Genetic predisposition to PEG-asparaginase hypersensitivity in children treated according to NOPHO ALL2008

Asparaginase is essential in childhood acute lymphoblastic leukaemia (ALL) treatment, however hypersensitivity reactions to pegylated asparaginase (PEG-asparaginase) hampers anti-neoplastic efficacy. Patients with PEG-asparaginase hypersensitivity have been shown to possess zero asparaginase enzyme activity. Using this measurement to define the phenotype, we investigated genetic predisposition to PEG-asparaginase hypersensitivity in a genome-wide association study (GWAS). From July 2008 to March 2016, 1494 children were treated on the Nordic Society of Paediatric Haematology and Oncology ALL2008 protocol. Cases were defined by clinical hypersensitivity and no enzyme activity, controls had enzyme activity ≥ 100 iu/l and no hypersensitivity symptoms. PEG-asparaginase hypersensitivity was reported in 13.8% (206/1494) of patients. Fifty-nine cases and 772 controls fulfilled GWAS inclusion criteria. The CNOT3 variant rs73062673 on 19q13.42, was associated with PEG-asparaginase allergy (P = 4.68 × 10^{-8}). We further identified two signals on chromosome 6 in relation to HLA-DQA1 (P = 9.37 × 10^{-6}) and TAP2 (P = 1.59 × 10^{-5}). This study associated variants in CNOT3 and in the human leucocyte antigen (HLA) region with PEG-asparaginase hypersensitivity, suggesting that not only genetic variations in the HLA region, but also regulation of these genes are of importance in the biology of this toxicity. Furthermore, our study emphasizes the importance of using asparaginase enzyme activity measurements to identify PEG-asparaginase hypersensitivity.

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