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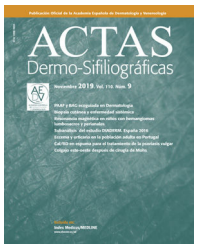

CASE AND RESEARCH LETTER

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.[1] *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.[2–4] *MC1R* expression in the brain is found in the vascular endothelium.[5] Weak MC1R activity predisposes to vascular endothelial dysfunction.[6] 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.[7] 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.[8] 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.[1] 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.[8] Somatically 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.[9] 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
Gender				0.821
Female	152 (46.9%)	73 (48.0%)	225 (47.3%)	
Male	172 (53.1%)	79 (52.0%)	251 (52.7%)	
Age				0.878
Median (Q1, Q3)	56.66 (44.98, 68.10)	56.01 (43.47, 69.45)	56.43 (44.62, 68.56)	
Brain vascular malformation				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%)	
Radiological diagnosis (detail)				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%)	
Eye color				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	
Hair color				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	
Phototype				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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