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Response to “A case of 5-FU related severe toxicity associated to the p.Y186C *DPYD* variant”

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We thank Zaanen *et al.* for their letter, “A case of 5-FU related severe toxicity associated to the p.Y186C *DPYD* variant.”¹ Our lab recently reported similar findings in a 60 year old African American female who carried p.Y186C; however, severe pancytopenia in the patient prevented us from assessing DPD enzyme function.² In their study Zaanen *et al.* addressed this limitation and showed reduced uracil catabolism in a p.Y186C carrier who had experienced 5-FU related toxicity.¹ The partial enzyme deficiency they reported was similar to what we previously demonstrated in healthy individuals heterozygous for p.Y186C.³

Using an *in vitro* system of recombinant expression in HEK293T/c17 cells previously developed in our lab,⁴ we report the impact of the p.Y186C amino acid substitution on the catabolic activity of DPD (Figure 1). DPD protein harboring p.Y186C was reduced in activity by 29% relative to the “wildtype” protein ($P=0.0064$). The amelioration of toxic symptoms following a 20% reduction in 5-FU dose, as reported by Zaanen *et al.*,¹ is consistent with this observed moderate decrease in enzyme function. Collectively, these findings suggest that moderately hypomorphic *DPYD* variants – and potentially mildly hypomorphic variants – may be significant contributors to severe 5-FU toxicity, even when present in the heterozygous state.

Zaanen *et al.* report that their patient was also heterozygous for p.C29R and p.I543V, two common variants which have been regarded as being without functional consequence. Based on our previous reports, we agree with the authors’ assertion regarding I543V; however our data have suggested that p.C29R may, by itself, actually increase DPD enzyme function.^{3, 4} Consistent with previous evidence for linkage between the potentially hyperactive p.C29R variant and p.Y186C,³ both variants were detected in the patients described by Zaanen *et al.*¹ and by us.² The enzyme activity of DPD harboring both variants was indistinguishable from the single p.Y186C substitution (Figure 1) when tested *in vitro*, suggesting that deleterious variants may mask the increase in activity noted for p.C29R.⁴

In summary, the clinical data presented by Zaanen *et al.* agrees with our previous report that established p.Y186C as a deleterious *DPYD* variant,³ and data presented in Figure 1

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provides further functional support of this conclusion. These findings suggest the potential value of testing for p.Y186C, in addition to *DPYD**2A, p.I560S, and p.D949V, for making genetics-based fluoropyrimidine dosing recommendations.⁵

References

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Figure 1.

Enzyme activity was quantitated for wildtype DPD (WT), DPD harboring Y186C (Y186C), DPD containing both C29R and Y186C (C29R/Y186C), and a negative control mimic of *DPYD**2A (*2A). Experiments were performed as three independent replicates, each presented as an “x.” Horizontal bars represent the mean of $\pm$ SD of replicate experiments. *P* values were calculated using two-tailed Student *t* tests. The mean and SD of enzyme activity for C29R, as previously reported,⁴ are presented as the area between the dotted lines labeled “C29R.” Equivalent expression of DPD and variants was confirmed by western blotting (data not shown).