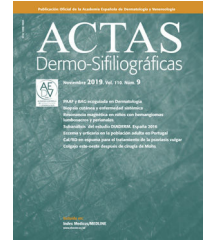




ACADEMIA ESPAÑOLA  
DE DERMATOLOGÍA  
Y VENEREOLÓGIA

# ACTAS Dermo-Sifiliográficas

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## CASE AND RESEARCH LETTER

### Melanocortin-1 Receptor (MC1R) Gene Variants are Not Associated With Vascular Brain Alterations



Las variantes del gen receptor  
de melanocortina-1 (MC1R) no están asociadas  
a las enfermedades vasculares cerebrales

To the Editor,

#### Introduction

The melanocortin-1 receptor (MC1R) gene is an important regulator of human skin pigmentation and loss-of-function variants are associated with a higher risk of developing melanoma.<sup>1</sup> MC1R gene variants have also been associated with Parkinson disease, late-onset Alzheimer's disease and age of onset modulation in Huntington's disease patients.<sup>2–4</sup> MC1R expression in the brain is found in the vascular endothelium.<sup>5</sup> Weak MC1R activity predisposes to vascular endothelial dysfunction.<sup>6</sup> Different types of brain vascular lesions can be differentiated on magnetic resonance imaging (MRI): aneurysms, arteriovenous malformations (AVM), developmental venous anomalies (DVA), capillary telangiectasia, and cavernous malformation.<sup>7</sup> Brain vascular lesions represent an abnormality in vessel development and a possible error may occur during vasculogenesis or, more likely, during angiogenesis. Brain angiogenesis is diminished after birth but may reactivate as a response to any of several triggers such as sensory enrichment, exercise, stress, hormones or chronic hypoxia. Interestingly, vascular malformations of the brain are not necessarily completely developed at birth, as active growth and *de novo* formation of CCM and AVM may occur in adulthood.<sup>8</sup> The study aimed to analyze the relationship between MC1R status and the presence of brain vascular lesions.

#### Material and methods

During the study period 1300 consecutive melanoma patients were visited at the Department of Dermatology at Hospital Clínic de Barcelona. Genomic DNA from blood samples

was isolated using the Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA) and the status of the MC1R gene was determined by PCR amplification and sequencing as previously described.<sup>1</sup> In the staging and/or follow-up protocol, brain MRI was requested for intermediate or high-risk melanoma patients. As inclusion criteria, only patients with at least one brain MRI were included. Brain vascular lesions were classified into distinct groups: aneurysms and vascular malformations (AVM, DVA, capillary telangiectasia, and cavernous malformation).

#### Results

A total of 476 patients were finally included in our study and the baseline characteristics of the cohort are summarized in Table 1. MC1R variants were found in 324 patients (68.1%) and 152 patients (31.89%) were wild-type. A total of 44 brain vascular abnormalities were incidentally detected during MRI examinations. Developmental venous abnormalities were present in 23 cases (4.8%), cavernous malformation in 16 cases (3.4%), brain aneurysm in 3 cases (0.6%) and brain arteriovenous malformations in 2 cases (0.4%). We analyzed the possible association between the presence of MC1R variants and vascular alterations detected by MRI. After the data processing, no statistically significant difference in the number or type of brain vascular lesions of the brain was found ( $P = .986$ ).

#### Discussion

Many factors affecting brain vascular lesions are yet to be clarified, such as the link between genetic mutations, mutant cell lineage, and clinical expression. It has been hypothesized that a mutation in one copy of a given gene may be followed by a second trigger (such as a somatic mutation) to a second copy of the gene or a mutation in another gene acting in the same cellular pathway causing a vascular brain lesion to appear.<sup>8</sup> Somatic mutated endothelial cells clonally expand to initiate cerebral cavernous malformations and subsequently incorporate wild-type endothelial cells and so increase the size of a cerebral cavernous malformation.<sup>9</sup> Taking into consideration the disturbing neurological symptoms of brain vascular lesions, such as focal neurological deficits, epilepsy and hemorrhagic stroke in the

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**Table 1** Basal Characteristics of the Cohort.

|  | MC1R variants (N = 324) | MC1R wild-type (N = 152) | Total (N = 476)      | p value |
|--|-------------------------|--------------------------|----------------------|---------|
| <b>Gender</b>                          |                         |                          |                      | 0.821   |
| Female                                 | 152 (46.9%)             | 73 (48.0%)               | 225 (47.3%)          |         |
| Male                                   | 172 (53.1%)             | 79 (52.0%)               | 251 (52.7%)          |         |
| <b>Age</b>                             |                         |                          |                      | 0.878   |
| Median (Q1, Q3)                        | 56.66 (44.98, 68.10)    | 56.01 (43.47, 69.45)     | 56.43 (44.62, 68.56) |         |
| <b>Brain vascular malformation</b>     |                         |                          |                      | 0.986   |
| Non-vascular malformation              | 294 (90.7%)             | 138 (90.8%)              | 432 (90.8%)          |         |
| Vascular malformation                  | 30 (9.3%)               | 14 (9.2%)                | 44 (9.2%)            |         |
| <b>Radiological diagnosis (detail)</b> |                         |                          |                      | 0.110   |
| Developmental venous anomaly           | 19 (5.9%)               | 4 (2.6%)                 | 23 (4.8%)            |         |
| Cavernous malformation                 | 7 (2.2%)                | 9 (5.9%)                 | 16 (3.4%)            |         |
| Brain aneurysm                         | 2 (0.6%)                | 1 (0.7%)                 | 3 (0.6%)             |         |
| Brain arteriovenous malformation       | 2 (0.6%)                | 0 (0.0%)                 | 2 (0.4%)             |         |
| None                                   | 294 (90.7%)             | 138 (90.8%)              | 432 (90.8%)          |         |
| <b>Eye color</b>                       |                         |                          |                      | 0.937   |
| Brown-black                            | 188 (63.9%)             | 93 (64.6%)               | 281 (64.2%)          |         |
| Green                                  | 55 (18.7%)              | 25 (17.4%)               | 80 (18.3%)           |         |
| Blue                                   | 51 (17.3%)              | 26 (18.1%)               | 77 (17.6%)           |         |
| Missing values                         | 30                      | 8                        | 38                   |         |
| <b>Hair color</b>                      |                         |                          |                      | 0.004   |
| Brown-black                            | 205 (70.0%)             | 113 (79.6%)              | 318 (73.1%)          |         |
| Blond                                  | 69 (23.5%)              | 29 (20.4%)               | 98 (22.5%)           |         |
| Red                                    | 19 (6.5%)               | 0 (0.0%)                 | 19 (4.4%)            |         |
| Missing values                         | 31                      | 10                       | 41                   |         |
| <b>Phototype</b>                       |                         |                          |                      | 0.084   |
| I                                      | 24 (8.1%)               | 5 (3.5%)                 | 29 (6.6%)            |         |
| II                                     | 149 (50.0%)             | 67 (46.5%)               | 216 (48.9%)          |         |
| III                                    | 105 (35.2%)             | 61 (42.4%)               | 166 (37.6%)          |         |
| IV                                     | 18 (6.0%)               | 11 (7.6%)                | 29 (6.6%)            |         |
| V                                      | 2 (0.7%)                | 0 (0.0%)                 | 2 (0.5%)             |         |
| Missing values                         | 26                      | 8                        | 34                   |         |

case of lesion rupture, further research is mandatory to shed light on the molecular mechanisms implicated.

In conclusion, given that almost 500 patients were included in our research we believe there is strong evidence indicating the lack of involvement of the *MC1R* gene in the development or progression of vascular malformations.

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## References

- Vallone MG, Tell-Marti G, Potrony M, Rebollo-Morell A, Badenas C, Puig-Butille JA, et al. Melanocortin 1 receptor (MC1R) polymorphisms' influence on size and dermoscopic features of nevi. *Pigment Cell Melanoma Res.* 2018;31:39–50.
- Tell-Marti G, Puig-Butille JA, Potrony M, Badenas C, Milà M, Malveyh J, et al. The MC1R melanoma risk variant p.R160W is associated with Parkinson disease. *Ann. Neurol.* 2015;77:889–94.

3. Tell-Marti G, Puig-Butille JA, Gimenez-Xavier P, Segu-Roig A, Potrony M, Badenas C, et al. The p R151C polymorphism in mc1r gene modifies the age of onset in Spanish Huntington's disease patients. *Mol. Neurobiol.* 2017;54:3906–10.
  4. Tell-Marti G, Puig-Butille JA, Potrony M, Plana E, Badenas C, Antonell A, et al. A common variant in the MC1R Gene (p.V92M) is associated with Alzheimer's disease risk. *J Alzheimer's Dis.* 2017;56:1065–74.
  5. Hartmeyer M, Scholzen T, Becher E, Bhardwaj RS, Schwarz T, Luger TA. Human dermal microvascular endothelial cells express the melanocortin receptor type 1 and produce increased levels of IL-8 upon stimulation with alpha-melanocyte-stimulating hormone. *J. Immunol.* 1997;159:1930–7.
  6. Rinne P, Ahola-Olli A, Nuutinen S, Koskinen E, Kaipio K, Eerola K, et al. Deficiency in melanocortin 1 receptor signaling predisposes to vascular endothelial dysfunction and increased arterial stiffness in mice and humans. *Arterioscler. Thromb. Vasc. Biol.* 2015;35:1678–86.
  7. Geibprasert S, Pongpech S, Jiarakongmun P, Shroff MM, Armstrong DC, Krings T. Radiologic assessment of brain arteriovenous malformations: what clinicians need to know. *Radiographics.* 2010;30:483–501.
  8. Leblanc GG, Golanov E, Awad IA, Young WL. Biology of vascular malformations of the brain. *Stroke.* 2009;40:e694–702.
  9. Detter MR, Snellings DA, Marchuk DA. Cerebral cavernous malformations develop through clonal expansion of mutant endothelial cells. *Circ. Res.* 2018;123:1143–51.
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