Abstract

Background: Human leukocyte antigen (HLA) molecules are encoded by the most polymorphic genes in the human genome. The genetic variation of these genes is considerable across different geographic subpopulations. We hypothesized that the genetic variation might contribute to the risk of melanoma both at population and subject level.

Methods: We developed a cancer risk predictor based on the complete HLA class I genotype of individuals. The HLA-score, used in the predictor describes the ability of the HLA class I alleles of an individual to bind putative tumour antigens and was identified as an indicator of the breadth of the tumour-specific T-cell response. We collected HLA data from subjects from 20 different geographic regions (ethnic populations) (n = 3278) as well as the corresponding melanoma incidence rates. The average HLA-scores were compared to the incidence rates. We also classified all US population consisting of melanoma and healthy subjects based on their HLA-score.

Results: On population level, we found significant correlation between the incidence rates of melanoma and average HLA-scores in different geographic regions (R² = 0.5005, p < 0.001, n = 20). The highest average HLA-scores (range 75-140) were obtained for the Far East Asian and Pacific regions, where the incidence rates are low (0.4-4.3 per 100,000 per year). The lowest average HLA-scores (range 50-90) were obtained in the European and US regions, where the rates are high (12.6-13.8 per 100,000 per year). On subject level, the results between the highest (HLA-score >94) and the most protected (HLA-score <96) was 5.69 comparing the top and bottom 20% of the HLA-score distribution (p < 0.05). These HLA-score ranges are consistent with the threshold values separating populations with low and high incidence rates of melanoma.

Conclusions: By developing a novel HLA-score predictor, we demonstrated that the HLA genotype and HLA-score could be used to determine the immunological risk of melanoma.

Study design

By developing a novel HLA-score predictor for individuals, we have identified that HLA class I alleles containing broader tumour-specific T-cell response have lower risk of developing melanoma. These results imply that the HLA genotype and HLA-score could be used to determine the immunological risk of melanoma.

Computing the HLA-score

For each HLA allele, we computed a significance score (HLA-score) based on how different the HLA allele is from the background alleles of a large database of immunogenetic risk of melanoma. We showed that individuals with HLA allele sets supporting broader genetic variation of these genes are considerable across different geographic subpopulations. We hypothesised that this genetic variation might contribute to the risk of melanoma both at population and subject level.

The Relative Risk (RR) in different subgroups of a mix US population based on HLA-score

Test population, n=1913 (general and melanoma subjects) were divided into five equal-size subgroups based on their HLA-score (s). The Relative Risk (RR) of each subgroup was computed.

The HLA-score for the prediction of cancer risk in different indications

We also tested the HLA-score method for other indications: l 5. For the other 6 indications, the achieved AUC value was significant.

Significant correlation between HLA score and melanoma incidence rates in 20 countries

We identified 20 countries (*the figure above*) with HLA genotype data from their dominant ethnicity, for which we determined the mean HLA-scores and compared them with the incidence rates of melanoma. The countries with low and high melanoma incidence rates are well separated by an apparent HLA-score of >90 threshold, which is consistent with the threshold values separating low and high risk subjects in the US (HLA-score >96).

Conclusions

• We showed here that HLA genotypes affect a person’s risk of developing cancer through an immunological mechanism - epitope binding ability of the autologous HLA.
• This further confirms our PEPI concept for the prediction of patient’s antigen-specific immune response based on their complete HLA genotypes.
• HLA-score predictor can be used as biomarker to identify subjects with increased biological risk.
• Eg: the 2.35-5.69 RR of melanoma for different cancers is either comparable or exceeds the 2.63 RR of HLA genotypes carrying the top and bottom 5% of the US.
• Genetic testing should include determining the subject’s HLA genotypes and calculating the HLA-score to better assess hereditary risks of cancer.

Correspondences: miklos.i@treosbio.com; eniko.toke@treosbio.com

Presented at the European Society for Medical Oncology Annual Congress, Barcelona, September 27 - October 1, 2019

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Infering the Correlation Between Incidence Rates of Melanoma and the Average Tumor-specific Epitope Binding Ability of HLA Class I Molecules in Different Populations