NT5C2 germline variants alter thiopurine metabolism and are associated with acquired NT5C2 relapse mutations in childhood acute lymphoblastic leukaemia

The antileukaemic drug 6-mercaptopurine is converted into thioguanine nucleotides (TGN) and incorporated into DNA (DNA-TG), the active end metabolite. In a series of genome-wide association studies, we analysed time-weighted means (wm) of erythrocyte concentrations of TGN (Ery-TGN) and DNA-TG in 1009 patients undergoing maintenance therapy for acute lymphoblastic leukaemia (ALL). In discovery analyses (454 patients), the propensity for DNA-TG incorporation (wm DNA-TG/wm Ery-TGN ratio) was significantly associated with three intronic SNPs in NT5C2 (top hit: rs72846714; $P = 2.09 \times 10^{-10}$, minor allele frequency 15%). In validation analyses (555 patients), this association remained significant during both early and late maintenance therapy ($P = 8.4 \times 10^{-6}$ and $1.3 \times 10^{-3}$, respectively). The association was mostly driven by differences in wm Ery-TGN, but in regression analyses adjusted for wm Ery-TGN ($P < 0.0001$), rs72846714-A genotype also associated with a higher wm DNA-TG ($P = 0.029$). Targeted sequencing of NT5C2 did not identify any missense variants associated with rs72846714 or wm Ery-TGN/wm DNA-TG. rs72846714 was not associated with relapse risk, but in a separate cohort of 180 children with relapsed ALL rs72846714-A genotype was associated with increased occurrence of relapse-specific NT5C2 gain-of-function mutations that reduce cytosol TGN levels ($P = 0.03$). These observations highlight the impact of both germline and acquired mutations in drug metabolism and disease trajectory.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, University of Southern Denmark, Landspitali University Hospital, Norwegian University of Science and Technology, Uppsala University, University of Gothenburg, Vilnius University, Talinn Children's Hospital, Aarhus University, University of Oslo, University of Tartu, University of Minnesota, New York University, Copenhagen University Hospital, University of Copenhagen, Technical University of Denmark
Pages: 2527-2535
Publication date: 2018
Peer-reviewed: Yes

Publication information
Journal: Leukemia
Volume: 32
ISSN (Print): 0887-6924
Ratings:
BFI (2019): BFI-level 2
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 6.45 SJR 5.131 SNIP 2.085
Web of Science (2017): Impact factor 10.023
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.47 SJR 5.041 SNIP 2.226
Web of Science (2016): Impact factor 11.702
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.43 SJR 5.189 SNIP 2.211
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 5.83 SJR 4.657 SNIP 1.952
Web of Science (2014): Impact factor 10.431
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 5.78 SJR 4.388 SNIP 1.802