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POT1 pathogenic variants: not all telomere pathway genes are equal in risk of hereditary cutaneous melanoma

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Multiple genes important in telomere maintenance, including *POT1*, *TERT*, *ACD* and *TERF2IP*, have been associated with hereditary cutaneous malignant melanoma (CMM).[1] In this issue of the *BJD*, Potrony *et al*. describe findings of pathogenic *POT1* germline variants in nearly 2% of individuals from 228 Spanish hereditary CMM families.[2] This work strengthens previously described connections between pathogenic variants (PVs) in genes important in telomere biology and CMM risk.

PVs in *CDKN2A* are the most common genetic cause of familial melanoma, occurring in 15–40% of families with a history of multiple individuals with CMM.[1] This study focuses on hereditary CMM families with at least two affected individuals who were negative for *CDKN2A* PVs. The results described here are consistent with previous work including a study from the U.K., the Netherlands and Australia in which *POT1* pathogenic variants were identified in about 4% of CMM families.[3] The frequency of *POT1* PVs in CMM families reported in the literature ranges from 0% in a Dutch study to 12.5% in one Italian study.[4,5]

Longer telomeres have been observed in individuals with PVs in *POT1* and those with CMM and may be associated with CMM risk through influence on increased replicative potential.[4,6] *POT1* is part of the shelterin complex that binds to telomeres and plays a role in protection of the chromosomal ends from loss.[7] In particular, promoter variants in *TERT* that encodes the telomerase enzyme have been associated with increased risk of CMM in nonfamilial cases.[8] Of note, in this series, Potrony *et al*. did not identify *TERT* promoter mutations in any of the familial cases but did identify one individual with multiple primary CMM carrying a rare c.−125C>T variant of uncertain clinical significance. This study, like other series, suggests that pathogenic *TERT* promoter variants are relatively rare in families with hereditary CMM.[9] Conversely, *POT1* PVs appear to be a more common cause of hereditary CMM.

A limitation of this study is that the pathogenicity of the *POT1* variants was not confirmed. The missense variant p.Ile78Thr (c.233T>C) falls within the *POT1* DNA binding domain and is predicted by *in silico* models to be pathogenic, but is functionally uncharacterized. Two variants identified in this study (c.255G>A and c.1792G>A) were shown to disrupt

Conflicts of interest

None to declare.

normal splicing and presumably result in a truncated protein, but these studies were only done *in vitro*.

This study has clinical implications for hereditary CMM and for *POT1* genetic testing in melanoma prone families. Firstly, it may help to expand the phenotype associated with *POT1* PVs, as one of the described families showed segregation of a *POT1* PV with melanoma and thyroid cancer. Another published study also showed segregation of a *POT1* variant in a family with CMM, dysplastic naevi and nonmedullary thyroid cancers.[10] Secondly, *POT1* is currently included on some, but not all gene panels for clinical genetic testing of hereditary melanoma. Knowledge of one's mutation status can result in unaffected carriers receiving better screening and detection of cancers at earlier ages, which may improve outcomes. There are currently no guidelines for clinical melanoma risk management in individuals with *POT1* PVs so studies like this one are critical for demonstrating the types and ages of cancer associated with these variants. Thus, these results may have utility for genetic testing laboratories who currently offer panels for hereditary melanoma and for clinicians who order genetic testing for patients with hereditary melanoma.

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