Epstein-Barr virus genotypic variants and uses thereof as risk predictors, biomarkers and therapeutic targets of multiple sclerosis (MS).

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**Patent Type**
Patent for invention.

**Ownership**
Sapienza University of Rome 100%.

**Inventors**
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**Industrial & Commercial Reference**
Pharmaceutical Industries, Biotechnology companies.

**Time to Market**
We derived a method based on digital droplet PCR (dd-PCR) for the detection of EBV genotypes associated with multiple sclerosis (MS).

**Availability**
License, Research, Experimentation, Collaboration, Start-up and Spin-off.

**Abstract**
We observed a correlation between relapsing-remitting multiple sclerosis (MS) and the abundance of 1.2 allele (and newly identified variants) and the reduced presence of 1.3B allele. The present invention relates to a nucleic acid coding for a variant of the EBNA2 for use as a biomarker for predicting the risk of developing MS and/or for screening and/or for the diagnosis and/or prognosis of the disease, and to an in vitro method for predicting the risk of developing and/or for screening for MS and/or for the diagnosis and/or prognosis of the disease, comprising the detection of the presence of said nucleic acid.

**Publications**
Epstein-Barr virus genotypic variants and uses thereof as risk predictors, biomarkers and therapeutic targets of multiple sclerosis (MS).

### Technical Description

Objective of the present invention: 1 - nucleic acid coding for a variant of the gene coding for EBNA2 for use as a biomarker to predict the risk for the development and/or diagnosis and/or prognosis of MS; 2 - in vitro method to predict the risk of MS development, where the presence of the variant of the viral nucleic acid is a high-risk index; 3 - in vitro method for diagnosis and/or MS prognosis; 4 - kits for the detection of nucleic acid, as described above, comprising amplification and detection of said nucleic acid.

All objectives characterized by the presence of EBNA2 subtype 1.2 or variants thereof with at least one substitution of the coding triplet for at least one of the amino acids selected from the group consisting of: aa. 134, aa. 236, aa. 245 and aa. 267 (table 1).

<table>
<thead>
<tr>
<th>EBV genome</th>
<th>Alleles</th>
<th>MS, n (%) (v = 63)*</th>
<th>HD, n (%) (v = 34)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B95-8</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B95-6</td>
<td>1.2*</td>
<td>25 (8)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>B99-8</td>
<td>1.38</td>
<td>10 (34)</td>
<td>21 (71)</td>
</tr>
<tr>
<td>B99-9</td>
<td>1.58*</td>
<td>5 (17)</td>
<td>0</td>
</tr>
<tr>
<td>901*</td>
<td>f</td>
<td>4 (13)</td>
<td>5 (17)</td>
</tr>
</tbody>
</table>

Abbreviations: EBNA2 = Epstein-Barr nuclear antigen 2; EBV = Epstein-Barr virus; HD = healthy donor; MS = multiple sclerosis.

Data analysis was performed considering only the first sampling in 10 cases (7 MS and 3 HD) where multiple genotype determinations were obtained at different time points.

\* p = 0.0000, Fisher exact test.

Table 2. Frequency of EBNA2 alleles in the peripheral blood of patients with MS and HD.

### Technologies & Advantages

The origin of MS is considered complex, and due the interplay between multiple genetic and environmental factors. There is no optimal therapy for MS: current treatments reduce the risk of relapses but there are strong safety and tolerability issues.

Our approach may contribute to the definition of risk to reduce the high socio-economic impact of MS, and would bear two major advantages:

- Proximity to an etiologic therapeutic approach, that may be specific for the viral variants;
- Classification of EBNA2 variance for MS risk may contributes the development of risk-assessment protocols (possibly to be integrated with other laboratory and neuroimaging bio-markers) for close check-up in clinical practice and even for disease prevention.

We are developing a scalable test capable of predicting MS risk independently, or in synergy with other laboratory or neuroimaging tools. Moreover, a functional meaning of the newly discovered genotype variants of EBNA2 would allow the design of new drugs targeting the virus in its fine interactions with the cellular proteins.

### Applications

Neuroinflammation and especially multiple sclerosis.

Possible application of the present invention in prediction of risk, diagnosis, and treatment of inflammatory demyelinating diseases of central nervous system and autoimmune diseases with the involvement of Epstein-Barr virus as etiologic and/or pathogenic factor.

The compound of the present invention, DNA, RNA or protein, finds industrial applicability, for example in the identification of primers and/or probes or as an antigenic compound.

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