The MNS blood group and resistance to malaria

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Malaria is thought to have been an important selective pressure during recent human evolution, and continues to cause a large disease burden today. In order to identify genetic variation that influences susceptibility to malaria, we have been conducting genome wide association studies of severe malaria in sub-Saharan Africa. Recently, we found a novel association signal near the glycophorin gene cluster, which encodes two red blood cell surface proteins (GYPA and GYPB) that serve as receptors for the malaria parasite Plasmodium falciparum, and also determine the diverse MNS blood group system. In this talk, I will describe how I have further characterised genetic variation at this locus, faced with the challenge of high sequence similarity between the paralagous genes. I identify an array of large copy number variants in human populations, some of which are predicted to underlie known blood group phenotypes, and find that the association with severe malaria is explained by a complex structural variant involving the loss of GYPB and gain of two GYPB-A hybrid genes. Finally, I will focus on this rearrangement, discussing its possible functional consequences and evidence for selection.