

## No impact of cancer and plague-relevant *FPR1* polymorphisms on COVID-19

Adriana Petrazzuolo<sup>a,b,c</sup>, Julie Le Naour<sup>d</sup>, Erika Vacchelli<sup>e</sup>, Pascale Gaussem<sup>d,e</sup>, Syrine Ellouze<sup>f</sup>, Georges Jourdi<sup>e,f</sup>, Eric Solary<sup>c,g,h</sup>, Michaela Fontenay<sup>f,i</sup>, David M. Smadja<sup>d,e</sup>, and Guido Kroemer<sup>d</sup>

<sup>a</sup>Equipe Labellisée Par La Ligue Contre Le Cancer, Université De Paris, Sorbonne Université, INSERM U1138, Centre De Recherche Des Cordeliers, Paris, France; <sup>b</sup>Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; <sup>c</sup>Faculty of Medicine Kremlin Bicêtre, Université Paris Saclay, Paris, France; <sup>d</sup>Hematology Department and Biosurgical Research Lab, (Carpentier Foundation) Assistance Publique Hôpitaux De Paris-Centre Université De Paris (APHP-CUP), Paris, France; <sup>e</sup>Innovative Therapies in Haemostasis, INSERM, Université De Paris, Paris, France; <sup>f</sup>Biological Hematology Department, Assistance Publique-Hôpitaux De Paris. Centre-Université De Paris, Paris, France; <sup>g</sup>INSERM U1287, Gustave Roussy Cancer Center, Villejuif, France; <sup>h</sup>Department of Hematology, Gustave Roussy Cancer Center, Villejuif, France; <sup>i</sup>Institut Cochin, CNRS UMR8104, INSERM U1016, Université De Paris, Paris, France; <sup>j</sup>Institut Universitaire De France, Paris, France; <sup>k</sup>AP-HP, Hôpital Européen Georges Pompidou, Paris, France; <sup>l</sup>Suzhou Institute for Systems Medicine, Chinese Academy of Medical Sciences, Suzhou, China; <sup>m</sup>Karolinska Institute, Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

### ABSTRACT

Formyl peptide receptor 1 (FPR1) is a pattern-recognition receptor that detects bacterial as well as endogenous danger-associated molecular patterns to trigger innate immune responses by myeloid cells. A single nucleotide polymorphism, rs867228 (allelic frequency 19–20%), in the gene coding for FPR1 accelerates the manifestation of multiple carcinomas, likely due to reduced anticancer immunosurveillance secondary to a defect in antigen presentation by dendritic cells. Another polymorphism in *FPR1*, rs5030880 (allelic frequency 12–13%), has been involved in the resistance to plague, correlating with the fact that FPR1 is the receptor for *Yersinia pestis*. Driven by the reported preclinical effects of FPR1 on lung inflammation and fibrosis, we investigated whether rs867228 or rs5030880 would affect the severity of coronavirus disease-19 (COVID-19). Data obtained on patients from two different hospitals in Paris refute the hypothesis that rs867228 or rs5030880 would affect the severity of COVID-19.

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### Introduction

Coronavirus disease 19-(COVID-19) poses a major challenge because of its dangerousness for susceptible individuals (*i.e.* persons with preexisting medical conditions, in particular, obesity and the elderly) as well as its political (mis-)management that disrupted the economic, cultural and social life of entire nations.<sup>1,2</sup> In nonsusceptible individuals lacking discernible risk factors,<sup>3,4</sup> infection by SARS-CoV-2, the agent responsible for COVID-19 is usually asymptomatic or paucisymptomatic, although exceptions have been reported.<sup>5–9</sup> For this reason, strategies for identifying individuals at risk might help to guide strategies for the selective confinement or vaccination of those persons who are at risk of severe or lethal SARS-CoV-2.<sup>5</sup>

Formyl peptide receptor 1 (FPR1) is a pattern-recognition receptor (PRR)<sup>10</sup> that is mostly expressed by myeloid cells including granulocytes, macrophages, and dendritic cells.<sup>11</sup> Like other PRRs, FPR1 recognizes pathogen-associated molecular patterns (PAMPs), which are microbial structures, and danger-associated molecular patterns (DAMPs), which are host molecules displayed on, or released by, stressed and dying cells.<sup>12–15</sup> As its name indicates, FPR1 recognizes formylated peptides, mostly peptides from bacteria that have undergone a prokaryote-specific post-translation protein modification called formylation.<sup>12</sup>

However, formylated peptides are also generated by mitochondria (which, in evolutionary terms, are relics of prokaryotes incorporated into the eukaryotic proto-organism).<sup>16,17</sup> Moreover, FPR1 interacts with other endogenous ligands including annexin A1 (ANXA1), a ubiquitous protein contained in the cytosol of all nucleated cells that leak into the extracellular space when cells die.<sup>18–23</sup> Thus, FPR1 plays a major role in the response to pathogens as well as in the regulation of immune and inflammatory responses.<sup>24</sup>

The roles of FPR1 in the response to infectious pathogens can be either positive or negative.<sup>11,22</sup> Thus, FPR1-deficient mice are more susceptible to lethal infection by *Escherichia coli* and *Listeria monocytogenes*<sup>25,26</sup> but resistant against *Yersinia pestis*, the agent causing plague.<sup>27</sup> Similarly, FPR1 has an ambiguous role in the context of noninfectious diseases.<sup>11</sup> FPR1-deficient mice are resistant against pathogenic inflammation in the context of ischemia-reperfusion damage of the heart,<sup>28</sup> celiac disease,<sup>29</sup> endotoxin-induced lung injury,<sup>30,31</sup> cigarette smoke-induced emphysema,<sup>32,33</sup> as well as bleomycin-induced pulmonary fibrosis.<sup>34</sup> Conversely, FPR1-negative mice are unable to mount immune responses against cancers following chemotherapy with anthracyclines or oxaliplatin.<sup>14,22,35</sup>

The ambiguous role of FPR1 extends to humans. In the context of plague, the single nucleotide polymorphism (SNP) rs5030880 (R190W affecting the extracellular loop 2

Table 1. Allelic frequencies of FPR1 SNPs and characteristics of patient population from Hôpital Cochin and Hôpital Européen George Pompidou.

SNP frequency	FPR1 rs867228				FPR1 rs5030880			
	Wild type (GG) n/tot (%)	Heterozygous (GT) n/tot (%)	Mutated Homozygous (TT) n/tot (%)	Wild type (TT) n/tot (%)	Heterozygous (TA) n/tot (%)	Mutated Homozygous (AA) n/tot (%)	Heterozygous (TA) n/tot (%)	Mutated Homozygous (AA) n/tot (%)
<b>Men</b>	88/139 (63.3)	42/139 (30.2)	9/139 (6.5)	114/140 (81.4)	24/140 (17.1)	2/140 (1.4)	24/140 (17.1)	2/140 (1.4)
<b>Women</b>	55/91 (60.4)	31/91 (34.1)	5/91 (5.5)	75/92 (81.5)	15/92 (16.3)	2/92 (2.2)	15/92 (16.3)	2/92 (2.2)
<b>Age ≤ 61</b>	33/48 (68.8)	11/48 (22.9)	4/48 (8.3)	39/48 (81.2)	9/48 (18.8)	0/48 (0)	9/48 (18.8)	0/48 (0)
<b>Age &gt; 61</b>	48/72 (66.7)	21/72 (29.2)	3/72 (4.2)	58/72 (80.6)	14/72 (19.4)	0/72 (0)	14/72 (19.4)	0/72 (0)
<b>BMI ≤ 27.2</b>	40/67 (59.7)	21/67 (31.3)	6/67 (9)	56/68 (82.4)	10/68 (14.7)	2/68 (2.9)	10/68 (14.7)	2/68 (2.9)
<b>BMI &gt; 27.2</b>	38/58 (65.5)	17/58 (29.3)	3/58 (5.2)	51/59 (86.4)	7/59 (11.9)	1/59 (1.7)	7/59 (11.9)	1/59 (1.7)
	32/54 (59.3)	18/54 (33.3)	4/54 (7.4)	52/64 (81.2)	12/64 (18.8)	0/64 (0)	12/64 (18.8)	0/64 (0)
<b>Fever</b>	69/106 (65.1)	31/106 (29.2)	6/106 (5.7)	90/107 (84.1)	17/107 (15.9)	0/107 (0)	17/107 (15.9)	0/107 (0)
<b>No Fever</b>	19/33 (57.6)	11/33 (33.3)	3/33 (9.1)	24/33 (72.7)	7/33 (21.2)	2/33 (6.1)	7/33 (21.2)	2/33 (6.1)
<b>Cough</b>	60/98 (61.2)	30/98 (30.6)	8/98 (8.2)	78/99 (78.8)	19/99 (19.2)	2/99 (2)	19/99 (19.2)	2/99 (2)
<b>No Cough</b>	28/41 (68.3)	12/41 (29.3)	1/41 (2.4)	36/41 (87.8)	5/41 (12.2)	0/41 (0)	5/41 (12.2)	0/41 (0)
<b>Dyspnea</b>	66/105 (62.9)	32/105 (30.5)	7/105 (6.7)	88/106 (83)	16/106 (15.1)	2/106 (1.9)	16/106 (15.1)	2/106 (1.9)
<b>No Dyspnea</b>	21/33 (63.9)	10/33 (30.3)	2/33 (6.1)	25/33 (75.8)	8/33 (24.2)	0/33 (0)	8/33 (24.2)	0/33 (0)
<b>ICU ≤ 20 days</b>	18/28 (64.3)	8/28 (28.6)	2/28 (7.1)	23/28 (82.1)	4/28 (14.3)	1/28 (3.6)	4/28 (14.3)	1/28 (3.6)
<b>ICU &gt; 20 days</b>	19/27 (70.4)	6/27 (22.2)	2/27 (7.4)	20/27 (74.1)	7/27 (25.9)	0/27 (0)	7/27 (25.9)	0/27 (0)

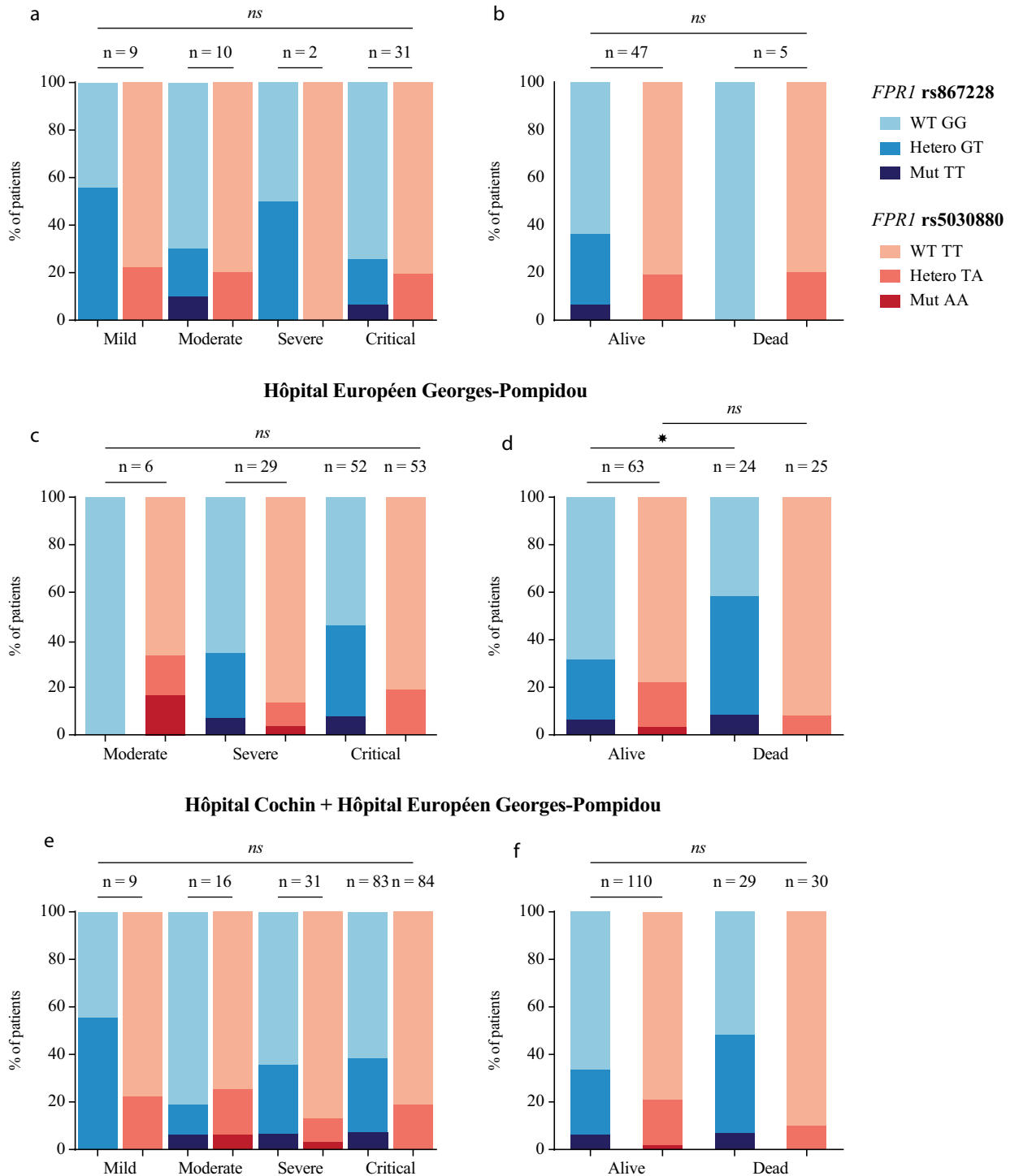
**Abbreviations:** BMI, body mass index; FPR1, formyl-peptide receptor 1; ICU, intensive care unit; SNP, single nucleotide polymorphism.

**Abbreviations:** CT, computed tomography; COVID-19, coronavirus disease 19; FPR1, formyl-peptide receptor 1; HEGP, Hôpital Européen George Pompidou; ICU, intensive care unit; PRR, pattern-recognition receptor; SNP, single nucleotide polymorphism;

of FPR1)<sup>36</sup> may constitute a resistance allele.<sup>27</sup> In the context of cancer, the loss-of-function SNP rs867228 (E346A affecting the intracellular C-terminus of FPR1)<sup>36</sup> is associated with reduced survival in breast and colorectal cancer patients treated by adjuvant anthracycline-based and oxaliplatin-based chemotherapy, respectively.<sup>35</sup> Moreover, rs867228 is associated with the precocious manifestation

of the breast, colorectal, esophageal, and head & neck cancer.<sup>37</sup>

Intrigued by these findings, in particular, the impact of FPR1 on lung inflammation, we wondered whether the cancer-associated FPR1 SNP rs867228 and the plague resistance-associated SNP rs5030880 might affect patient susceptibility to severe COVID-19.



**Figure 1.** Severity and survival of patients diagnosed with COVID19 bearing at least one copy of the variant allele of rs867228 and rs5030880 SNPs. Proportion of patients diagnosed with critical, severe, moderate and mild COVID19 disease from Hôpital Cochin (a) and Hôpital Européen George Pompidou (HEGP) (c). Patients' survival is shown as proportion of alive and dead subjects from Hôpital Cochin (b) and HEGP (d). Severity (e) and survival (f) of cumulative data from the two above mentioned hospitals. Statistical significance was calculated using the chi-squared test.

## Materials and methods

### Patients

This non-interventional multicenter CPP2020-04-048b study enrolled 140 patients (Table 1) who were diagnosed with COVID-19 based on positive RT-PCR of pharyngeal swabs. One hundred and forty patients were successfully genotyped for rs5030880 and 139 patients for rs867228 SNPs. Patients were stratified according to disease severity. Mild disease was defined by no or limited clinical symptoms, not requiring computed tomography (CT) scanning or hospitalization. Moderate disease was defined as being symptomatic, with dyspnea and radiological findings of pneumonia upon thoracic CT scan, requiring hospitalization with a maximum of 9 L/min of oxygen. Severe disease was defined as respiratory distress requiring admission at the intensive care unit (ICU). Critical disease was defined as respiratory failure, septic shock, and/or multiple organ dysfunction.

### DNA extraction

DNA was isolated from peripheral blood after elimination of red blood cells using Maxwell® 16 LEV Blood DNA Kit (Hôpital Cochin) or DNeasy Blood & Tissue Kits (Hôpital Européen George Pompidou) from Promega Corporation (Wisconsin, USA) and Qiagen™ (Germany), respectively.

### Genotyping

After extraction, genomic DNA was quantified using a NanoDrop instrument 1000 Spectrophotometer (Thermo Fisher Scientific™, Rockford, IL, USA). Then, DNA was amplified using the assay C\_3266374\_1 and C\_25628595\_20 (Thermo Fisher Scientific™, Rockford, IL, USA) for rs867228 and rs5030880 SNPs, respectively. Genotype-specific fluorescently labeled-probes allowed allelic discrimination upon a comparison of signals from fluorescent probes (VIC and FAM).

### Statistical analysis

Statistical analysis of data from Hôpital Cochin and Hôpital Européen George Pompidou was performed individually as well as cumulatively. Additionally, heterozygous and mutated patients were grouped for the statistical analysis. Proportions of patients falling in each category were compared using the fisher's exact test or chi-squared test to investigate survival or severity, respectively, using the GraphPad Prism software (San Diego, CA, USA). \*  $p$  value < .05; ns, nonsignificant.

## Results and discussion

One hundred forty patients diagnosed with COVID-19 were enrolled in this study following the usual procedures (written informed consent, permission by the ethical committee, anonymization of all records) at two major Paris hospitals, Hôpital Cochin, and Hôpital Européen George Pompidou (HEGP). Patients were stratified according to COVID-19 severity

(Table 1) and were genotyped for the cancer-relevant SNP rs867228 and the plague-relevant SNP rs5030880. Results were represented for patients from Hôpital Cochin (Figure 1a,b), HEGP (Figure 1c,d) or both hospitals (Figure 1e,f). In the overall population, rs867228 is found in homozygosity (TT) and heterozygosity (GT) at a frequency of 3.8% and 15.7% and rs5030880 at a frequency of 1.4% (AA) and 10.5% (TA), respectively. Both SNPs were found at a frequency that is similar to that reported to the general population. No significant trend in favor of a disease severity-associated under- or overrepresentation of either of the two SNPs was detected, suggesting that none of the two SNPs has a major impact on disease severity. Thus, within the limits of this study (which may be underpowered to detect small effects), the results invalidate the hypothesis that major disease-relevant SNPs in *FPR1* would have a strong impact on COVID-19 pathogenesis.

Genome-wide association studies have shown that progression of COVID-19 to respiratory failure is associated with locus 3p21.31, spanning the genes solute carrier family 6 member 20 (*SLC6A20*), leucine zipper transcription factor-like 1 (*LZTFL1*), C-C motif chemokine receptor 9 (*CCR9*), FYVE and coiled-coil domain autophagy adaptor 1 (*FYCO1*), C-X-C motif chemokine receptor 6 (*CXCR6*) and X-C motif chemokine receptor 1 (*XCRI*), as well as with locus 9q34.2 coinciding with the alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase (ABO) blood group locus, but no association with 19q.13.3, where *FPR1* is located.<sup>38</sup> Another study demonstrated that SNPs affecting angiotensin I converting enzyme 2 (*ACE2*) and two key host factors of SARS-CoV-2 were likely associated with the genetic susceptibility of COVID-19.<sup>39,40</sup> Thus, the literature published during the execution of this study confirms the conjecture that SNPs in *FPR1* have no major disease-modulatory role in COVID-19.<sup>41</sup>

In conclusion, neither rs867228 nor rs5030880 affects the severity of the clinical course of COVID-19. It appears plausible to speculate that polymorphisms affecting the function of PRRs such as *FPR1* or Toll-like receptors are prevalent in the population to create heterogeneity in the response to major life-threatening infectious pathogens, avoiding, for example, excessive inflammatory responses in a fraction of the population. In this sense, such PRR polymorphisms might have a similar function as the heterogeneity in major histocompatibility complex (MHC) genes.<sup>42,43</sup> While MHC polymorphisms create interindividual variation in cognate antigen recognition because of their impact on the immunopeptidome, PRR polymorphism would create variation in the recognition of innate adjuvant signals.<sup>44</sup> The combination of both mechanisms then may increase the chance that a sizable fraction of the population is protected against one or the other infectious agent. However, at this point, it remains to be determined which communicable diseases are modulated in their severity by rs867228 or rs5030880.

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## ORCID

Julie Le Naour  <http://orcid.org/0000-0002-3749-2171>  
 Erika Vacchelli  <http://orcid.org/0000-0001-8010-0594>  
 Guido Kroemer  <http://orcid.org/0000-0002-9334-4405>

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