Identification of Drug Responder Population by Genomics Signatures and Genetic Classifiers

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Genome-wide Profiling of SNPs in Biomarker Discovery: Treatment of Multiple Sclerosis (MS)

Context & Opportunities

The recent development of bioassay technologies allows the availability of massive genetic and genomic data to researchers. It is expected that this will contribute to a better understanding of the diseases as well as the mechanism of action of pharmaceutical treatments under development. This is also expected to facilitate the research about **Personalized Medicine**: To give the right treatment to the right patients. Indeed, for many diseases we observe that only a part of the patient population "responds" to a treatment, while the other part does not.

One objective for the researchers is to use the now available genetic and genomic data to define the sub-group of patients "responders" to the treatment. This question is getting increasing interest in the pharmaceutical research, as it will **improve the medical value** of the treatments for the patients and the payers.

Objectives & Strategy

Teriflunomide* (Aubagio™) is an effective treatment for Multiple Sclerosis (MS) disease, with approximately 60% response rate. A GWAS (pharmaco-genetic analysis) is conducted in the attempt to characterize the subjects responders (towards Personalized Medicine). Here we present the organization used, the sequence of tasks to perform, as well as the statistical analyses defined to address the objectives.

Objectives

- Discover biomarkers predictive of teriflunomide treatment outcome in MS: For efficacy endpoints and for safety endpoints.
- Discover genetic associations at the level of the SNPs, genes and biological pathways: Teriflunomide Mechanism of Action, suggest new drug targets for MS

Process, mapped on the capabilities of the TM4P (TM for Patients) Platform

1. DNA samples collected during clinical trials (1.500 patients)
2. DNA extraction and Genotyping
3. QC and normalize data to identify SNPs
4. Statistical analysis by Sanofi Biostatistics (multi-variant modeling & algorithms)
5. Additional analysis of data, e.g., mapping of genetic markers to pathways

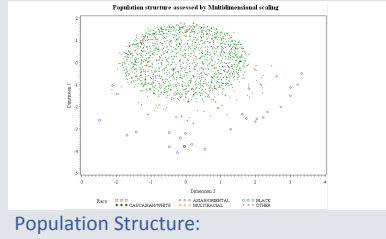
Analysis & Conclusion

Analysis

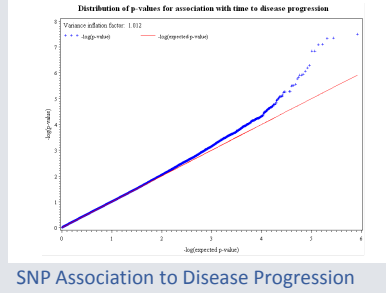
- Multivariate modeling of the clinical response
  1. Selection of relevant SNPs among 800.000 SNP passing QC
  2. Screening of SNP marginally associated to clinical endpoint
  3. Multivariate penalized regression with selected SNP
  4. Re-iterate screening of SNP adjusted on SNP selected at step 2
  5. Multivariate penalized regression with new set of selected SNP
  6. Re-iterate steps 1-4 until no more SNP is selected

Conclusions

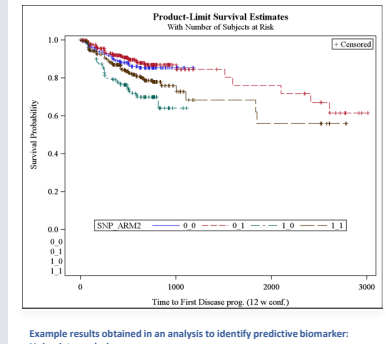
- First GWAS performed and analyzed internally by Sanofi
- First GWAS performed to develop a classifier for a treatment response in CNS
- Development of a Statistical Analysis Plan anticipating the issues induced by a GWAS analysis, and to apply fit-for-purpose and state-of-the-art methods
- Certain statistically significant associations were identified.
- The results will now be subjected to further analysis to assess their biologic causality or plausibility.
- Any finding will have to be confirmed in an independent study.



Population Structure:
Exclusion of Non-Caucasian Samples



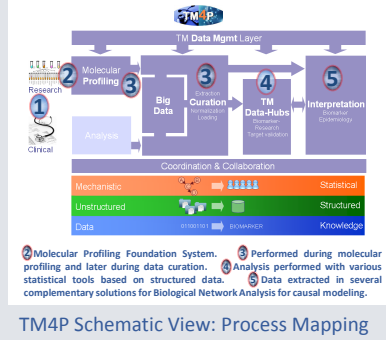
SNP Association to Disease Progression
(work in progress)



Example results obtained in an analysis to identify predictive biomarker: Univariate analysis

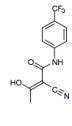
Blue curve: disease free survival for control arm, patients without the variant
Red curve: disease free survival for active arm, patients without the variant
Green curve: disease free survival for control arm, patients with the variant
Brown curve: disease free survival for active arm, patients with the variant

Disease free survival by Treatment Arm:
Presence of Genetic Marker (work in progress)



2 Molecular Profiling Foundation System. 3 Performed during molecular profiling and later during data curation. 4 Analysis performed with various statistical tools based on structured data. 5 Data extracted in several complementary solutions for Biological Network Analysis for causal modeling.

TM4P Schematic View: Process Mapping



* Sanofi's AUBAGIO (teriflunomide) is an immuno-modulator with anti-inflammatory properties. The exact mechanism of action for AUBAGIO is not fully understood, but it may involve a reduction in the number of activated lymphocytes in the central nervous system (CNS). AUBAGIO is approved in the U.S., Australia and Argentina for the treatment of relapsing forms of MS.

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