A *PGC1β* genetic variant associated with nevus count and melanoma mortality

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Dear Editor,

Proteins of the peroxisome proliferator-activated receptor γ coactivator 1 (PGC1) family are transcriptional coactivators well known for regulating mitochondrial biogenesis and other metabolic functions in multiple tissues [1]. Recently, PGC1 coactivators have also been linked to pigmentation and melanoma skin cancer. In a genome-wide association study [2], our group determined the A allele of SNP rs32579 in the *PGC1β* gene was significantly associated with greater tanning ability, which was successfully replicated in additional samples [3]. Furthermore, we demonstrated that the rs32579 A allele was correlated with upregulation of *PGC1β* gene expression and lower risk of melanoma [3]. However, whether this SNP influences risk of melanoma death remains a question of interest.

We thus investigated the association between the genetic variant rs32579 A and melanoma mortality among 858 melanoma cases. All patients were accrued from a hospital-based case-control study of melanoma skin cancer at The University of Texas MD Anderson Cancer Center (MDACC). Melanoma-specific death was the primary endpoint of the current analysis. We calculated survival time from the date of diagnosis to the date of death from melanoma or the date of the last follow-up, whichever came first. Multivariate Cox proportional hazards regression models, adjusted for age, sex, tumor stage, Breslow thickness, tumor cell mitotic rate, and top two principal components of genetic variance, were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between rs32579 and melanoma mortality. Our result showed that A allele was associated with a lower risk of melanoma disease-specific death (***Table 1***, HR=0.64, 95% CI=0.45-0.91,

p-value=0.013). Previously, the telomere-mitochondrion connection was shown to be regulated by PGC1s [4], and telomere length was positively correlated with nevus count [5]. We therefore further examined the possible association between this variant and nevus count, a well-known risk factor for malignant melanoma. Among 15,952 individuals of European Ancestry in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), the number of nevi decreases by 0.06 per each A allele (p-value=0.018). Detailed methods of this additional analysis on nevus count have been described previously [6]. Information on study population, genotyping procedure, quality control and imputation are provided in ***Supplementary Materials***, for the MDACC study, the NHS and the HPFS.

PGC1β and PGC1α normally co-express with each other, and they share a large degree of sequence homology and functional overlap [1]. PGC1α-positive melanomas have been found to have higher rates of survival under oxidative stress compared to PGC1α-negative melanoma [7]. Last year, Luo *et al.* reported that PGC1α suppressed melanoma metastasis through direct regulation of parallel-acting transcriptional programs [8]. Though not on PGC1β, these findings may support our observations in the current population study.

In summary, we so far have shown that this SNP was associated with tanning ability, nevus count, and both melanoma risk and mortality, which further emphasizes the critical role of PGC1s in multiple steps of melanocyte formation and melanoma development. BRAF inhibition regulates PGC1α expression in BRAF-mutated melanoma, which affects the therapeutic efficacy of BRAF inhibitors [9]. Future studies are warranted to investigate the effect modification of this *PGC1β* variant on BRAF inhibitors in melanoma treatment.

Table 1. Association between *PGC1β* rs32579 [#] and melanoma-specific death

Genotype	No. of patients	No. of deaths	HR (95%CI) *	P-value
GG	454	56	1.00 (Ref)	
GA	331	34	0.62 (0.40-0.97)	
AA	73	5	0.44 (0.17-1.10)	
Additive model (G – ref allele, A – test allele)			0.64 (0.45-0.91)	0.013

SNP rs32579 is located on chromosome 5 with BP position at 149210848. The G allele is the major allele, and the A allele is the minor allele. Minor allele frequency = 0.28.

* Cox proportional hazards regression model, adjusted for age, sex, tumor stage, Breslow thickness, tumor cell mitotic rate, and the top two principal components.

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Conflicts of interest

The authors declare no conflict of interest.

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