

**P026** Structural and functional characterisation of Toll-like receptor pathway single nucleotide polymorphisms  
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Detection of microbial invasion and activation of downstream immune responses in mammals are mediated by Toll-like receptors (TLRs). Whilst the TLR ectodomains detect microbial molecules, their intracellular TIR homology domains couple the elicited signal to a group of TIR-domain containing adaptor molecules, which integrate and diversify incoming signals. Several single nucleotide polymorphisms (SNPs) have been described in both TLRs and TLR adaptor molecules. The corresponding single amino acid substitutions may profoundly affect receptor and adaptor function, yet the functional relevance of these SNPs remains poorly understood. To characterise these effects further, several SNPs in TLR2 and 4 were analysed functionally and epidemiologically, showing that some single amino acid changes significantly alter TLR functionality. We also generated *in silico* 3-dimensional structural models of Toll-like receptor 2 and 4 domains using homology modelling, followed by energy minimisation and molecular dynamics refinement. These structural studies helped interpret the effect of these residue changes in a structural context, and draw further conclusions about the structure-function relationships in TLR signalling.