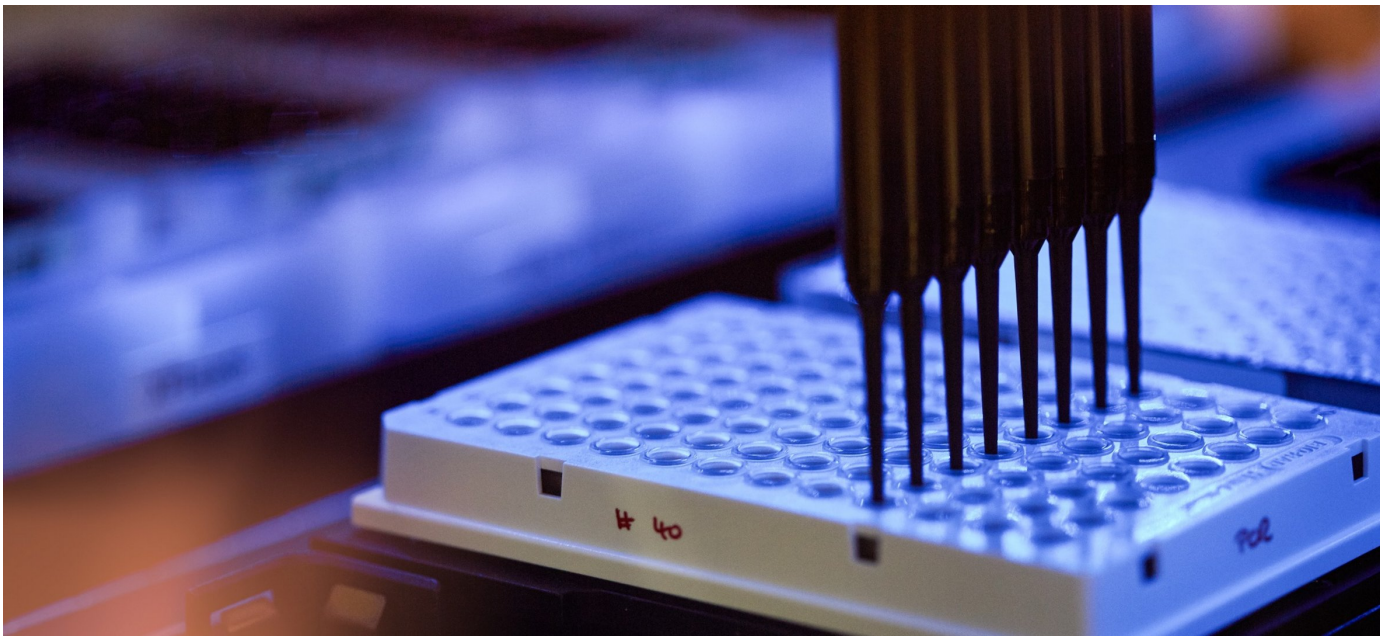
Analysis of pharmacogenomic variants by WGS data for AML patients with altered response to treatment



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With the decrease of sequencing costs, the number of freely available "omics" data sets also increases, opening a nearly unlimited quantity of molecular genetic information. For the last decades the classical way of elucidating multifaceted molecular networks of diseases has been to break down the system into smaller, more traceable parts. However, the genomic revolution of the last years has shown that a comprehensive understanding of such complex systems can only be obtained through the integration of different molecular levels and, at best, clinical information.

The focus here is the identification of disease drivers that perturb the healthy state and lead to a subsequent transition into a disease state. Such drivers represent promising entry points for efficient targeted treatment design, potentially limiting side effects and increasing the probability of treatment success. An extended knowledge of a patients' molecular profile might also be key for a more accurate prediction of a person's response to therapy. That's where pharmacogenomics comes into play, which aims to predict the effect and consequences of various drug treatments for a particular individual based on their genetic background and/or their expression profile. So far most of the research in this field has focused on the role of single nucleotide polymorphisms, copy number variations or differences in gene expression levels of drug metabolizing or transporting genes and drug targets. *Schärfe et al.* 2017 followed that line with their publication regarding the genetic variation in human drug-related genes. The study focused on the integrated analysis of 60,706 human exomes and drug-related databases, accumulating also a list of 217 cancer drug target genes carrying functional variants. Based on this list ***Meggendorfer et al.*** investigated the genetic background (WGS data) of AML patients refractory to treatment for associations of polymorphisms (SNPs) in those genes and/or disease associated mutations. The cohort comprised 247 AML patients who were all treated with a standard chemotherapy protocol. However, AML is genetically very diverse and the response to treatment varies considerably among patients. The 247 AMLs were divided into two groups: the responder group (cytomorphological complete remission after first induction; n = 186) and the group of patients with only partial remission or progressive disease after second induction (n = 61). Interestingly, both the morphological subtypes as well as the mutation frequencies of AML genes were similar in the two groups.

A slightly different picture merged for the co-occurrences of two variants (incl. SNPs and somatic variants). Considerably less co-occurrences of SNPs and somatic variants could be found in the responder group, which were all unique. In contrast 772 recurrent co-occurrences of SNPs and somatic variants could be found in patients who did not, or only partially, respond to treatment. 51% of the patients from the non-responder group were involved in the reconstructed co-occurrence network which also revealed coincidences of *IDH2*, *KMT2A-PTD*, *SF3B1* and *TP53* mutations with multiple missense SNPs. Secondly, recurrent (in at least 10% of the patients) SNP co-occurrences were more frequently found in the non-responder group. 6 of those SNP pairs were associated with the MAPK family signalling cascade. Despite the pleiotropic nature of occurring aberrations in cancer, alterations in the evolutionarily conserved MAPK pathways are a common feature. The MAPK/ERK signalling pathway comprises multiple signalling and activating molecules and can function as a tumour suppressor (*Burotto et al.* 2014). The balance between the different signals determines the outcome and also affects sensitivity to drug therapy (*Dhillon et al.* 2007). Hence, the identified SNP pairs might impact treatment response by potentially interfering with the MAPK pathways. In addition, post-transcriptional regulation mechanisms impact gene expression, modify the proteome and consequently might also affect therapeutic approaches. Most of the regulatory mechanisms target the 3'UTR and, hence, it was noteworthy that multiple non-coding SNPs were found in the 3'UTR of the drug target genes. Again, the frequency was higher in the non-responder group compared to the responder group. Base-exchanges in the 3'UTR region might affect mRNA-miRNA interactions by creating, negating, or changing the miRNA-binding sites. The miRNA binding site is usually defined as a 6-8bp 'seed' region. Due to the comparatively short length, single base exchanges can already have a significant effect by altering the potential binding partners.

This study shows the potential of the combination of genomic data and *in silico* analyses to predict treatment response for individual patients. Even though the field of pharmacogenomics is still in its infancy and many more studies have to be performed before a routine application is even conceivably, the potential is nevertheless tremendous. There is no doubt that with the increase of available 'omics' data, better data integration methods will be developed to facilitate the creation of interaction networks as a basis for in silico perturbation experiments.

Resources

Burotto, M, et al. "The MAPK pathway across different malignancies: a new perspective." Cancer 120.22 (2014): 3446-3456.

Dhillon, AS, et al. "MAP kinase signalling pathways in cancer." Oncogene 26.22 (2007): 3279.

Schärfe, CPI, et al. "Genetic variation in human drug-related genes." Genome medicine 9.1 (2017): 117.

Die Autorin

Dr. Wencke Walter

Bioinformatikerin, M.Sc.

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wencke.walter@mll.com