Genetic contribution to weight gain after initiation of antiretroviral therapy in treatment naïve patients with HIV

J Berenguer1, J Iarrani2, JM Bellón2, C Diez2, MA Jiménez-Sousa3,4, R Navarro-Soler1, JA Ibarra1,1, I Suárez-García5, C Amador6, A Curran10, F Villarroya11,12, P Domingo13, S Resino3,5, and Cohort of the Spanish Research Network (CorIS).

1Hospital General Universitario Gregorio Marañón, Madrid; 2Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Madrid; 3Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFC), Madrid; 4Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid; 5Centro Nacional de Micologia (ISCI), Majadahonda; 6Hospital Universitario 12 de Octubre (IIS Mad); 7Hospital Universitario Donostia (IIS Biodonostia), San Sebastián; 8Hospital Universitario Infantia Sofia, San Sebastián de los Reyes; 9Hospital de la Marina Baja, Villajoyosa; 10Hospital Universitario Vall d’Hebron, Barcelona; 11Departamento de Bioquímica y Biomedicina Molecular, Universidad de Barcelona, Barcelona; 12Hospital de la Santa Creu i Sant Pau, Barcelona.

Background & Aim

- Overweight and obesity are growing problems in PWH, among whom ART initiation is often associated with weight gain [1-7].
- Weight gain after the onset of ART can be partly explained by a return-to-health phenomenon. Other factors associated with higher weight gain include black race, female gender, high viral load, low CD4 count, and use of regimens including INSTI and TAF [8-13].

- To the best of our knowledge, the role of genetic factors in weight gain after ART initiation in naïve PWH has not been analyzed so far.

- Our objective was to study the association of polymorphisms of genes potentially involved in obesity with weight gain in this clinical scenario.

Study analysis

- Identification of baseline characteristics associated with weight gain
  - Multivariable linear regression analysis.
- Genetic association analysis
  - The Hardy-Weinberg equilibrium (HWE) was evaluated by the Chi-square test, considering the equilibrium when P>0.05.
  - Adjusted linear or logistic regressions were conducted as appropriate to assess the influence of SNPs on the variables of interest.
  - Different inheritance models (dominant, recessive, and additive) were tested, selecting the model that best fitted the data.
  - Unadjusted and adjusted linear mixed models for longitudinal data were used to account for the repeated measurements with BMI, with SNPs and time, and their interaction was taken as a fixed effect and the patient as a random effect.

Factors associated with weight gain at 96 wks after ART initiation (multivariable linear regression analysis)

Patients characteristics

- Baseline and 96 wk distribution of weight & BMI

Association of SNPs with BMI change at 96 wk by adjusted linear mixed models

Discussion

- ZC3H4 rs3810021 A allele has been associated with BMI in the general population (1). Variants in the ZC3H4 have been found to be positively associated with emotional eating and uncontrolled eating, suggesting that its links to obesity may, in part, be mediated by eating behaviors (2).
- Large-scale GWAS have identified associations between SULT1A2/FAM20A rs7138863 with BMI and obesity (1, 3). The underlying mechanisms are poorly understood.
- We used the GTEx (Genotype-Tissue Expression) Portal (4) and we found:
  - rs3810021 polymorphism may contribute to the expression of SULT1A2, a hepatic enzyme gene involved in the metabolism of xenobiotics and obesity (2).
  - An association between rs7138863 with A allele with higher expression of C1Q2/CTSL1 complex (C1q-like/membrane-type metalloprotease (MMP)-like) (5).

Obesity-related SNPs genotyped selected from a meta-analysis of GWAS BMI loci in European pops

- Table 1: Genotype frequency in the Spanish reference population (IISPM) and the European reference population (CEPH).

Table 1: Genotype frequency in the Spanish reference population (IISPM) and the European reference population (CEPH)

<table>
<thead>
<tr>
<th>SNP</th>
<th>IISPM Genotype</th>
<th>IISPM Frequency</th>
<th>European Genotype</th>
<th>European Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3810021</td>
<td>AG/AA</td>
<td>0.321</td>
<td>AG/AA</td>
<td>0.358</td>
</tr>
<tr>
<td>rs7138863</td>
<td>TT/CT/TT</td>
<td>0.470</td>
<td>TT/CT/TT</td>
<td>0.457</td>
</tr>
<tr>
<td>rs12446632</td>
<td>CC/AC</td>
<td>0.143</td>
<td>CC/AC</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Funding:

- MSD Investigator Studies Program (MISP) Ref# IISP 60091.
- Spanish AIDS Research Network (RD12/0025), which is included in the Spanish i+D Plan and is co-funded by ISCIII-Subdirección General de Evaluación and European Funding for Regional Development (FEDER)