A three-dimensional structural model to evaluate MC1R variants. The importance of rare variants.

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INTRODUCTION

The aetiology of melanoma is complex and likely involves multiple low penetrance susceptibility genes, interactions among these genes, the influence of environmental exposure and the interaction of genotypes and environment. However, only one gene, the melanocortin 1 receptor gene, MC1R, is known to unequivocally account for substantial variation in the incidence of sporadic malignant melanoma. MC1R is highly polymorphic in white populations, with more than 100 non-conservative variants having been already reported.

RESULTS

LOCATION OF RARE VARIANTS FOUND IN THE SPANISH POPULATION

INDIVIDUAL ANALYSIS OF MC1R VARIANTS AND MELANOMA RISK

PHENOTYPE OF RARE VARIANTS CARRIERS

CONCLUSIONS

MC1R is a susceptibility gene for melanoma in the Spanish population:
- 41 variants were described in our population
- 31 rare variants, being the Y298H variant described for the first time in our population
- 6 individual MC1R variants were associated with melanoma risk
- 25 variants appeared to have structural implications and were grouped in three different putatively-functional MC1R regions: the GTPase/PKC signalling region, an alleged a-MSH-binding extracellular region, and a novel central core protein region.

- It is the first time that a three-dimensional model is used to evaluate a complex set of rare variants in MC1R

MATERIALS AND METHODS

This case-control study included 710 consecutive Spanish melanoma patients and 460 control subjects. Phenotypic information was collected using a standardized questionnaire. MC1R was analyzed by sequencing. Then, all MC1R variants detected in the Spanish population were mapped in a three-dimensional model of the MC1R protein.

POSITION OF ALL MC1R VARIANTS DETECTED IN THE SPANISH POPULATION

Position of Red hair colour (RHC) and non red hair colour (NRHC) variants

Position of potentially functional rare variants according to MC1R structure

Receptor’s core central region

Important residues in PKC MC1R interacting domain

MC1R variants identified in the Spanish population using the bi-dimensional structure of the human melanocortin 1 receptor (modified from García-Borrón et al; 2005 Pigment Cell Res.).