Melanoma Susceptibility genes beyond pigmentation phenotype

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Melanoma susceptibility

Effect size

High risk genes

High

Intermediate

Modest

Low

Allele frequency

Very rare

Rare

Low frequency

Common

Effect size

**Melanoma susceptibility**

- **High**
  - CDKN2A, CDK4
  - TERT, POT1, ACD, TERF2IP
  - BAP1

- **Intermediate**
  - MC1R
  - MITF-E318K

- **Modest**
  - SLC45A2, IRF4, PLA2G6, FTO, MX2, ATM, ARNT, TYRP1, TYR

- **Low**
  - OCA2, ASIP

**Allele frequency**

- **Very rare**
  - ARNT
- **Rare**
  - TERT, PARP1, CASP
- **Low frequency**
  - CCND1
- **Common**

• Master regulator of pigmentation

• High polymorphic gene


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**Increased risk in CDKN2A mutation carriers.**

<table>
<thead>
<tr>
<th>G101W patients (CDKN2A)</th>
<th>O.R.</th>
<th>p</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>V60L (no RHC)</td>
<td>2.55</td>
<td>0.043</td>
<td>1.03-6.3</td>
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<tr>
<td>R160W (RHC)</td>
<td>4.02</td>
<td>0.01</td>
<td>1.3-11.1</td>
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<tr>
<td>&gt;1 variant</td>
<td>3.96</td>
<td>0.003</td>
<td>1.6-9.7</td>
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<tr>
<td>&gt;1 RHC variant</td>
<td>14.33</td>
<td>0.001</td>
<td>2.8-70.9</td>
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</table>

Goldstein AM et al. Int J Cancer. 2007
Kanetsky PA et al. Cancer. 2010
Kanetsky PA et al. Cancer. 2010
**Table 4** Association of MC1R variant p.R163Q and lentigo maligna melanoma (LMM) tumours

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No LMM, n (%)^a</th>
<th>LMM, n (%)^b</th>
<th>OR (95% CI)^c</th>
<th>P-value</th>
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<tbody>
<tr>
<td>G/G</td>
<td>1466 (96·1)</td>
<td>143 (92·9)</td>
<td>1·00</td>
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<tr>
<td>G/A or A/A</td>
<td>59 (3·9)</td>
<td>11 (7·1)</td>
<td>2·16 (1·07–4·37)</td>
<td>0·044^d</td>
</tr>
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</table>

^a Percentage of total population
^b Percentage of total melanoma population
^c Odds ratio with 95% confidence interval
^d Significant at the 0·05 level
**MC1R gene variants and sporadic malignant melanoma susceptibility in the Canary Islands population**

Elizabeth Córdoba-Lanús · José G. Hernández-Jiménez · Chaxirasi Medina-Coello · Adriana Espinoza-Jiménez · Ana González · María-del-Cristo Rodríguez-Pérez · Gregorio Carretero-Hernández · Pablo Almeida · José Suárez-Hernández · Antonio Perera-Molinero · Ricardo Fernández-de-Misa

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**Table 3** Association of variants in the **MC1R** gene with malignant melanoma (MM) in Caucasian individuals

<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene position</th>
<th>SNP ID</th>
<th>MM cases vs. healthy controls</th>
<th>OR_{adj} (95 % CI)^a</th>
<th>p value</th>
<th>p value^c</th>
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</thead>
<tbody>
<tr>
<td>V60L</td>
<td>+178 (G/T)</td>
<td>rs 1805005</td>
<td>0.14 (n = 509) MAF</td>
<td>0.99 (0.75–1.32)</td>
<td>0.96</td>
<td>NS</td>
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<tr>
<td>D84Ed</td>
<td>+252 (C/T)</td>
<td>rs 1805006</td>
<td>0.03 (n = 491) MAF</td>
<td>2.88 (0.90–9.18)^b</td>
<td>0.056</td>
<td>NS</td>
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<tr>
<td>R151Cd</td>
<td>+451 (C/T)</td>
<td>rs 1805007</td>
<td>0.06</td>
<td>2.76 (1.59–4.78)^b</td>
<td>0.0003*</td>
<td>0.0018*</td>
</tr>
<tr>
<td>R160Wd</td>
<td>+478 (C/T)</td>
<td>rs 1805008</td>
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<td>2.15 (0.86–5.41)^b</td>
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<td>NS</td>
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<td>R163Q</td>
<td>+488 (G/A)</td>
<td>rs 885479</td>
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<td>5.62 (2.54–12.42)^b</td>
<td>&lt;0.0001*</td>
<td>0.0006*</td>
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<td>T314T</td>
<td>+942 (A/G)</td>
<td>rs 2228478</td>
<td>0.08</td>
<td>0.96 (0.69–1.35)</td>
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<tr>
<td>Family A</td>
<td>Family B</td>
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<td></td>
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<tr>
<td>----------</td>
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</tr>
<tr>
<td>Ind. A1</td>
<td>Ind. B1</td>
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<tr>
<td>Ind. A2</td>
<td>Ind. B2</td>
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1st Digestion (collagenase)

2d Digestion T/E

Feeder

3-D model of artificial skin

PCT/ES02/00087
The expression patterns detected in phenotypically skin cells correlate to the pattern observed in skin tumours (in-silico validation)

## Deregulated Pathways in RHC MC1R variants

<table>
<thead>
<tr>
<th>Term</th>
<th>STATUS</th>
<th>Adj. pvalue</th>
</tr>
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<tbody>
<tr>
<td>DNA replication (hsa03030)</td>
<td>UP</td>
<td>3.83E-14</td>
</tr>
<tr>
<td>Cell cycle (hsa04110)</td>
<td>UP</td>
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<tr>
<td>Mismatch repair (hsa03430)</td>
<td>UP</td>
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<tr>
<td>Nucleotide excision repair (hsa03420)</td>
<td>UP</td>
<td>7.01E-06</td>
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<tr>
<td>Parkinson’s disease (hsa05012)</td>
<td>UP</td>
<td>3.10E-05</td>
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<tr>
<td>Oxidative phosphorylation (hsa00190)</td>
<td>UP</td>
<td>6.91E-05</td>
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<tr>
<td>Huntington’s disease (hsa05016)</td>
<td>UP</td>
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<td>1.60E-02</td>
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<tr>
<td>Endocytosis (hsa04144)</td>
<td>DOWN</td>
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MC1R confers risk independently of its role in pigmentation

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"The MC1R melanoma risk variant p.R160W is associated with Parkinson disease".

<table>
<thead>
<tr>
<th>MC1R Variants</th>
<th>Amino Acid Change</th>
<th>Alleles</th>
<th>Minor Allele</th>
<th>MAF&lt;sup&gt;a&lt;/sup&gt; PD, n = 870</th>
<th>MAF&lt;sup&gt;a&lt;/sup&gt; Controls, n = 736</th>
<th>Adj. p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Genotype Frequency</th>
<th>PD Patients vs Controls</th>
<th>Adj. OR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Adj. p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Adj. p&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>0.003</td>
<td>0.98</td>
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<td>0.01</td>
<td>0.0009</td>
<td>0.063</td>
<td>0.95</td>
<td>0.05</td>
<td>0.98</td>
<td>0.02</td>
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<td>0.98</td>
<td>0.02</td>
<td>0.962</td>
<td>0.037</td>
</tr>
</tbody>
</table>

<sup>a</sup>Alleles are denoted as 1 (wild-type allele) or 2 (variant or minor allele).
<sup>b</sup>Adjusted for gender and age.
<sup>c</sup>Adjusted for gender and age and corrected by Bonferroni correction for multiple comparisons.
<sup>d</sup>Red hair color variant vs non-red hair color variant.
Adj. = adjusted; CI = confidence interval; MAF = minor allele frequency; NA = not assessed in previous studies; OR = odds ratio; PD = Parkinson disease.
Network of upregulated genes in RHC MC1R skin cells (557 genes)
Hub genes are not related to pigmentation

Oxidative phosphorilation

DNA repair and Cell homesotasis

Autophagy
Network of downregulated genes in RHC MC1R skin cells (450 genes)
Hub genes are not related to pigmentation

Apoptosis

Autophagy
### Hub Genes and Their p-values

<table>
<thead>
<tr>
<th>Hub Genes</th>
<th>p-value</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
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<td>ATG10</td>
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<td>ATG4C</td>
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### Pathways
- **Autophagy**
- **DNA Repair**
- **DNA Damage**
- **Oxidative Phosphorylation**
- **Early Endosomes**
- **Lysosomes**

### Experimental Details
- **14 Red Hair Colour individuals**
- **25,000 genes**
- **Human HT-12 V3 BeadChips, Illumina**
- **2441 differentially expressed genes**
- **7 Black hair colour individuals**
Damaged organelles or proteins
ROS production
Oxidative Stress
Starvation

AUTOPHAGY

Cur. Op. in Pharma. 2011; (11)

Cell Homoestasis
Apoptosis
Genomic stability
Oncogene-induced senescence
**Conclusions**

1. MC1R genotypes provide information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes.

2. Phenotypically normal skin cells carrying MC1R variants present constitute genomic signatures similar to those observed in skin cancer.

3. MC1R variants may increase the susceptibility to skin cancer independently of the UV radiation by:
   
   (i) Increasing basal oxidative stress and DNA damage in skin cells.
   (ii) Promoting deregulation of autophagy.