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## The Fanconi anemia family of genes and its correlation with breast cancer susceptibility and breast cancer features

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**Abstract** Fanconi anemia (FA) family of proteins participates in the DNA repair pathway by homologous recombination, and it is currently formed by 13 genes. Some of these proteins also confer susceptibility to hereditary breast and ovarian cancer (HBOC), since *FANCD1* is the *BRCA2* breast cancer susceptibility gene, and *FANCN/PALB2* and *FANCI/BRIPI* explain 2% of non-*BRCA1/2* HBOC families. Thus, there is an important connection between FA and BRCA pathways. In a previous case-control association study analysing *FANCA*, *FANCD2* and

*FANCL*, we reported an association between *FANCD2* and sporadic breast cancer (BC) risk (OR = 1.35). In order to know whether variants in other FA genes could also be involved in this association, we have extended our study with the rest of FA genes and some others implicated in the BRCA pathway. We have also analyzed the correlation with survival, nodal metastasis and hormonal receptors (ER– and PR–). A total of 61 SNPs in ten FA genes (*FANCB*, *FANCC*, *FANCD1*, *FANCD2*, *FANCD3*, *FANCD4*, *FANCD5*, *FANCD6*, *FANCD7*, *FANCD8*, *FANCD9*) and five FA related genes (*ATM*, *ATR*, *BRCA1*, *H2AX* and *USP1*) were studied in a total of 547 consecutive and nonrelated sporadic BC cases and 552 unaffected controls from the Spanish population. Association analyses reported marginal statistically significant results with the minor allele of intronic SNPs in three genes: *BRCA1*, *BRCA2/FANCD1*, and *ATM*. Survival association with SNPs on *FANCC* and *BRCA2/FANCD1* genes were also reported. Sub-group analyses revealed associations between SNPs on *FANCI* and *ATM* and nodal metastasis status and between *FANCI/BRIPI* and *FANCN/PALB2* and PR– status.

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### Introduction

Several breast cancer (BC) susceptibility genes have been identified, the most important high risk genes being the tumor suppressor genes *BRCA1* [1] and *FANCD1/BRCA2* [2, 3] and other middle-penetrance genes such as *ATM* [4], *FANCI/BRIPI* [5] and *FANCN/PALB2* [6], among others. All of these genes are related directly or indirectly to the Fanconi anemia (FA) family of genes, and their coded

proteins work together in the homologous recombination DNA repair pathway [7–10].

To date, 13 responsible FA genes have been identified [11–24]: eight of them (*FANCA*, *-B*, *-C*, *-E*, *-F*, *-G*, *-L* and *-M*) code for proteins that form the multi-subunit nuclear FA core complex, two code for proteins that are activated by ubiquitination (*FANCI* and *-D2*) and the last three interact with BRCA1 and predispose to breast cancer (*FANCN*, *-DI* and *-J*) [25, 26]. Other proteins are also involved in the DNA repair pathway in relation with the function of the FA family of proteins, such as ATM, ATR [27], BRCA1 [28], H2AX [29] and USP1 [30].

Previous work in our group studied the relationship between BC and *FANCA*, *-L* and *-D2*, acting as low penetrance genes (LPG), and results reported an association between the synonymous SNP rs2272125 (L1366L) on *FANCD2* and BC (OR per-allele = 1.35; 95% CI. 1.09–1.67;  $p = 0.005$ ) [31]. This made us to postulate that there could be other members of FA family of genes involved in the sporadic BC risk, because no previous studies had tested this hypothesis. Thus, a comprehensive association study of the rest of FA genes, which includes *FANCB*, *-C*, *-DI*, *-E*, *-F*, *-G*, *-I*, *-J*, *-M* and *-N*, together with the five FA-related genes *ATM*, *ATR*, *BRCA1*, *H2AX* and *USP1*, and BC risk was performed, comprising a total of 61 SNPs.

## Results and discussion

Associations of polymorphisms with BC risk and clinical and tumor characteristics

Differences in minor allele frequency (MAF) between BC cases and controls reported association for the noncoding SNPs rs637064 (intronic) on *ATM* ( $p = 0.037$ ), rs799923 (intronic) on *BRCA1* ( $p = 0.048$ ), and rs206146 (intronic) and rs15869 (3'UTR) on *BRCA2/FANCD1* ( $p = 0.039$  and  $p = 0.033$ , respectively) (data not shown).

Results from univariate genotype analysis are shown in Table 1. Both intronic SNPs rs206146 and rs15869 in *BRCA2/FANCD1* were statistically significant in a per-allele analysis (OR = 1.23,  $p = 0.040$  and OR = 1.24,  $p = 0.034$ , respectively), but after a multivariate adjustment, trend but not statistical significance were observed ( $p = 0.333$  and  $p = 0.344$ , respectively) (data not shown). No other previous studies described this association since only one study described the association of *FANCD1/BRCA2* with sporadic BC risk [32], and most of the studies performed analyses of *FANCD1/BRCA2* on familial BC type. The *BRCA1* SNP rs799923 showed an estimated OR per minor allele of 0.81 ( $p = 0.041$ ) and OR = 0.77 ( $p = 0.056$ ) under the multivariate analysis, whereas rs16941, a non-synonymous coding change (G1038E),

showed a marginal association with BC (OR = 1.17,  $p = 0.082$ ), statistically significant after multivariate correction (OR = 1.27,  $p = 0.037$ ). The estimated OR per minor allele in the *ATM* SNP rs637064 was 1.19 ( $p = 0.041$ ). This OR was not statistically significant in the multivariate analysis adjusting for the potential confounding factors: age, number of live births, age at menarche and menopause status (OR = 1.11,  $p = 0.302$ ), although risk effect was maintained. These two genes have been commonly studied in hereditary BC [33], but there are few reports in sporadic BC type with contradictory results [34]. No genotype associations were detected in the other FA and FA-related genes tested. Our results in a homogeneous Spanish population group suggest a small implication of some of these FA genes as LPG in breast cancer. However, other evidences have established an important role of *FANCF*, *FANCC* and *FANCG* genes in diverse type of cancers other than BC [17, 35, 36], and these results could be in agreement with some indirect studies that analyze the cancer risk in carriers of mutation in FA genes [37, 38].

Despite the small association detection of the other FA gene members with sporadic BC, we tested for SNP association with the four clinical and tumor characteristics: survival, nodal metastasis, ER+ and PR+. Several studies have described the BC tumor heterogeneity [33, 39]; therefore, this issue has been taken into account in sporadic BC association studies by stratification of BC samples [40]. Results are summarized in Table 1. Two SNPs, one located 3' downstream of *FANCC*, rs1045276 (OR = 1.95,  $p = 0.020$ ), and a synonymous SNP on *BRCA2/FANCD1*, rs1801406 (K1132K) (OR = 0.49,  $p = 0.046$ ), showed association with a poorer and better survival, respectively. However, these survival analyses should be taken with caution since death rate in this sample collection is low, and statistical power is limited. The analysis of the tumor characteristics reported association of nodal metastasis with the intronic SNPs rs7168941 (*FANCI*) ( $p = 0.030$ ), but not with BC ( $p = 0.089$ ). The SNP rs8032440 (*FANCI*) was associated with absence of nodal metastasis ( $p = 0.045$ ) and disease ( $p = 0.048$ ), whereas rs637064 (*ATM*) showed association with nodal metastasis ( $p = 0.029$ ) and BC ( $p = 0.008$ ). These findings are not supported for any other previous study. No statistically significant association with estrogen receptor was detected, whereas positive progesterone receptor was observed among the noncoding SNPs rs7220740 (located at 3' downstream of *FANCI/BRIP1*) ( $p = 0.007$ ) and rs447529 (intronic SNP of *FANCN/PALB2*) ( $p = 0.030$ ) minor allele carriers. These SNPs were associated with the disease according to the stratified sub-group of PR positive BC samples ( $p = 0.039$  for both of them). Mavaddat and colleagues evaluated progesterone status and did not find any evidence of association with both genes [41]. No other

**Table 1** Genotype and phenotype frequencies comparison between cases and controls in the 15 genes selected

Gene	SNP	Additive model <sup>a</sup>		Survival		Nodal Metastasis <sup>b</sup>		ER positive <sup>b</sup>		PR positive <sup>b</sup>		
		OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)*	p-value	
Genes of FA family												
	FANCB	rs5935816	0.98 (0.82–1.17)	0.841	1.16 (0.68–1.99)	0.581	1.03 (0.77–1.37)	0.864	0.90 (0.61–1.31)	0.566	0.85 (0.62–1.18)	0.334
		rs2905223	0.98 (0.82–1.17)	0.818	1.17 (0.68–1.99)	0.570	1.05 (0.79–1.41)	0.731	0.91 (0.63–1.33)	0.626	0.87 (0.63–1.20)	0.396
	FANCC	rs554879	0.99 (0.84–1.18)	0.947	1.17 (0.68–2.02)	0.578	0.78 (0.59–1.05)	0.096	0.85 (0.58–1.23)	0.386	0.88 (0.64–1.21)	0.422
		rs4647554	1.01 (0.85–1.21)	0.886	0.77 (0.44–1.33)	0.339	1.24 (0.92–1.65)	0.156	1.02 (0.69–1.49)	0.933	1.24 (0.89–1.74)	0.203
rs1045276		0.94 (0.75–1.17)	0.574	<b>1.95 (1.11–3.43)</b>	<b>0.020</b>	1.02 (0.71–1.48)	0.909	1.22 (0.75–1.97)	0.429	0.79 (0.53–1.18)	0.252	
FANCD1/BRCA2	rs206116	1.19 (1.00–1.42)	0.056	0.87 (0.52–1.48)	0.613	0.99 (0.74–1.32)	0.933	1.16 (0.80–1.70)	0.434	1.07 (0.78–1.48)	0.666	
	rs3092989	0.91 (0.72–1.15)	0.422	1.37 (0.70–2.68)	0.365	0.81 (0.54–1.24)	0.333	0.89 (0.54–1.48)	0.655	1.29 (0.82–2.01)	0.271	
	rs1801439	1.02 (0.65–1.60)	0.940	0.71 (0.10–5.26)	0.739	1.86 (0.83–4.19)	0.134	1.27 (0.41–3.94)	0.682	2.01 (0.76–5.32)	0.159	
	rs1801406	0.97 (0.81–1.17)	0.776	<b>0.49 (0.24–0.99)</b>	<b>0.046</b>	1.09 (0.79–1.51)	0.593	1.08 (0.71–1.64)	0.722	0.90 (0.63–1.29)	0.571	
	rs206079	1.02 (0.87–1.21)	0.798	1.59 (0.93–2.72)	0.092	1.08 (0.81–1.44)	0.600	0.91 (0.62–1.33)	0.631	0.97 (0.70–1.34)	0.847	
FANCE	rs9534262	0.92 (0.78–1.09)	0.323	0.74 (0.44–1.26)	0.271	0.86 (0.64–1.15)	0.294	1.04 (0.71–1.51)	0.841	1.04 (0.75–1.43)	0.823	
	rs206146	<b>1.23 (1.01–1.50)</b>	<b>0.040</b>	1.00 (0.56–1.78)	0.999	1.02 (0.74–1.41)	0.895	1.02 (0.67–1.57)	0.915	0.95 (0.66–1.37)	0.794	
	rs15869	<b>1.24 (1.02–1.52)</b>	<b>0.034</b>	1.11 (0.63–1.97)	0.722	1.07 (0.77–1.48)	0.692	0.92 (0.60–1.41)	0.695	0.93 (0.65–1.34)	0.693	
	rs2395626	1.00 (0.85–1.19)	0.963	0.98 (0.56–1.72)	0.954	<b>0.74 (0.55–1.00)</b>	<b>0.048</b>	0.98 (0.68–1.42)	0.927	1.06 (0.77–1.45)	0.727	
	rs760782	0.96 (0.79–1.15)	0.640	1.04 (0.59–1.85)	0.896	0.83 (0.61–1.14)	0.253	1.02 (0.68–1.52)	0.943	1.07 (0.75–1.50)	0.721	
FANCF	rs3740615	1.09 (0.87–1.36)	0.476	0.68 (0.32–1.49)	0.340	0.88 (0.61–1.29)	0.518	1.02 (0.64–1.61)	0.941	0.94 (0.64–1.38)	0.745	
	rs4447177	1.11 (0.90–1.36)	0.335	0.93 (0.50–1.73)	0.815	0.98 (0.70–1.37)	0.907	1.16 (0.74–1.83)	0.513	1.36 (0.92–2.00)	0.122	
FANGC	rs568300	1.03 (0.83–1.27)	0.823	1.08 (0.59–1.96)	0.813	1.02 (0.72–1.44)	0.930	1.28 (0.78–2.12)	0.332	1.15 (0.76–1.73)	0.504	
	rs2258240	0.83 (0.67–1.03)	0.084	1.12 (0.61–2.07)	0.720	1.11 (0.77–1.59)	0.579	0.72 (0.46–1.14)	0.159	0.94 (0.64–1.40)	0.766	
	rs1053318	0.90 (0.76–1.08)	0.250	1.27 (0.73–2.21)	0.405	1.11 (0.83–1.49)	0.472	0.94 (0.64–1.37)	0.732	1.06 (0.77–1.46)	0.745	
FANCI	rs7168941	0.86 (0.65–1.15)	0.319	1.20 (0.53–2.74)	0.663	<b>1.74 (1.06–2.87)</b>	<b>0.030</b>	1.81 (0.83–3.96)	0.137	1.24 (0.68–2.26)	0.481	
	rs8032440	0.84 (0.53–1.33)	0.443	0.06 (0.00–22.82)	0.346	<b>0.37 (0.14–0.98)</b>	<b>0.045</b>	2.32 (0.52–10.46)	0.272	1.52 (0.56–4.11)	0.407	
	rs8080599	1.12 (0.89–1.42)	0.331	0.45 (0.16–1.26)	0.128	0.72 (0.48–1.07)	0.101	1.28 (0.76–2.14)	0.354	1.09 (0.72–1.63)	0.687	
FANCL/BRPI	rs2048718	1.13 (0.97–1.32)	0.121	1.70 (0.93–3.11)	0.088	0.903 (0.68–1.20)	0.481	0.84 (0.58–1.20)	0.334	0.89 (0.66–1.20)	0.442	
	rs4988351	1.05 (0.87–1.26)	0.635	1.23 (0.69–2.19)	0.490	0.97 (0.70–1.35)	0.855	1.09 (0.71–1.67)	0.702	0.99 (0.70–1.41)	0.970	
	rs9897928	1.13 (0.92–1.40)	0.243	1.28 (0.70–2.33)	0.419	1.05 (0.75–1.46)	0.776	1.07 (0.70–1.65)	0.754	0.89 (0.62–1.27)	0.509	
FANCM	rs7220740	0.88 (0.74–1.06)	0.186	0.99 (0.51–1.94)	0.987	1.17 (0.86–1.59)	0.317	1.44 (0.97–2.16)	0.074	<b>1.60 (1.14–2.27)</b>	<b>0.007</b>	
	rs8020533	1.08 (0.83–1.41)	0.576	0.62 (0.23–1.66)	0.340	1.24 (0.82–1.88)	0.308	1.02 (0.59–1.79)	0.935	0.93 (0.58–1.50)	0.770	
	rs226981	0.98 (0.83–1.16)	0.788	1.66 (0.96–2.85)	0.068	1.09 (0.82–1.45)	0.541	1.15 (0.80–1.66)	0.441	1.27 (0.93–1.72)	0.128	
	rs3736772	1.31 (0.98–1.75)	0.066	0.37 (0.09–1.47)	0.159	1.39 (0.89–2.15)	0.146	1.04 (0.57–1.89)	0.912	1.01 (0.60–1.71)	0.962	
	rs8058061	0.86 (0.59–1.27)	0.457	0.79 (0.19–3.35)	0.748	0.87 (0.41–1.84)	0.718	1.36 (0.57–3.23)	0.493	2.16 (0.98–4.77)	0.056	

Table 1 continued

Gene	SNP	Additive model <sup>a</sup>		Survival		Nodal Metastasis <sup>b</sup>		ER positive <sup>b</sup>		PR positive <sup>b</sup>	
		OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)*	p-value
<i>FANCD/PALB1</i>	rs249941	1.07 (0.86–1.33)	0.543	1.04 (0.54–2.00)	0.919	1.18 (0.83–1.66)	0.363	1.14 (0.71–1.84)	0.591	0.96 (0.66–1.41)	0.844
	rs16940342	1.01 (0.81–1.26)	0.940	0.62 (0.29–1.38)	0.239	0.76 (0.52–1.12)	0.169	1.26 (0.76–2.10)	0.371	1.15 (0.77–1.73)	0.498
	rs447529	0.90 (0.68–1.17)	0.418	0.85 (0.35–2.08)	0.724	0.68 (0.42–1.12)	0.129	1.60 (0.82–3.13)	0.165	<b>1.86 (1.06–3.25)</b>	<b>0.050</b>
	Genes related to FA family of genes										
<i>ATM</i>	rs228589	1.08 (0.91–1.28)	0.378	0.80 (0.47–1.36)	0.402	0.78 (0.59–1.04)	0.087	1.11 (0.78–1.57)	0.571	1.21 (0.90–1.63)	0.207
	rs189037	1.07 (0.91–1.27)	0.399	0.82 (0.49–1.37)	0.446	0.76 (0.58–1.01)	0.059	1.23 (0.88–1.74)	0.232	1.24 (0.93–1.66)	0.146
	rs625120	1.01 (0.87–1.18)	0.908	1.08 (0.63–1.84)	0.783	0.80 (0.60–1.07)	0.139	1.17 (0.82–1.67)	0.385	1.34 (0.99–1.82)	0.061
	rs228590	1.08 (0.91–1.28)	0.406	1.03 (0.61–1.72)	0.922	0.78 (0.59–1.04)	0.093	1.13 (0.80–1.60)	0.499	1.30 (0.96–1.75)	0.087
	rs228599	1.06 (0.89–1.25)	0.538	1.07 (0.64–1.79)	0.793	0.80 (0.60–1.07)	0.135	1.13 (0.79–1.61)	0.502	1.31 (0.97–1.77)	0.083
	rs599164	1.09 (0.92–1.29)	0.324	1.04 (0.62–1.75)	0.873	0.83 (0.62–1.10)	0.198	1.15 (0.80–1.63)	0.456	1.35 (1.00–1.84)	0.051
	rs637064	<b>1.19 (1.01–1.40)</b>	<b>0.041</b>	1.07 (0.63–1.81)	0.797	<b>0.63 (1.03–1.82)</b>	<b>0.029</b>	1.03 (0.68–1.35)	0.793	1.14 (0.64–1.15)	0.300
	rs647681	1.09 (0.92–1.28)	0.321	1.04 (0.63–1.73)	0.895	0.82 (0.62–1.09)	0.180	1.05 (0.75–1.49)	0.769	1.31 (0.98–1.77)	0.072
	rs1801516	0.95 (0.75–1.20)	0.677	1.19 (0.56–2.52)	0.655	1.08 (0.74–1.59)	0.679	0.75 (0.47–1.21)	0.238	0.87 (0.57–1.33)	0.524
	rs660429	1.08 (0.91–1.28)	0.401	0.97 (0.58–1.62)	0.893	0.77 (0.58–1.02)	0.067	1.14 (0.80–1.61)	0.479	1.31 (0.97–1.76)	0.082
	rs227060	0.96 (0.81–1.14)	0.625	1.02 (0.60–1.74)	0.931	1.07 (0.80–1.42)	0.658	0.90 (0.63–1.30)	0.583	0.82 (0.60–1.12)	0.202
	rs227064	1.05 (0.88–1.24)	0.620	1.00 (0.60–1.68)	0.990	0.78 (0.58–1.05)	0.096	1.12 (0.79–1.60)	0.524	1.31 (0.97–1.78)	0.082
	rs664143	1.07 (0.90–1.27)	0.475	1.07 (0.64–1.78)	0.804	0.79 (0.59–1.06)	0.112	1.14 (0.80–1.63)	0.469	1.33 (0.98–1.81)	0.065
	rs170548	0.94 (0.79–1.11)	0.467	0.92 (0.53–1.61)	0.779	1.06 (0.80–1.42)	0.686	0.92 (0.64–1.32)	0.650	0.84 (0.62–1.15)	0.276
	rs4585	1.05 (0.88–1.25)	0.598	1.08 (0.64–1.84)	0.768	0.75 (0.56–1.01)	0.056	1.12 (0.78–1.60)	0.534	1.34 (0.99–1.82)	0.060
	rs6782400	0.98 (0.82–1.16)	0.783	0.59 (0.32–1.07)	0.080	0.96 (0.72–1.29)	0.793	1.10 (0.74–1.63)	0.633	1.05 (0.76–1.47)	0.761
rs7636909	1.09 (0.92–1.31)	0.321	1.37 (0.79–2.38)	0.263	0.81 (0.60–1.09)	0.161	0.89 (0.60–1.32)	0.568	0.92 (0.66–1.30)	0.640	
rs12635931	1.00 (0.78–1.29)	0.978	0.40 (0.15–1.23)	0.083	1.10 (0.72–1.66)	0.667	0.81 (0.47–1.38)	0.434	0.90 (0.56–1.44)	0.652	
rs799923	<b>0.81 (0.66–0.99)</b>	<b>0.041</b>	0.72 (0.34–1.54)	0.397	1.13 (0.78–1.63)	0.529	1.05 (0.65–1.69)	0.856	1.13 (0.76–1.70)	0.550	
rs16941	1.17 (0.98–1.39)	0.082	1.34 (0.75–2.36)	0.322	1.01 (0.75–1.37)	0.947	0.85 (0.58–1.24)	0.394	0.78 (0.57–1.08)	0.132	
rs8176265	1.12 (0.94–1.32)	0.211	1.45 (0.86–2.46)	0.162	1.02 (0.76–1.37)	0.908	0.81 (0.56–1.17)	0.268	0.74 (0.54–1.02)	0.064	
rs8176318	1.13 (0.96–1.34)	0.153	1.48 (0.87–2.51)	0.146	1.03 (0.77–1.39)	0.838	0.82 (0.57–1.18)	0.280	0.74 (0.54–1.02)	0.063	
rs8551	1.05 (0.89–1.24)	0.575	0.73 (0.43–1.23)	0.232	0.93 (0.71–1.23)	0.626	1.17 (0.82–1.68)	0.379	1.24 (0.92–1.69)	0.158	
rs7759	1.02 (0.86–1.21)	0.829	0.92 (0.54–1.58)	0.764	1.09 (0.82–1.44)	0.549	0.99 (0.69–1.42)	0.946	1.11 (0.81–1.52)	0.52	
rs7350	1.00 (0.84–1.18)	0.977	0.95 (0.55–1.63)	0.844	1.06 (0.80–1.40)	0.702	0.87 (0.61–1.24)	0.424	1.01 (0.74–1.37)	0.977	
rs9436223	0.97 (0.81–1.17)	0.771	1.28 (0.71–2.33)	0.411	0.92 (0.68–1.25)	0.596	1.08 (0.72–1.60)	0.716	0.96 (0.69–1.34)	0.820	
rs583609	0.99 (0.82–1.19)	0.876	1.21 (0.67–2.19)	0.519	0.94 (0.69–1.27)	0.675	1.10 (0.74–1.64)	0.645	0.96 (0.69–1.35)	0.825	

<sup>a</sup> Nonadjusted additive model of genotype analysis

<sup>b</sup> Cases only considered

\*OR odds ratio estimated under additive model, CI confidence interval. Statistically significant results ( $p < 0.05$ ) indicated in bold

association among genotypes and tumor characteristics was detected.

In summary, we have completed the study of the whole FA pathway and some associated genes as LPG. In addition to our FANCD2 BC susceptibility gene description, we have found a trend of association with BC for noncoding SNPs in the already well-described BC high risk genes *BRCA1*, *BRCA2/FANCD1* and *ATM*. On the other hand, although we recognize that there is potential for misclassification of phenotypic characteristics due to the subjective nature of the phenotypic attributes considered and the limited sample size, we have found an encrypted association with disease in genes *FANC-C*, *-I*, *-J*, *-N*, *ATM* and *BRCA2/FANCD1*. Replication in new independent series for both association studies and phenotypic characteristics are necessary before to confirm or rule out these preliminary results.

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