How do mutations in the cytoplasmic PAS domain of hERG affect channel structure?

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The human *ether a go-go related gene* (hERG) encodes for a K^+ channel predominately expressed in the heart. Mutations in this gene cause prolongation of the QT interval on the surface electrocardiogram and are associated with a marked increased risk of ventricular arrhythmias and sudden cardiac death. Over 300 mutations in hERG have been identified however only a small number of these have been characterized at the molecular level. Many mutant hERG proteins exhibit intracellular trafficking defect, in that they fail to exit from the ER and do not reach the cell surface.

The N-terminus of hERG contains a (PAS) domain, which is a hot spot for mutations. To investigate the molecular basis of the defect caused by these mutants, we have studied the biophysical properties of the isolated PAS domain for WT and 11 mutant constructs. The PAS domain constructs were evaluated for thermal stability (Table) and ability to form quaternary interactions with other domains in the channel. All but two mutants (R56Q and I42N) reduced the thermal stability of the PAS domain. 10/11 of the full-length PAS domain mutants of hERG expressed in HEK293 cells exhibited a trafficking defect. However, none of these mutants resulted in a dominant negative suppression when co-expressed with WT hERG channels.

Mutant/WT	Melt temp (°C)	Trafficking defective at 37°C	Rescued at 26°C
F29L	48.12	Yes	Yes
I42N	57.77	Yes	Yes
Y43C	40.08	Yes	No
R56Q	56.11	No	
C64Y	52.39	Yes	Yes
T65P	49.25	Yes	Yes
A78P	49.82	Yes	Yes
L86R	41.00	Yes	No
I96T	46.60	Yes	Yes
M124R	45.09	Yes	Yes
WT	57.20		

This suggests that PAS domain mutants will result in only a moderate clinical phenotype. This is consistent with recent clinical data from the International Long QT Syndrome registry showing that patients with mutations in the N-terminus (which includes the PAS domain) have a less severe phenotype than patients with mutations in the pore domain.