**File S2. Evidences supporting positive selection in the PLEK2 region.**

A ~1Mb region significantly enriched in candidate SNPs of selection was detected in European populations only (Table S3). This region encompasses functional variants controlling the expression of the *PLEK2* gene in skin cells exposed to sun, i.e., eQTLs in the GTEx database (Ardlie et al. 2015) (no eQTL found in skin not exposed to sun (Ardlie et al. 2015)). *PLEK2* overexpression causes large lamellipodia (Hu et al. 1999), is characteristic of disseminated tumor cells (Naume et al. 2007) and has been detected in analyses of the blood of ~80% of melanoma patients. *PLEK2* serves as a biomarker for the disease (Luo et al. 2011). In addition, the survival probability was found diminished in patients with the highest *PLEK2* overexpression (<https://www.proteinatlas.org/ENSG00000100558-PLEK2/pathology/tissue/melanoma>). At the protein level, expression has been found higher in melanoma cells than in normal tissue (Uhlen et al. 2015).

In this study, we found that alleles downregulating *PLEK2* harbor signatures indicative of positive selection. Interestingly, these variants which affect the sensitivity to UV-induced melanoma appear to have been under selection in European populations, while this selection signal was not found in Africa and Asia (Table S3). Prevalence of UV-induced melanoma is more than 20 times more common in European Americans than in African Americans (the lifetime risk of getting melanoma is 2.5% and 0.1% in European and African Americans respectively, the American Cancer Society). Finally, in current Europeans, the level of *PLEK2* expression in skin and the risk of developing UV-induced melanoma both increase with age (Glass et al. 2013) (mean age of patients is ~63 years old in US but melanoma is not uncommon among those younger than 30, the American Cancer Society). The latter observation is consistent with the role of natural selection in the maintenance of low *PLEK2* expression in early stages of life. All these observations suggest that the European-specific signal of recent selection shared among all European populations is due to mutations downregulating the expression of the *PLEK2* gene. Note, the pedigree-based recombination rate (Rutgers maps v3) in PLEK2 is equal to 0.53cM/Mb (Matise et al. 2007), a value similar to the recombination rate in the LCT region (O'Reilly et al. 2008).

In addition, we may speculate that the alleles downregulating *PLEK2* could have been favored by selection during the late Pleistocene climatic warming (~20 to ~10kya) ending the last ice age (~110 to ~10kya) (Cooper et al. 2015). Cold paleoclimate in Europe likely favored both light skin pigmentation and increased sensitivity to UV-induced melanoma (Key et al. 2016; Lopez et al. 2014). As high expression of *PLEK2* may decrease the survival probability in melanoma patients, the alleles downregulating *PLEK2* could have been recently favored during this period as supported by a selection signal of ~1-1.2Mb indicative of a recent onset of selection. This speculative interpretation needs to be further tested by formally estimating the age of selection in this genomic region to verify if the onset of selection coincides with the increase of regional temperatures and solar luminosity in the northern hemisphere.

GTEx (Genotype-Tissue Expression Project) <http://gtexportal.org/home/>, DAA (Digital Aging Atlas) <http://ageing-map.org/>, the human protein atlas <http://www.proteinatlas.org>, the American Cancer Society <https://www.cancer.org/>, NCBI gene database <https://www.ncbi.nlm.nih.gov/gene/26499>

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