DPYD VARIANTS AND ASSOCIATION WITH FLUOROPYRIMIDINE TOXICITY IN ASIAN PATIENTS

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INTRODUCTION

- Patients who carry inherited variants in *DPYD* have greater risk of severe, including fatal, toxicity from fluoropyrimidine chemotherapy.
- Pre-treatment *DPYD* testing is recommended throughout Europe, but guidelines outside of Europe are lacking.
- The MASCC *DPYD* Working Group is collecting data to write an internationally-relevant testing guideline, starting with data from Asians.

METHODS

- Scopus and PubMed databases were searched to identify articles with data relevant to the association of fluoropyrimidine toxicity risk with *DPYD* variants.
- Variants included those validated in European cohorts (*DPYD*2A*, *DPYD*13*, p.D949V, and *DPYD HapB3*), and variants found predominantly in Asian cohorts.

RESULTS

- Analysis of n=50 articles indicates lower incidence of fluoropyrimidine toxicity and DPD deficiency in East Asian patients vs. Europeans thus enabling higher fluoropyrimidine chemotherapy doses in East Asian countries (~25% greater)[1].
- Major *DPYD* variants that increase toxicity risk in Europeans are less common in Asians, with differences between East and South Asian populations (Table 1).
- Four *DPYD* variants (c.496A>G, *5, *6, and *9B) are more common in Asians than Europeans, but all are considered full DPD activity by CPIC (Table 1)[2].

Table 1. Allele Frequency (AF) of *DPYD* Variants in Asians and Europeans

DPYD Allele	Activity Score	Protein Change	Genetic Change	rsID	East Asian AF	South Asian AF	Euro. AF
DPYD*2A	0.0		1905+1G>A	rs3918290	0.000	0.004	0.006
DPYD*13	0.0	1560S	1679T>G	rs55886062	0.000	0.000	0.001
HapB3	0.5		1236G>A	rs56038477	0.000	**0.017**	0.012
	0.5	D949V	2846A>T	rs7376798	0.000	0.000	0.000
	0.5	Y186C	577A>G	rs115232898	0.000	0.000	0.000
	1.0	M166V	496A>G	rs2297595	**0.015**	**0.091**	0.010
DPYD*5	1.0	1543V	1627G>A	rs2297595	**0.253**	0.094	0.195
DPYD*6	1.0	V732I	2194G>A	rs1801160	0.019	**0.098**	0.046
DPYD*9B	1.0	C29R	85T>C	rs1801265	0.072	**0.255**	0.224

Bold indicates higher allele frequency in Asian vs. European populations. Activity Score is based on the CPIC *DPYD* Functionality Table. Allele frequencies are from GnomAD.

CONCLUSIONS

- Pre-treatment *DPYD* testing of variants validated in European patients would have a smaller benefit for South Asians but are completely absent in East Asians.
- Ongoing investigation will assess the potential benefit of *DPYD* testing that includes variants carried by Asian patients as well as DPD phenotype data, followed by other population including African and Hispanic.
- Additional information about this ongoing MASCC Guideline project will be presented by Co-Chair Dr. Fabienne Thomas during the MASCC/ISOO Guidelines Session Sat., June 29, 11:30-13:00, Théâtre Louis Pasteur, Floor 2.

REFERENCES

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