

P015 NF- κ B Activation is repressed in TRAPS Patients Possessing the R92Q Mutation of TNF Receptor 1
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Tumour necrosis factor- α is a key molecule in inflammatory disease, mediating its actions through two receptors, *TNFRSF1A* and *TNFRSF1B*. We have previously described 25 *TNFRSF1A* mutations which lead to the pro-inflammatory disorder, TNFR-associated periodic fever syndrome (TRAPS), including the low penetrance variant R92Q.

Here we investigate whether R92Q causes defective *TNFRSF1A* signalling and NF- κ B activation, which might in turn result in TRAPS and other inflammatory diseases. The pattern of subcellular I κ B- α and RelA (p65) NF- κ B subunit localisation from control peripheral blood mononuclear cells and R92Q variants was primarily cytosolic, as expected in normal cells. However, EMSA analysis revealed elevated NF- κ B levels in the nucleus of R92Q cells. Additionally we observed that R92Q results in repressed activation of NF- κ B in response to stimulation with either TNF or LPS.

These findings indicate that the R92Q *TNFRSF1A* variant leads to a defect in NF- κ B signalling. We hypothesise that altered NF- κ B activation may explain some of inflammatory processes which occur in TRAPS and could therefore open new routes for therapeutic disease intervention.