Prevalence of Pathogenic Variants of FAN1 in More Than 5000 Patients Assessed for Genetic Predisposition to Colorectal, Breast, Ovarian, or Other Cancers

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Prevalence of pathogenic variants of *FAN1* among more than 5000 consecutive patients referred to one genetic clinic for suspected hereditary predisposition to colorectal, breast/ovarian or other cancers.

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I, the designated Corresponding Author, certify that myself and each of my co-authors have contributed to manuscript as follows:

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- Emmanuelle Mouret-Fourme: study concept and design; acquisition of data; analysis and interpretation of data; statistical analysis; critical revision of the manuscript.
- Chrystelle Colas : acquisition of data; critical revision of the manuscript.
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Abbreviations:

CRC = Colorectal cancer; *FAN1* = *FANCD2/FANCI*-Associated Nuclease 1; KIN = karyomegalic interstitial nephropathy; NGS = new generation sequencing; NCCN = National Comprehensive Cancer Network; pMMR = mismatch repair-proficient; WES = whole exome sequencing

Introduction

Despite significant advances in the molecular diagnosis of hereditary colorectal cancer (CRC) during the past decades, numerous clinical situations suggestive of major genetic predisposition remain unexplained. In 2015, Segui *et al.* identified *FAN-1* (*FANCD2/FANCI-Associated Nuclease 1*) gene as a potential major gene of predisposition to colorectal polyps/cancer (1). Indeed, whole exome sequencing (WES) led to the identification of a heterozygous nonsense truncating alteration of this gene in three affected relatives from a Spanish family with unexplained aggregation of mismatch repair-proficient (pMMR) CRC. Another nonsense variant of *FAN1* and three missense variants, two of which being predicted as damaging by *in silico* algorithms, were further identified in 177 unrelated pMMR Amsterdam-positive Spanish families. Despite these data, Broderick *et al.* considered that the contribution of *FAN1* in hereditary CRC was doubtful as evidence of co-segregation was weak with a non-significant non parametric linkage segregation score at 1.05 ($p=0.125$) using all five families reported by Segui *et al.* and as no other alterations of *FAN1* were identified on WES in five colorectal tumors arising in patients with either truncating or predicted damaging missense variation of this gene (2). Moreover, the authors performed WES in 863 familial CRC cases of European ancestry and in 1604 controls with no history of malignancy. They found no significant increase in the burden of *FAN1* mutations in cases *versus* controls.

Methods

In order to further explore the contribution of *FAN1* in the genetic predisposition to colorectal polyps/cancer, we assessed and compared the prevalence of pathogenic variants of *FAN1* in consecutive patients who were referred to our cancer genetic clinic between May 2015 and November 2017 because their personal and/or familial

history was suggestive of a genetic predisposition to CRC, breast or breast/ovarian cancer or other cancers/conditions. These patients met the French national genetic testing criteria that are very similar to those recommended by the NCCN (<https://www.nccn.org>).

Molecular analysis consisted in screening for pathogenic variants a panel of 56 genes using new generation sequencing (NGS). The panel includes *FAN1* as our laboratory is involved in the molecular diagnosis of karyomegalic interstitial nephropathy (KIN) due to bi-allelic pathogenic variants of *FAN1*. Bioinformatic analysis of the NGS data was restricted to a panel of genes associated with the clinically suspected predisposition. *FAN1* analysis was secondarily performed for the purposes of the study in patients who agreed to participate.

Results

FAN1 analysis was performed in a total of 5136 patients with a clinically suspected genetic predisposition to CRC (Group 1; n=436), breast or breast/ovarian cancer (Group 2; n=3991), or other cancers/conditions (Group 3; n=709). A mono-allelic pathogenic variant (nonsense and frameshift indel) of *FAN1* was identified in 18 patients (0.35%) in the entire series: 2 in Group 1; 14 in Group 2, and 2 in Group 3 corresponding to a frequency of heterozygotes of 0.46%, 0.35% and 0.28% respectively (Table 1). The frequency of heterozygotes in patients from Group 1 was not significantly different from that of Groups 2 or 3 (Fisher exact test, p-value=0.7 and 0.6 respectively), or from the expected frequency in the general population assessed in the 1000 Genomes and in the gnomAD v2.1 populations (Fisher exact test, p-value=0.3 and 0.1 respectively).

One of the two patients in Group 1 with a pathogenic variant of *FAN1* was a male with multiple hamartomatous polyps, and the other was a female diagnosed with

endometrial adenocarcinoma at 53 years of age. No CRC was reported in the relatives of either patient. Moreover, no CRC was reported in the first/second degree relatives of the 16 index cases in Groups 2 or 3 with a pathogenic variation of *FAN1*.

Discussion

The results of our study argue against the implication of pathogenic variants of *FAN1* in unexplained cases of suspected genetic predisposition to colorectal polyps/cancer. Three other observations reinforce this conclusion: no CRC was declared in the close blood relatives of four index cases with KIN and bi-allelic germline mutation of *FAN1* identified in our laboratory, nor in patients with some neurodevelopmental disabilities associated the 15q13.3 microdeletion that encompasses *FAN1* (3); the prevalence of pathogenic variants of *FAN1* identified from exome data of 1449 colorectal adenocarcinomas available in cBioPortal (<http://www.bioportal.org>) is not significantly different from that reported in the gnomAD database (Fisher exact test, p-value=1). Based on these results and on previously published data, the French *Groupe Génétique et Cancer* decided not to include *FAN1* in the recently designed consensus panel of genes that French genetic counseling centers should offer to all patients with a clinically suspected genetic predisposition to colorectal polyps/cancers.

References

- 1 - Segui N, et al. *Gastroenterology* 2015; 149: 563-566.
- 2 - Broderick P, et al. *Gastroenterology* 2017; 152: 75-77.
- 3 - Lowther C, et al. *Genet Med* 2015; 17:149-157

Table 1: Pathogenic variants of *FAN1* identified in the three groups of patients included in the entire series

cDNA change	Putative AA change	Type	Number of patients		
			Group 1 (n=436)	Group 2 (n=3991)	Group 3 (n=709)
c.31_34del	p.(Lys11Glyfs*45)	frameshift deletion		1	
c.32_35del	p.(Lys11Serfs*45)	frameshift deletion		1	
c.53C>A	p.(Ser18*)	nonsense		1	
c.560_561del	p.(Thr187Serfs*3)	frameshift deletion		1	
c.773C>G	p.(Ser258*)	nonsense		1	
c.922_923del	p.(Val308Cysfs*5)	frameshift deletion		1	1
c.959del	p.(Glu320Glyfs*28)	frameshift deletion	1		
c.966dup	p.(Ser323Ilefs*3)	frameshift insertion		1	
c.1397_1398del	p.(Ser466*)	frameshift deletion		1	
c.1606C>T	p.(Arg536*)	nonsense		2	
c.2036_2037del	p.(Arg679Thrfs*5)	frameshift deletion		1	
c.2116C>T	p.(Arg706*)	nonsense		1	
c.2128C>T	p.(Arg710*)	nonsense		2	
c.2616del	p.(Asp873Thrfs*17)	frameshift deletion	1		
c.2854C>T	p.(Arg952*)	nonsense			1

cDNA: complementary DNA; AA: amino acid;

Group1: patients with suspected genetic predisposition to colorectal polyps/cancer.

Group 2: patients with suspected genetic predisposition to breast or breast/ovarian cancer.

Group 3: patients with suspected genetic predisposition to other cancers/conditions.