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Short Communication Open Access

# Low Frequency of Germline TERT and MITF Mutations in Brazilian Melanoma-Prone Patients

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**Abstract**

Recent studies have reported rare germline mutations affecting the MITF gene, and the promoter of the TERT gene in melanoma families. Here we looked at the prevalence of these rare penetrant mutations in a series of 48 patients (either familial melanoma or multiple melanomas), all of them negative for CDKN2A and CDK4 mutations. A single mutation was detected in a multiple melanoma patient, who was a heterozygous carrier of the E318K MITF variant. However, this variant was also detected in 1 out of 125 controls. This preliminary data points to a low frequency of MITF and TERT mutations in this Brazilian group of melanoma-prone patients.

**Keywords:** TERT; MITF; CDKN2A; Melanoma predisposition; Germline mutation

## Short Communication

Cutaneous melanoma is a rare and aggressive form of cancer, responsible for the majority of deaths caused by skin malignancies [1]. Approximately 10% of the melanoma cases occur in a familial context due to the segregation of germline mutations [2]. The major known gene of melanoma predisposition is CDKN2A, which mutations segregate with up to 40% of familial melanoma [3]. The identification of melanoma susceptibility genes is relevant for proper genetic counseling of individuals at high-risk and also to provide mechanistic insights on melanomagenesis.

Recent works [4-6] have identified two distinct genes exhibiting germline activating mutations in melanoma-prone individuals. One of these alterations is a highly penetrant T>G mutation in the promoter of the TERT gene at -57 bp from the start site, which encodes one subunit of the telomerase. This mutation creates a new anchoring site for the Ets transcription factor family, thus shifting the expression level of TERT [4]. Somatic mutations in the promoter region of TERT were also disclosed in tumors, such as cutaneous and conjunctival melanomas [4,7,8]. However, until now, there are no other reports of TERT germline mutations in familial melanoma.

The second variant consists of a G>A transition in the exon 10 of MITF (rs149617956; E318K), a known melanoma gene expressed in melanocytes, responsible for the activation of genes involved in development and survival [9]. The E318K mutation affects the SUM Oylation of the MITF protein, therefore increasing its transcriptional activity. This E318K variant was found at higher frequency in melanoma families than in general population, representing an intermediate risk variant. However, E318K frequency seems to vary according to the population [10,11], and it has not been investigated among Brazilians. The E318K alteration has been associated with development of multiple primary melanomas, as well as concomitant occurrence of melanoma and renal carcinoma [10,12,13]. Additionally, MITF amplifications and other mutations have already been reported in melanoma samples [9].

The aim of this study was to evaluate the contribution of germline MITF and TERT on the burden of cutaneous melanoma in patients negative for CDKN2A mutations. This study was approved by the Ethics Committee of the AC Camargo Cancer Center (São Paulo, Brazil). All individuals signed an informed consent prior to their inclusion in the study. The cohort comprised 48 unrelated probands selected either based on the classic familial melanoma syndrome criteria [14] (31 patients) or on the occurrence of multiple primary melanomas (MPM; ≥2 tumors; 17 patients). All patients were negative for pathogenic mutations in CDKN2A and CDK4 [15]. DNA samples of patients were obtained from peripheral blood. The exon 10 of MITF [5] and the TERT promoter region [4] were investigated by capillary sequencing, using the Applied Biosystems 3130 XL equipment.

| Gene / alteration | Genomic position (hg19) | Melanoma patients (n=48) | Healthy controls (n=125) |
|---|---|---|---|
| MITF / c.G1075A | chr3: 70,014,091 | 1 | 1 |
| TERT / c.T-57G | chr5: 1,295,161 | 0 | not tested |

**Table 1:** Genomic variants investigated in MITF and TERT genes, with the respective genomic positions and frequency of these variants in the cohort of melanoma-prone patients.

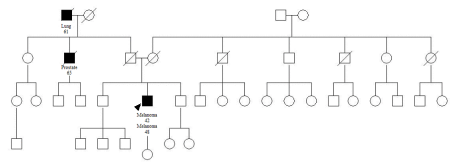

**Figure 1:** Pedigree of the melanoma patient that was found to be a carrier of the variant E318K of the MITF gene

Mutations at TERT promoter were not detected in our cohort, differently of the previous works that described the mutation segregating in melanoma families [5,6]. One among the 48 melanoma patients was found to be a heterozygous carrier of the MITF E318K variant. This variant was also investigated in a control group of 125 individuals without a personal history of cancer, and one carrier was detected among controls (OR=2.64, IC 95%=0.16–43; p=0.5, Fischer's Exact test; Table 1). The patient carrying the MITF variant was included in the cohort due to development of 2 primary melanomas (42 years-old at diagnosis) without referring other cases in the family (pedigree in Figure 1).

Unfortunately, the family members were not available to investigate the presence of this variant. This result is in agreement with the reported association of MITF E318K with multiple primary melanomas in two recent works [13,16] corroborating the relation between the presence of E318K variant and the development of multiple primary melanomas.

It is important to document the prevalence of these rare mutations in different ethnic groups to further substantiate their role in melanomagenesis. Our data points to a low frequency of TERT and MITF mutations in the genetic etiology of Brazilian melanoma-prone patients, at least based on this small cohort. Even in the context of families, many different rare genes can be implicated in melanoma susceptibility, and further whole-genome investigation of melanoma families with unknown genetic etiology could reveal new melanoma genes.

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