



HAL
open science

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

Valentina Silvestri, Piera Rizzolo, Ines Zanna, Mario Falchetti, Giovanna Masala,
Simonetta Bianchi, Laura Papi, Giuseppe Giannini, Domenico Palli, Laura Ottini

► **To cite this version:**

Valentina Silvestri, Piera Rizzolo, Ines Zanna, Mario Falchetti, Giovanna Masala, et al.. mutations in male breast cancer: a population-based study in Central Italy. *Breast Cancer Research and Treatment*, 2010, 122 (1), pp.299-301. <10.1007/s10549-010-0797-z>. <hal-00535447>

HAL Id: hal-00535447

<https://hal.science/hal-00535447v1>

Submitted on 11 Nov 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

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

Valentina Silvestri · Piera Rizzolo · Ines Zanna ·
Mario Falchetti · Giovanna Masala · Simonetta Bianchi ·
Laura Papi · Giuseppe Giannini · Domenico Palli ·
Laura Ottini

Received: 7 February 2010 / Accepted: 9 February 2010 / Published online: 24 February 2010
© Springer Science+Business Media, LLC. 2010

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

Valentina Silvestri and Piera Rizzolo equally contributed to the work.

V. Silvestri · P. Rizzolo · M. Falchetti · G. Giannini ·
L. Ottini (✉)
Department of Experimental Medicine, “Sapienza”
University of Rome, 00161 Rome, Italy
e-mail: laura.ottini@uniroma1.it

I. Zanna · G. Masala · D. Palli
Molecular and Nutritional Epidemiology Unit, Cancer Research
and Prevention Institute—ISPO, 50139 Florence, Italy

S. Bianchi
Department of Pathology, University of Florence,
50139 Florence, Italy

L. Papi
Medical Genetics Unit, Department of Clinical Physiopathology,
University of Florence, 50139 Florence, Italy

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	N. heterozygotes (%)		<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.

Acknowledgements We wish to thank Dr. Raffaele Palmirotta and all his staff of the Department of Laboratory Medicine & Advanced Biotechnologies (IRCCS San Raffaele Pisana) for their precious suggestions and technical support. The study was supported by a grant from *Associazione Italiana per la Ricerca sul Cancro* (AIRC) to L.O. (IG 8713) and by Regione Toscana in the frame of the High-Risk Cancer Family Project.

References

- Ottini L, Palli D, Rizzo S, Federico M, Bazan V, Russo A (2010) Male breast cancer. *Crit Rev Oncol Hematol* 73(2):141–155
- Ottini L, Rizzolo P, Zanna I, Falchetti M, Masala G, Ceccarelli K, Vezzosi V, Gulino A, Giannini G, Bianchi S, Sera F, Palli D (2009) *BRCA1/BRCA2* mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. *Breast Cancer Res Treat* 116(3):577–586
- Rahman N, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, Reid S, Spanova K, Barfoot R, Chagtai T, Jayatilake H, McGuffog L, Hanks S, Evans DG, Eccles D, Breast Cancer Susceptibility Collaboration (UK), Easton DF, Stratton MR (2007) *PALB2*, which encodes a *BRCA2*-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 39(2):165–167
- Cao AY, Huang J, Hu Z, Li WF, Ma ZL, Tang LL, Zhang B, Su FX, Zhou J, Di GH, Shen KW, Wu J, Lu JS, Luo JM, Yuan WT, Shen ZZ, Huang W, Shao ZM (2009) The prevalence of *PALB2* germline mutations in *BRCA1/BRCA2* negative Chinese women with early onset breast cancer or affected relatives. *Breast Cancer Res Treat* 114(3):457–462
- Erkko H, Xia B, Nikkila J, Schleutker J, Syrjakoski K, Mannermaa A, Kallioniemi A, Pylkas K, Karppinen SM, Rapakko K,

- Miron A, Sheng Q, Li G, Mattila H, Bell DW, Haber DA, Grip M, Reiman M, Jukkola-Vuorinen A, Mustonen A, Kere J, Aaltonen LA, Kosma VM, Kataja V, Soini Y, Drapkin RI, Livingston DM, Winqvist R (2007) A recurrent mutation in PALB2 in Finnish cancer families. *Nature* 446(7133):316–319
6. Thellenberg C, Malmer B, Tavelin B, Grönberg H (2003) Second primary cancers in men with prostate cancer: an increased risk of male breast cancer. *J Urol* 169(4):1345–1348
 7. Hemminki K, Scélo G, Boffetta P, Mellekjær L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride M, Kliewer EV, Chia K-S, Pompe-Kirn V, Martos C, Jonasson JG, Li X, Brennan P (2005) Second primary malignancies in patients with male breast cancer. *Br J Cancer* 92(7):1288–1292
 8. Sauty de Chalon A, Teo Z, Park DJ, Odefrey FA, kConFab, Hopper JL, Southey MC (2009) Are PALB2 mutations associated with increased risk of male breast cancer? *Breast Cancer Res Treat*. doi:[10.1007/s10549-009-0673-x](https://doi.org/10.1007/s10549-009-0673-x)
 9. Chen P, Liang J, Wang Z, Zhou X, Chen L, Li M, Xie D, Hu Z, Shen H, Wang H (2008) Association of common PALB2 polymorphisms with breast cancer risk: a case-control study. *Clin Cancer Res* 14(18):5931–5937
 10. Cao AY, Yu KD, Yin WJ, Jin W, Di GH, Shen ZZ, Shao ZM (2009) Five common single nucleotide polymorphisms in the PALB2 gene and susceptibility to breast cancer in eastern Chinese population. *Breast Cancer Res Treat*. doi:[10.1007/s10549-009-0637-1](https://doi.org/10.1007/s10549-009-0637-1)