Feasibility of particle genetics in humans

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In the field of personalized medicine, despite the identification of genetic determinants associated with human disease, the promise of an individual phenotypic prediction from the genotype is limited, among others, by random stochastic processes involved in gene expression per se. Indeed, genetically identical cells grown in the same environment often display a large range of phenotypic trait values meaning that some cells deviate significantly from the population average [1]. This cell-to-cell variability might have dramatic effects, for instance when extreme values appear in oncogenes expression levels.

The idea is to investigate how genotype influences random cell-to-cell variability of gene expression by looking at how the genetic background shapes the statistical distribution of some surface proteins expression levels, or single cell trait, in human cells.

We are interested in seven clinically relevant markers which noisy expression could affect different processes such as B cell differentiation, pathogen response or disease susceptibility, using lymphoblastoid cell lines (LCLs) [2]. Measurements are made by flow cytometry on thousands of individual cells, at single cell resolution. Cell cycle stage was determined via DAPI staining whereas FSC and SSC signal were used as proxies for cell size. Data processing was performed with Bioconductor librairies [3] within a dedicated R pipeline. In order to eliminate genetic and environment interactions, clonality of the cell line was assessed by sequencing [4].

We observed inter-cell line variability in expression as well as differences in CV (Coefficient of Variation) values suggesting cell-to-cell variability within population, independently of the clonality status (mono or polyclonal populations). We now then intend to identify the genetic sources of 'noise' to find genetic loci that influence the statistical distribution of protein expression levels (especially the CV), thus contributing to understand the influence of probabilistic expression in human complex traits.

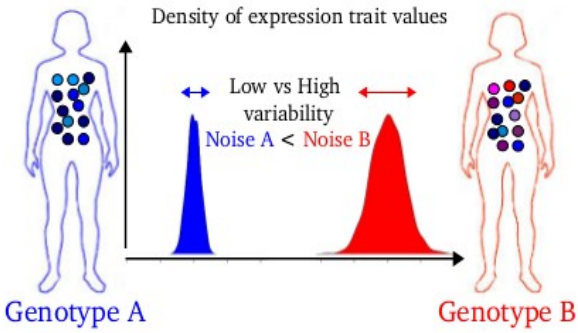
Références

[1] Yvert, G. (2014). 'Particle genetics': treating every cell as unique. Trends in Genetics, 30(2), 49-56.
[2] Küppers, R. (2003). B cells under influence: transformation of B cells by Epstein-Barr virus. Nature Reviews Immunology, 3(10), 801-12.
[3] Huber, W., et al. (2015). Orchestrating high-throughput genomic analysis with Bioconductor. Nature Methods, 12(2), 115-121.

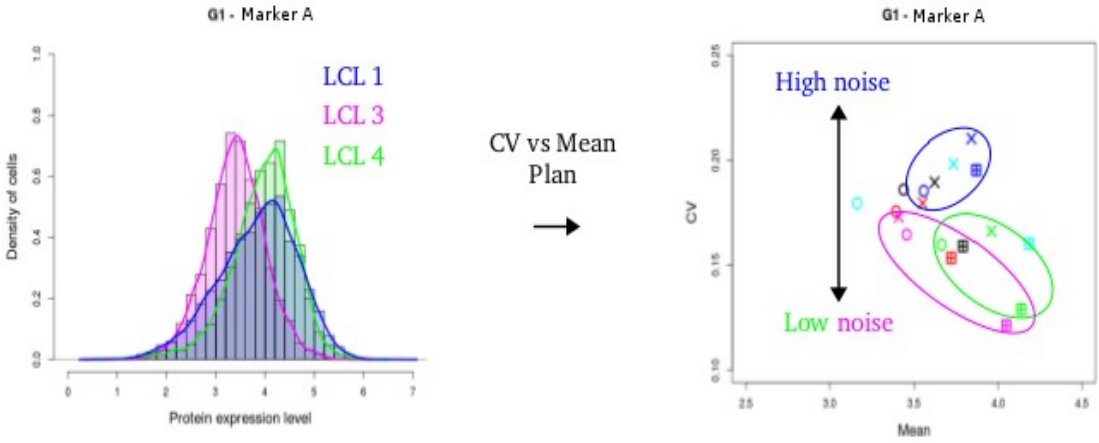
[4] Safonova, Y., et al. (2015). IgRepertoireConstructor: a novel algorithm for antibody repertoire construction and immunoproteogenomics analysis. Bioinformatics, 31(12), i53-i61.

Figures

A. Two genotypes at a given locus are compared; the distributions of a single cell trait value among clonal cells are color-coded.



B. Variability of protein expression is compared between cell lines, showing reproducible inter-cell line noise variability.



C. Pipeline of data analysis.