Publicacions més rellevants de la línia de recerca:
Estadística Genètica

Referència: Calle,M.L., Urrea, V., Vellalta, G. Malats, N. and Van Steen, K. Improving strategies for detecting genetic patterns of disease susceptibility in association studies. *Statistics in Medicine*, **27** (2008), pp. 6532–6546.

Abstract: The analysis of gene interactions and epistatic patterns of susceptibility is especially important for investigating complex diseases such as cancer characterized by the joint action of several genes. This work is motivated by a case-control study of bladder cancer, aimed at evaluating the role of both genetic and environmental factors in bladder carcinogenesis. In particular, the analysis of the inflammation pathway is of interest, for which information on a total of 282 SNPs in 108 genes involved in the inflammatory response is available. Detecting and interpreting interactions with such a large number of polymorphisms is a great challenge from both the statistical and the computational perspectives. In this paper we propose a two-stage strategy for identifying relevant interactions: (1) the use of a synergy measure among interacting genes and (2) the use of the model-based multifactor dimensionality reduction method (MB-MDR), a model-based version of the MDR method, which allows adjustment for confounders.

Referència: Guey L.T. , García-Closas M., Murta-Nascimento C., Lloreta J., Palencia L., Kogevinas M., Rothman N., Vellalta G., Calle M.L., Marenne G., Tardón A., Carrato A., García-Closas R., Serram C., Silverman D.T., Chanock S., Real F.X. and Malats N. Genetic Susceptibility to Distinct Bladder Cancer Subphenotypes. *European Urology*, (2009), `doi:10.1016/j.eururo.2009.08.001`.

Abstract: Background: Clinical, pathologic, and molecular evidence indicate that bladder cancer is heterogeneous with pathologic/molecular features that define distinct subphenotypes with different prognoses. It is conceivable that specific patterns of genetic susceptibility are associated with particular subphenotypes. Objective: To examine evidence for the contribution of germline genetic variation to bladder cancer heterogeneity. Design, setting, and participants: The Spanish Bladder Cancer/EPICURO Study is a case-control study based in 18 hospitals located in five areas in Spain. Cases were patients with a newly diagnosed, histologically confirmed, urothelial cell carcinoma of the bladder from 1998 to 2001. Case diagnoses were reviewed and uniformly classified by pathologists following the World Health Organisation/ International Society of Urological Pathology 1999 criteria. Controls were hospital- matched patients ($n = 1149$). Measurements: A total of 1526 candidate variants in 423 candidate genes were analysed. Three distinct subphenotypes

were defined according to stage and grade: low-grade nonmuscle invasive ($n = 586$), high-grade nonmuscle invasive (n = 219), and muscle invasive ($n = 246$). The association between each variant and subphenotype was assessed by polytomous risk models adjusting for potential confounders. Heterogeneity in genetic susceptibility among subphenotypes was also tested. Results and limitations: Two established bladder cancer susceptibility genotypes, NAT2 slow-acetylation and GSTM1-null, exhibited similar associations among the subphenotypes, as did VEGF-rs25648, which was previously identified in our study. Other variants conferred risks for specific tumour subphenotypes such as PMS2-rs6463524 and CD4-rs3213427 (respective heterogeneity p values of 0.006 and 0.004), which were associated with muscle-invasive tumours (per-allele odds ratios [95% confidence interval] of 0.56 [0.41 - 0.77] and 0.71 [0.57 - 0.88], respectively) but not with non-muscle-invasive tumours. Heterogeneity p values were not robust in multiple testing according to their false-discovery rate. Conclusions: These exploratory analyses suggest that genetic susceptibility loci might be related to the molecular/pathologic diversity of bladder cancer. Validation through large-scale replication studies and the study of additional genes and single nucleotide polymorphisms are required.

Referència: Robert G., Peña R. Cabrera C., Coma G., Ruiz-Hernandez R., Guerola R., Clotet B., Ruiz L., Esté J.A., Calle M.L. and Bofill M. Skewed expression and up-regulation of the IL-12 and IL-18 receptors in resting and activated CD4 T cells from HIV-1-infected patients. *Journal of Leukocyte Biology*, **82** (2007), pp. 72–78.

Abstract: IL-12 and IL-18 synergistically induce the production of IFN-γ by resting and activated T cells. To evaluate whether this induction was affected in HIV-1-infected patients, PBMC or isolated CD4 T cells were cultured with IL-12 plus IL-18, anti-CD3 plus anti-CD28, or PHA for 72 h. Cell samples were labeled daily to assess the levels of IL-12 receptor β1 (IL-12Rβ1), IL-12Rβ2, and IL-18Rα. Culture supernatants were analyzed for the presence of Th1- and Th2-related cytokines by ELISA or cytometric bead array and analyzed by flow cytometry. A twofold increase in the percentage of CD4-resting T cells expressing IL-12Rβ1 and IL-18Rα from HIV-1-infected patients was observed when compared with cells from HIV-1-negative donors. Higher IL-12Rβ1 and IL-18Rα expression correlated ($r = 0.87$; $p < 0.007$) to increased production of IFN-γ by isolated CD4 T cells in the presence of IL-12 and IL-18. Moreover, exogenous IL-12 and IL-18 induced the upregulation of IL-12Rβ2 to twice higher in CD4 T cells from HIV-1-positive individuals compared with controls. Conversely, upon activation with anti-CD3 and anti-CD28 antibodies, only 25% of the CD4+ T cells from HIV-1 patients showed an increase in the IL-12β2 when compared with 50% in healthy controls. Furthermore, the percentage of IL-12Rβ1-positive cells correlated inversely with the CD4 nadir of patients, suggesting that deregulation of the IL-12 and IL-18 pathways may play a role in the immunopathogenesis of HIV-1 infection.