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Relating genomic variation to drug response in childhood acute lymphoblastic leukemia by multiplexed targeted sequencing

Agata Wesolowska[1*], Marlene D Dalgaard[2], Louise Borst[2], Laurent Gautier[1], Mads Bak[3], Nils Weinhold[1], Betina F Nielsen[2], Jacob Nersting[2], Niels Tommerup[3], Søren Brunak[1], Thomas Sicheritz Ponten[1], Henrik Leffers[2], Kjeld Schmiegelow[2], Ramneek Gupta[1]

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Acute lymphoblastic leukemia (ALL) is the most common childhood cancer with incidence rate in USA and Europe of 3.5 cases per 100 000 children. The overall current cure rate is ~ 75% and around 25% of treated children die from resistant disease, relapse or treatment toxicities. Several single nucleotide polymorphisms (SNPs) are known to be key determinators for interidividual differences in treatment resistance and toxic side effects [1]. Because childhood ALL treatment protocols include up to 13 different chemotherapeutic agents, it is hard to evaluate the impact of individual SNPs. So far focus has mainly been on the widely used glucocorticosteroids, methotrexate and thiopurines, or on metabolic pathways and transport mechanisms that are common to several drugs, such as the glutathione S-transferases. However, beyond the thiopurine methyltransferase polymorphisms, the candidate-gene approach has not established clear associations between polymorphisms and treatment response.

Instead of single SNP or gene investigation, we have designed a high- throughput assay for ~ 20 000 targeted SNPs to explore combined gene- dosage effects. The assay applies multiplexed targeted sequencing as a cost-effective technique for genotyping. Such a multiple-SNP assay will allow the investigation of effects mediated via pathways where one of several SNPs (in the same or different genes) may lead to very similar clinical phenotypes due to related molecular mechanisms. In selection of genes, we have included those involved in pharmacology, immunology, DNA-repair mechanisms, mitosis activity genes, and genes that affect apoptosis, neurotoxicity and thrombosis. We have also included binding partners of key proteins from protein-protein interaction data, and proteins known to interact with the 13 compounds commonly used for treatment. The selected SNPs target coding regions and known regulatory regions including predicted microRNA target sites. The study will include up to 2000 children with ALL, divided into a retrospective study (600-800 samples) and a prospective study.

This poster will present current status and challenges of the project and demonstrate the multiplexed targeted sequencing as a cost-effective technique for genotyping.

Author details
[1]Center for Biological Sequence Analysis, Technical University of Denmark, Lyngby, Denmark. [2]Pediatric Oncology labs and Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark. [3]Institute for Cellular and Molecular Medicine, Panum Institute, Copenhagen, Denmark.

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[1]Center for Biological Sequence Analysis, Technical University of Denmark, Lyngby, Denmark
Full list of author information is available at the end of the article