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.

General information
State: Published
Organisations: Department of Health Technology, Aarhus University Hospital, Rigshospitalet, University of Gothenburg, Uppsala University, Karolinska Institutet, Landspitali University Hospital, University of Turku, St Olavs University Hospital, University Children’s Hospital Tallinn, Vilnius University
Number of pages: 13
Pages: 405-417
Publication date: 2019
Peer-reviewed: Yes

Publication information
Journal: British Journal of Haematology
Volume: 184
Issue number: 3
ISSN (Print): 0007-1048
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Web of Science (2017): Impact factor 5.128
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2017): CiteScore 3.43 SJR 2.036 SNIP 1.389
Web of Science (2017): Impact factor 5.128
Web of Science (2017): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2016): CiteScore 3.55 SJR 2.086 SNIP 1.544
Web of Science (2016): Impact factor 5.67
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3.51 SJR 2.297 SNIP 1.64
Web of Science (2015): Impact factor 5.812
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.17 SJR 2.138 SNIP 1.626
Web of Science (2014): Impact factor 4.971
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 3.26 SJR 2.002 SNIP 1.674
Web of Science (2013): Impact factor 4.959
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1