Positive Selection Drives the Rapid Fixation of Dephosphorylation in IRF9

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Abstract

The arms race between humans and pathogens drives the evolution of the human genome. Here, based on the HPO (Human Phenotype Ontology) annotation, we focused on human genes related to recurrent infections of virus, (RVI), bacterial (RBI) and recurrent fungal infections (RFI) to understand positive selection on pathogen-responsive genes. Interestingly, cross-species positive selection analyses revealed that the proportion of unique genes under positive selection was higher for RVI (78.57%) than for RFI (57.14%) and RBI (58.68%). Based on results of the branch-site test, we further focused on the amino acid site Val129 of IRF9, which has a significant signal of positive selection based on multiple evidence. Interestingly, this novel and derived amino acid (V) has been rapidly fixed before the "out-of-Africa" event ˜500,000 years ago from the ancestral state S, which is conserved among 88.5% of mammalian lineages. Phosphorylation analysis revealed that the conserved ancestral S may serve as the phosphorylation site of IRF9. Further analyses suggested that the rapid dephosphorylation of IRF9 via the change of S to V may have conferred potential molecular adaptations by boosting and extending the immune activity of IRF9. This study provides an interesting mode in which strong positive Darwinian selection drives the rapid fixation of a hominin specific amino acid leading to molecular adaptation for immune response.

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