**MDM4 POLYMORPHISMS ASSOCIATED WITH AN INCREASED RISK OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CAUCASIAN POPULATIONS**

**Abstract**

Acute lymphoblastic leukaemia (ALL) is a well-known malignant disorder affecting both children and adults. Although the therapeutic limits have been maximized and optimized greatly, a better understanding of ALL is required for further improvements as prognostic value and cancer risk, to name a few. The genetic background has been revealed as critical to further improve the prognosis and diagnosis of ALL and other multiple malignant disorders. Hence this project proposes to study the individual genetic polymorphisms in MDM4, a downstream gene in the p53 pathway in order to determine the susceptibility to this affection in the Caucasian population in Barcelona, Spain.

Multiple studies of the p53 pathway elements - being the most relevant the ones regarding p53 and its negative regulator MDM2 - have proven useful to assign targets for ALL therapy and to broaden the understanding of this cancer. Interestingly, the role of polymorphic variants in the p53 pathway genes has been significantly related with cancer susceptibility.

The p53 pathway is essential to mediate cellular stress responses such as DNA damage, hypoxia and aberrant proliferation. P53, a well-characterized transcription factor, is the core regulator to initiate cell-cycle arrest, apoptosis, senescence and DNA repair. Under no cellular stress conditions, p53 is usually repressed by its direct negative regulator: MDM2, which binds to p53 and targets it for degradation through ubiquitination. MDM4 represses p53 by binding too, inhibiting p53 transcriptional activity while inhibiting MDM2 degradation. MDM4 has been reported to have an astonishing structural similarity with MDM2. Likewise, it seemed fairly reasonable to use MDM2 as an antecedent to further compare with MDM4.

Further studies have shown the correlation between specific genetic variants and ALL susceptibility in MDM2 and p53 but the correlation between MDM4 genetic variants and ALL has yet to be reported

**Material and Methods**

Sources of the mouthwash samples: (i) The Caucasian (CEU) population of the International HapMap project and (ii) Barcelona’s anonymous donors and (iii) ALL cancer patients from Barcelona’s Hospital Vall d’Hebron.

It is mandatory to hand them an Informed Consent Statement according to the Committee on Bioethics.

DNA extraction is required using the phenol-chloroform protocol.

The DNA samples will be amplified in GeneAmp® PCR System 5800 thermo cycle. To estimate the annealing temperature, Im Calculator web tool is required.

The product will be genotyped by Sanger’s method using the Big Dye® Terminator v3.1 DNA Cycle Sequencing Kit on a 3730XL DNA Analyzer.

The primers used were selected using Primer Design™ Tool including an M-13 5’ TETRAAAACGACGCTAG / M-13 5’ CAGGAAACAGCTATGACC tail to validate the sequence by having double coverage from either side. Moreover, it may be instrumental to delineate the break points of heterogeneous insertion / deletions or strong stops induced by difficult sequences such as an extended homopolymer.

**Expected results**

- The most likely result is accepting the alternative hypothesis and refute the null one (rs4245739 A>C polymorphism).
- A detailed amount of information regarding non neutral haplotypes and alleles and whether they are or they aren’t under selection pressure.
- The study may identify novel associated SNPs, which can be translated into novel susceptibility markers for ALL and possible targets for further studies.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Variants</th>
<th>Associated risk with</th>
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<tr>
<td>rs4245739</td>
<td>A&gt;C</td>
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<td>C&gt;T</td>
<td>Retinoblastoma</td>
<td>Yet to be reported</td>
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**References**