherapy with anthracyclines or oxaliplatin against established cancers fails to reduce tumor growth in FPR1-deficient mice unless poly I:C is injected.[7]

The single nucleotide polymorphism (SNP) rs867228 ((worldwideallelic frequency 19 to 20%) is a loss-of-function variation in *FPR1* (causing the E346A amino acid substitution in the intracellular C-terminus of FPR1)" with "is a loss-of function variation in *FPR1* causing the E346A amino acid substitution in the intracellular C-terminus of FPR1.) is a loss-of-function variation in *FPR1* (causing the E346A amino acid substitution in the intracellular C-terminus of FPR1).[8] rs867228 negatively affects the survival of breast and colorectal cancer patients treated by immunogenic chemotherapy.[6] This was observed in two independent cohorts of breast cancer patients undergoing adjuvant anthracycline-based chemotherapy in which homozygosity (TT) or heterozygosity (GT) had a negative impact on overall and metastatic-free survival as compared to individuals bearing the wild type alleles (GG).[6,9] Similarly, in patients with colorectal cancer treated with oxaliplatin-based chemotherapy, homozygosity (TT) in rs867228 had a negative effect on overall survival.[6] *In vitro*, DCs from individuals bearing rs867228 can not approach dying cancer cells in microfluidic chambers, revealing an immune defect that might explain the poor prognosis of cancer patients harboring this SNP.[10]

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Table 1. Impact of rs867228 on age at diagnosis in carcinomas versus non-epithelial cancers

Parameter	Pan-cancer	Pan-carcinoma*	Pan-non-carcinoma**
Number of patients (%)			
T/T, n	462 (5%)	343 (4%)	88 **(5%)**
T/G, n	3378 (33%)	2577 (34%)	608 (32%)
G/G, n	6354 (62%)	4743 (62%)	1192 (63%)
Mean age at diagnosis			
T/T, years ± SD	57.7 ± 13.8	59.0 ± 13.0	54.4 ± 14.9
T/G, years ± SD	59.2 ± 14.5	60.5 ± 13.6	55.0 ± 16.0
G/G, years ± SD	60.0 ± 14.4	61.6 ± 13.5	55.4 ± 16.0
T/T or T/G, years ± SD	59.0 ± 14.4	60.4 ± 13.6	55.0 ± 16.1
T/G or G/G, years ± SD	59.7 ±.14.5	61.2 ± 13.5	55.3 ± 16.1
Median age at diagnosis			
T/T, years ± IQR	59.6 ± 18.8	60.2 ± 17.9	58.5 ± 24.1
T/G, years ± IQR	60.6 ± 20.0	61.6 ± 18.6	56.3 ± 24.4
G/G, years ± IQR	61.2 ± 19.1	62.6 ± 17.9	56.4 ± 23.3
T/T or T/G, years ± IQR	60.5 ± 20.0	61.4 ± 18.8	56.4 ± 24.4
T/G or G/G, years ± IQR	61.0 ± 19.4	62.2 ± 18.1	56.3 ± 23.6
Statistics comparisons of age			
T/T vs T/G, *p* value	**0.0207**	**0.0317**	0.7445
T/T vs G/G, *p* value	**0.0004**	**0.0003**	**0.624**
T/G vs G/G, *p* value	**0.0117**	**0.0013**	0.7292
T/T or T/G vs G/G, *p* value	**0.0009**	**0.0001**	0.6459
T/G or G/G vs T/T, *p* value	**0.0016**	**0.0015**	0.6573

*Carcinoma: ACC, BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, OV, PAAD, PCPG, PRAD, READ, STAD, THCA, UCS, UCEC.
**Non-carcinoma: DLBC, GBM, LAML, LCML, LGG, MESO, UVM, SARC, SKCM.
Groups were compared by means of the two-sided Mann–Whitney U test. Significant *p* values are indicated in bold.

Abbreviations: ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma end endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; IQR, interquartile range; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LCML, chronic myeloid leukemia; LGG, low grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SD, standard deviation; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma; UCS, uterine carcinosarcoma; UCEC, uterine corpus endometrial carcinoma; UVM, uveal melanoma.

Table 2. Impact of rs867228 on prognosis

Parameter	Pan-cancer	Pan-carcinoma	Pan-non-carcinoma
PFS (T/G *vs* T/T) HR	1.07 (0.91–1.24)	0.99 (0.83–1.19)	1.3 (0.95–1.78)
PFS (T/G *vs* T/T) *p* value	0.416	0.925	0.099
PFS (G/G *vs* T/T) HR	1.05 (0.91–1.22)	0.98 (0.82–1.16)	1.33 (0.98–1.8)
PFS (G/G *vs* T/T) *p* value	0.511	0.797	0.07
PFI (T/G *vs* T/T) HR	1.08 (0.91–1.28)	0.98 (0.8–1.2)	1.34 (0.97–1.87)
PFI (T/G *vs* T/T) *p* value	0.388	0.868	0.08
PFI (G/G *vs* T/T) HR	1.06 (0.9–1.25)	0.96 (0.79–1.17)	1.37 (0.99–1.89)
PFI (G/G *vs* T/T) *p* value	0.512	0.691	0.057
DFI (T/G *vs* T/T) HR	1.02 (0.75–1.39)	0.97 (0.7–1.33)	2.53 (0.61–10.57)
DFI (T/G *vs* T/T) *p* value	0.89	0.83	0.203
DFI (G/G *vs* T/T) HR	0.93 (0.69–1.26)	0.88 (0.64–1.2)	2.25 (0.55–9.21)
DFI (G/G *vs* T/T) *p* value	0.646	0.408	0.259
OS (T/G *vs* T/T) HR	1 (0.84–1.19)	0.94 (0.76–1.16)	1.17 (0.82–1.65)
OS (T/G *vs* T/T) *p* value	0.994	0.575	0.386
OS (G/G *vs* T/T) HR	1 (0.85–1.19)	0.94 (0.76–1.15)	1.25 (0.89–1.75)
OS (G/G *vs* T/T) *p* value	0.968	0.539	0.199
DSS (T/G *vs* T/T) HR	0.97 (0.78–1.21)	0.9 (0.7–1.17)	1.14 (0.76–1.7)
DSS (T/G *vs* T/T) *p* value	0.802	0.448	0.523
DSS (G/G *vs* T/T) HR	0.99 (0.81–1.22)	0.9 (0.7–1.17)	1.28 (0.87–1.89)
DSS (G/G *vs* T/T) *p* value	0.952	0.441	0.21

Abbreviations: DFI, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; PFI, progression-free interval; PFS, progression-free survival.

In the world population, rs867228 affects In the world population, rs867228 affects 4% and 30-32% of individuals in homozygosity (TT) and heterozygosity (GT), respectively, totaling 34-36%. We did not identify any cancer type in which these frequencies would be significantly different from the control groups“ with”In the world population, rs867228 affects 19 to 20% of individuals in homozygosity (TT) and heterozygosity (GT). We did not identify any cancer type in which this frequency would be significantly different from the control groups individuals in homozygosity (TT) and heterozygosity (GT), respectively, totaling 34–36%. We did not identify any cancer type in which these frequencies would be significantly different from the control groups, meaning that rs867228 is not a cancer susceptibility gene variant.[7] However, pan-cancer analysis of the “The Cancer Genome Atlas” (TCGA) revealed that patients bearing rs867228 were diagnosed significantly earlier than patients harboring the wild type alleles (GG), by a mean of 2.3 y for homozygosity (TT) and by a mean of 0.8 y for heterozygosity (GT).[7] This difference was also detectable for a pan-carcinoma analysis, yet was not observed for patients affected by non-epithelial tumors (**Table 1**). Of note, rs867228 did not affect the prognosis of cancer patients (**Table 2**). Analysis of individual cancer types using dominant (Figure 1a) and recessive (Figure 1b) models revealed that this SNP has a particularly strong effect on breast cancer, where homo- or heterozygosity (TT or GT) accelerate diagnosis by a mean of 2.1 y for all breast cancer subtypes and by 4.9 y for the luminal B subtype (Figure 1a). Moreover, breast cancer patients affected by basal subtype and exhibiting the TT genotype were diagnosed 11.3 y earlier than the ones bearing the other genotypes (Figure 1b). Other cancer categories for which rs867228 homozygosity (TT) was associated with anticipated diagnosis are esophageal carcinoma (by 6.6 y), head and neck and colorectal cancer (both by approximately 4 y). Similar, though non-significant, trends were observed for multiple other cancer types. For example, there is a non-significant correlation between homozygosity for rs867228 at the age of diagnosis for colon adenocarcinomas in the TCGA (n = 417) (Figure 1a and b). However, there is a significant effect on the larger (n = 1785) and more homogeneous (French-only) PETACC-8 cohort of colorectal cancer when employing the recessive model (Figure 1b), thus calling for additional analyses in other cohorts covering other malignancies.

FPR1 has multiple functions, not only in immunosurveillance but also in the acute response to inflammatory signals and the resolution of inflammation.[14,15] It is possible, yet remains to be demonstrated, that rs867228 affects both anticancer immunosurveillance and procarcinogenic inflammation, likely in an opposite fashion, thus explaining its capacity to accelerate the age of cancer diagnosis without affecting the incidence of malignant disease nor the prognosis of tumor patients. Irrespective of this speculation, it appears that the diagnosis-accelerating effect of rs867228 is demographically relevant. Indeed, at an estimated lifetime cancer risk of 25%, 2 billion individuals among the actual world population will develop (or have developed) different types of malignancies. In the homozygous state, rs867228 accelerates cancer

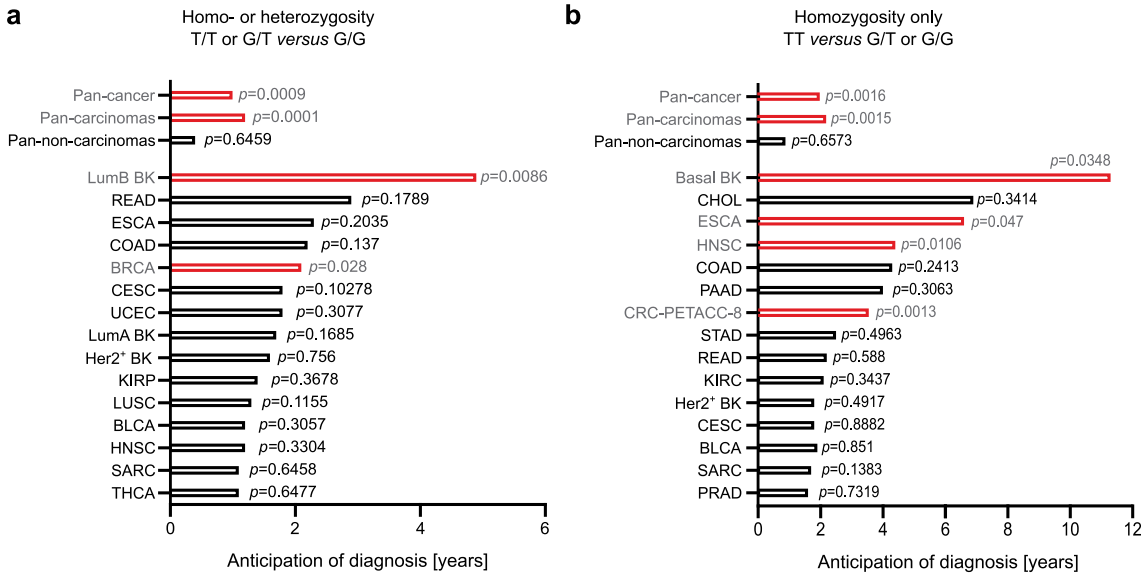

Figure 1. Precocious cancer diagnosis induced by rs867228 in different types of malignancy. (a) Dominant model, comparing age at diagnosis of rs867228 homo- and heterozygous patients (~38% of TCGA patients) to patients lacking this polymorphism. (b) Recessive model, comparing age at of rs867228 homozygous patients (~4% of TCGA patients) to the rest of the population. All data were retrieved from TCGA[11] with the exception of the colorectal cancer (CRC)-PETACC-8 cohort (NCT00265811).[7,12] Note that the most relevant effects are observed for luminal B (LumB) and basal breast cancer (BK). Patients enrolled in the CRC-PETACC-8 trial were genotyped for FPR1 rs867228 and the mean age at diagnosis were compared using one-way ANOVA and compared two by two with Tukey correction for multiple testing. TCGA germline[11] and clinical data[13] was accessed via GDC Data Portal and groups were compared using two-sided Mann–Whitney U test.

diagnosis by 2.3 years in 4% of this population (around 80 million persons). In the heterozygous state, rs867228 accelerates cancer diagnosis by 0.8 year in 30% of the world population that has developed or will develop cancer (around 600 million persons), suggesting that rs867228 potentially reduces healthy life span of the current human population. However, it remains to be determined whether the acceleration of cancer by rs867228 would not be compensated by a delayed manifestation of inflammation-driven diseases of the brain,[16] heart,[17] lung[18] or liver,[19] as this is suggested by preclinical experimentation.

The mechanisms through which rs867228 contributes to accelerated manifestations of cancers remain obscure. Although it is tempting to speculate that this effect might result from compromised immunosurveillance, it might also involve reduced inflammatory reactions, knowing that FPR1 tends to stimulate tissue inflammation.[15] Moreover, at this point, it cannot be excluded that FPR1 would influence other general cancer-predisposing phenotypes including diabetes and overweight. Future adjusted analyses must clarify this issue.

Beyond these theoretical considerations, the diagnosis of rs867228 might be incorporated into cancer prevention campaigns, at least for specific, highly prevalent tumor types such as breast and colorectal carcinoma. In this context, it will be important to study how rs867228 interacts with other genetic and environmental risk factors and whether individuals carrying rs867228 should be subjected to precocious and intensified screening procedures as well as to pronounced lifestyle interventions for efficient cancer interception. Moreover, it remains to be determined whether specific immunoprophylactic interventions such as the administration of TLR3 agonists[7] or the supplementation of immunostimulatory vitamins[20] or probiotics[21] would be efficient in retarding the manifestation of neoplasia in the target population.

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Conflicts of interest

The authors declare no conflict of interest.

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