

Statistical power to detect disease variants can be increased by weighting candidates by their evidence of natural selection. To demonstrate that this theoretical idea works in practice, we performed an association study of 10 putative resistance variants in 471 severe malaria cases and 474 controls from the Luo in Kenya. We replicated associations at HBB (P p .0008) and CD36 () but also showed that the same variants are unusually differentiated in frequency between P p .03 the Luo and Yoruba (who historically have been exposed to malaria) and the Masai and Kikuyu (who have not been exposed). This empirically demonstrates that combining association analysis with evidence of natural selection can increase power to detect risk variants by orders of magnitude—up to for P p .000018 HBB and for P p .00043 CD36.