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***PALB2* mutations in male breast cancer: a population-based study in Central Italy**

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To the Editor,

Male breast cancer (MBC) is a rare disease compared to female breast cancer (FBC). However, MBC shares many similarities with FBC, including genetic predisposition factors such as *BRCA1/2* mutations. The frequency of *BRCA1/2* mutations is quite different in ethnically diverse population- and clinic-based MBC series, ranging between 4 and 40% for *BRCA2* and up to 10% for *BRCA1* [1]. In a population-based series of 108 MBCs from Central Italy, we reported that about 9% of MBCs were *BRCA1/2* carriers [2], suggesting the contribution of additional susceptibility genes.

Several studies identify *PALB2* as a moderate-penetrance breast cancer (BC) susceptibility gene, accounting for about 1% of *BRCA1/2* negative familial/early onset BCs [3, 4]. *PALB2* mutations were found in families with both FBC and MBC cases, suggesting that *PALB2* may be

involved in MBC risk [3]. As for *BRCA1/2*, there are evidences that *PALB2* might play a role in prostate cancer (PC) [5]. Interestingly, PC patients have an increased risk of BC [6] and, on the other hand, MBC patients show an increased risk of PC [7], suggesting that these tumours may share risk factors.

The role of *PALB2* in MBC predisposition is still largely unknown. An interesting evaluation about this latter is provided in the recent article by Sauty de Chalon et al. [8]. Yet in the above mentioned study *PALB2* pathogenic mutations were not found in 25 MBCs belonging to 25 *BRCA1/2* negative families and, based on *PALB2* mutation frequency (~1%), it cannot be excluded that these findings may indeed be due to the small series analysed.

By using direct sequencing, we performed a screen for germline mutations of *PALB2* coding region and intron–exon boundaries in 97 *BRCA1/2* negative MBCs, previously identified in a population-based series of 108 MBCs [2]. Age at first BC diagnosis ranged between 35 and 90 years (mean 63.9 years), 25.8% of the patients reported a first-degree family history (FH) of breast/ovarian cancer and 14.4% had a personal history of cancer(s) at sites other than breast. In particular, prostate (28.5%) and bladder (28.5%) carcinomas were the most frequently observed metachronous cancers. Table 1 shows all the *PALB2* variants identified in our study. No truncating mutations were found. A novel missense variant, I1180T, was identified in a young man diagnosed with BC at 42 years of age and with negative FH. *In silico* analysis (PolyPhen, SIFT, Align-GVGD and Pmut) showed that I1180T is likely to be deleterious, since it occurs in the WD40-4 conserved domain that regulates *PALB2* interaction with *BRCA2*. This variant was not found in 90 male population controls analysed (Table 1). Three additional missense variants (Q559R, E672Q and G998E) and one synonymous (T1100T) variant, all previously

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Table 1 *PALB2* genetic variants found in a population-based series of 97 *BRCA1/2* negative MBCs and 90 healthy adult male population controls from Central Italy

Location	Nucleotide ^a change	Amino acid substitution	<i>N. heterozygotes (%)</i>		<i>In silico</i> analysis			
			Cases	Controls	PolyPhen	SIFT	A-GVGD	Pmut
Coding ^b								
Exon 4	c.1676A>G	p.Q559R	24/97 (24.7)	15/90 (16.6)	Benign	Tolerated	Neutral	Neutral
Exon 5	c.2014G>C	p.E672Q	11/97 (11.3)	9/90 (10)	Benign	Affect protein function	Neutral	Neutral
Exon 9	c.2993G>A	p.G998E	11/97 (11.3)	9/90 (10)	Possibly damaging	Affect protein function	Likely deleterious	Pathological
Exon 12	c.3300T>G	p.T1100T	12/97 (12.3)	11/90 (12.2)	–	–	–	–
Exon 13	c.3539T>C	p.I1180T	1/97 (1)	0/90 (0)	Possibly damaging	Affect protein function	Likely deleterious	Pathological
Non-coding ^b								
5'UTR	c.-47G>A	–	3/97 (3)	–	–	–	–	–
IVS3	c.212-58A>C	–	12/97 (12.3)	11/90 (12.2)	–	–	–	–
IVS3	c.212-49T>C	–	1/97 (1)	–	–	–	–	–
IVS3	c.212-46insT	–	1/97 (1)	–	–	–	–	–

^a Nucleotide ID: NG_007406.1, NCBI^b Novel variants are indicated in bold

reported [3], were identified in our series. Both *in silico* analysis and frequency in population controls indicated a neutral effect for Q559R and E672Q (Table 1). With regard to the G998E variant, *in silico* analysis predicted a deleterious effect, but its high frequency (10%) in controls reduces the likelihood of a pathogenic role (Table 1). Furthermore, two novel (IVS3-49T>C and IVS3-46insT) and two previously reported (5'UTR-47G>A and IVS3-58A>C) [4, 5] non-coding variants were identified (Table 1). *In silico* analysis (SpliceSiteFinder and SpliceSitePredictions) indicates that these variants do not affect splicing. Overall, a novel possibly damaging *PALB2* mutation (I1180T) was found in 1% (1/97) of the MBCs analysed. Interestingly, 11.3% of the MBCs (11/97) were found to carry a combination of *PALB2* variants, including Q559R, E672Q, G998E, T1100T and IVS3-58A>C. Although these variants may be individually neutral, it cannot be excluded that a combination of variants may confer susceptibility for MBC as reported for FBC [9, 10]. However, the co-existence of these variants was observed in 6.6% (6/90) of our controls.

Founded on a large population-based series, our results do not indicate a major role of *PALB2* on MBC susceptibility on the other hand they hint that *PALB2* is deemed to have a role as moderate-penetrance gene at a comparable extent as for FBC. Functional studies are needed to better investigate the pathogenic role of the novel I1180T variant identified in our series. Furthermore, collaborative studies are required to evaluate whether, following a polygenic model, the co-existence of multiple *PALB2* variants may

act as low-penetrance alleles, thus explaining a subset of *BRCA1/2* negative MBCs.

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