Introduction

We have reported that thiopurine induced myelosuppression is associated with variants in *NUDT15* in patients with IBD of European ancestry. However, because we used a retrospective phenotype-first approach our findings were limited by ascertainment and recall bias. Before clinical implementation, further work is needed to define the penetrance, expressivity, and variant pathogenicity of *NUDT15* carriage. We used a reverse-phenotyping retrospective cohort design to investigate the six-month risk of myelosuppression in patients with *NUDT15* variants.

Methods

We screened whole exome data and identified 451/23082 patients with a loss of function *NUDT15* variant (*2, *3, *4, *5, *6 &*9) from the IBD BioResource. We matched these patients, based on ethnicity, to 916 participants without *NUDT15* or *TPMT* variants who were treated with a thiopurine. Myelosuppression was defined as a white cell count (WCC) $<3.5x10^9$/L or a neutrophil count $<2.0x10^9$/L that occurred within six months of achieving the maximum thiopurine dose, or in the absence of blood test results, a decision to dose reduce or withdraw the thiopurine due to myelosuppression. Severe myelosuppression was defined as a WCC $<2.5x10^9$/L or neutrophil count $<1.0x10^9$/L and a decision to either reduce or withdraw the thiopurine.

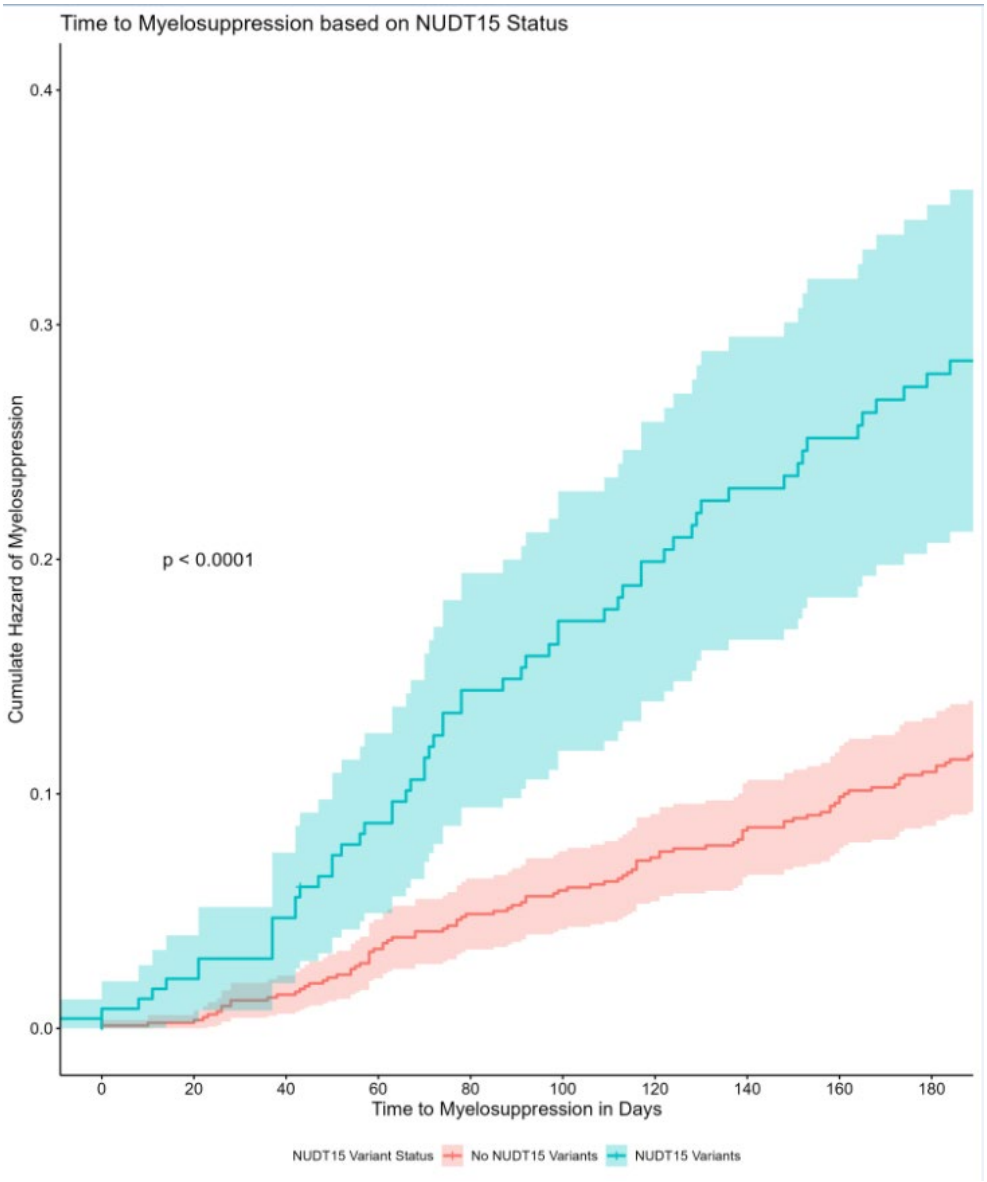
Results

NUDT15 variants were more commonly seen in individuals of East and South Asian ancestry (East Asian 21.7% [10/46], South Asian 13.6% [151/962], African 1.6% [5/322], European 1.3% [271/21304], other 6.8% [20/296], p <0.001). Overall, 239/457 patients who carried a *NUDT15* variant allele were treated with a thiopurine. There were no differences in the median-weight drug-adjusted doses (1.79 mg/kg/day vs 1.87 mg/kg/day, p=0.2) amongst patients with and without *NUDT15*.

Amongst patients with wild-type *NUDT15* and *TPMT* 13.7% had an episode of myelosuppression, but severe myelosuppression and hospitalisations were uncommon. The time to myelosuppression was shorter in patients with *NUDT15* variants. Rates of myelosuppression, severe myelosuppression, and hospitalisations were greater in patients with *NUDT15* variants. Carriage of *3, *6, *9 were all associated with a shorter time to myelosuppression compared to wild-type *NUDT15* (p=0.047). Carriage of *3, was associated with a shorter time to myelosuppression than *6 and *9 (p=0.032). The number needed to genotype to prevent a single case of myelosuppression in European participants was 786 (95%CI 451-3045) and in South Asians was 26 (95%CI 19-42).

Conclusion

About a third of patients in the UK who carry an *NUDT15* variant have myelosuppression when treated with a thiopurine. Further work to define the cost-effectiveness of pharmacogenetic testing to prevent myelosuppression and to permit suspension of blood test monitoring in patients without a *TPMT* or *NUDT15* variant is underway.



NUDT15 Genotype	Myelosuppression (WCC <3.5x10⁹/L OR Neutrophil <2.0x10⁹/L)	Severe myelosuppression (WCC <2.5x10⁹/L OR Neutrophil <1.0x10⁹/L)	Myelosuppression related hospitalisation
Wild-Type	13.7% (115/840)	0.7% (6/840)	0.1% (1/840)
Carriage of any NUDT variant	32.6% (78/239) OR 3.05 (2.18-4.26, p<0.001)	10.4% (25/239) OR 9.19 (3.70-26.38, p<0.001)	2.9% (7/239) OR 7.00 (1.00-142.57, p=0.09)
***3**	40% (54/135) OR 4.20 (2.82-6.24, p<0.001)	12.6% (17/135) OR 9.75 (3.64-29.50, p<0.001)	4.4% (6/135) OR 8.25 (1.11-172.60, p=0.07)
***6**	26.8% (12/56) OR 1.72 (0.85-3.25, p=0.11)	8.9% (5/56) OR 10.24 (2.44-43.60, p=0.001)	0% 0/56 -
***9**	25% (10/40) OR 2.10 (0.95-4.27, p=0.05)	5% (2/40) OR 4.10 (0.53-22.14, p=0.12)	2.5% (1/40) -

Cumulative hazard of developing myelosuppression from the start of the thiopurine exposure to date of myelosuppression in days and the odds ratio and frequency of developing myelosuppression