A novel mutation in the DRY motif of the P2Y12 receptor results in chronic bleeding in a patient

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As part of the Genotyping and Phenotyping of Platelets consortium we have identified a number of novel mutations in G protein-coupled receptor (GPCR) genes that contribute to bleeding tendency in patients, including mutations in the P2Y12R. Recently we have identified a patient, with a chronic bleeding disorder expressing a novel missense mutation (R122C) in their P2Y12R. Importantly this mutation is found within the DRY motif of this receptor which in other GPCRs plays a critical role in regulating conformational states. We therefore examined the consequences of this mutation upon P2Y12R function in both the patient’s platelets and cell lines.

In studies using platelets from the R122C patient ADP-stimulated aggregation was significantly reduced as a result of a significant impairment of P2Y12R activity. Cell line studies indicated that versus wild type receptor the R122C variant expressed poorly at the cell surface and had significantly compromised ADP responses. The export of the R122C variant to the cell surface appeared normal but once expressed at the cell surface this mutant displayed a high degree of agonist-independent constitutive internalization where after, unlike the wild type P2Y12R, it then trafficked to lysosomes.

These studies demonstrate the critical importance of the DRY motif of the P2Y12R in maintaining the receptor in a basal non-activated state and the pathophysiological consequences that can occur if the integrity of this motif is compromised.