Trypsin encoding PRSS1-PRSS2 variation influence the risk of asparaginase-associated pancreatitis in children with acute lymphoblastic leukemia: a Ponte di Legno toxicity working group report

Asparaginase-associated pancreatitis is a life-threatening toxicity to childhood acute lymphoblastic leukemia treatment. To elucidate genetic predisposition and asparaginase-associated pancreatitis pathogenesis, ten acute lymphoblastic leukemia trial groups contributed remission samples from patients aged 1.0-17.9 years and treated from 2000-2016. Cases were defined (n=244) by at least two of the following criteria: i) abdominal pain, ii) pancreatic enzymes >3 x upper normal limit, iii) imaging compatible with asparaginase-associated pancreatitis. Controls (n=1320) completed intended asparaginase therapy, 78% receiving ≥8 pegylated-asparaginase injections, without developing asparaginase-associated pancreatitis. rs62228256 on 20q13.2 showed the strongest association (OR=3.75; P=5.2x10^-8). Moreover, rs13228878 (OR=0.61; P=7.1x10^-6) and rs10273639 (OR=0.62; P=1.1x10^-5) on 7q34 showed significant association. A Dana Farber Cancer Institute ALL Consortium cohort consisting of patients treated protocols from 1987-2004 (controls=285, cases=33), and the Children's Oncology Group AALL0232 cohort (controls=2653, cases=76) were available as replication cohorts for the 20q13.2 and 7q34 variants, respectively. While rs62228256 was not validated (P=0.86), both rs13228878 (P=0.03) and rs10273639 (P=0.04) were. rs13228878 and rs10273639 are in high linkage disequilibrium (r^2=0.94) and associated with elevated expression of the trypsinogen encoding PRSS1 gene and are known risk variants for alcohol-associated and sporadic pancreatitis in adults. Intra-pancreatic trypsinogen cleavage to proteolytic trypsin induces autodigestion and pancreatitis. Asparaginase-associated pancreatitis and non-asparaginase associated pancreatitis shares genetic predisposition and targeting the trypsinogen activation pathway may enable identification of effective interventions towards asparaginase-associated pancreatitis.