characterize the host response to SIV infection of *C. atys* and African green monkeys[19,20]. Here, we examined the mechanisms of AIDS resistance of a natural SIV host genome-wide using genome sequencing. We identified candidate genes that show sequence changes that are specific to *C. atys* and two gene products (ICAM-2 and TLR-4), which show structural differences between *C. atys* and *M. mulatta* that may influence cell-surface expression (ICAM-2) and downstream signalling (TLR-4) of these proteins. Our findings may also explain prior results showing that not all natural SIV hosts respond to infection in the same way, suggesting that in each primate species, multiple distinct mechanisms may contribute to the phenotype, rather than mutations in single genes, as has been purported, and eventually refuted, in other studies[21]. Further comparative studies with additional natural SIV host species may identify additional similarities (or differences) in the genes involved in the evolutionary pathways that led to AIDS resistance in different species of African nonhuman primates.

In this study, we used whole-genome sequencing and comparative genomic analysis to identify candidate genes regulating host resistance to AIDS. Future studies in which these candidate genes are manipulated *in vivo* during SIV infection are needed to characterize to what extent these genes may influence the non-pathogenic nature of SIV infection in sooty mangabeys.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Author Contributions D.P. and S.E.B. designed and performed experiments and analysed data. S.E.B. and G.K.T. designed and performed bioinformatics analyses. F.K. and B.H.H. designed experiments. T.H.V., M.P. and A.C. contributed to the study design and data interpretation. R.B.N. performed custom annotation of macaque and mangabey genomes and Sanger sequencing. Z.P.J. collected samples and analysed data. Y.H. contributed to sequencing. A.E. contributed to genome assembly. M.R., D.M.M., and R.A.G. supervised and/or managed the sequencing of the *C. atys* genome. R.A.H. and Y.L. performed genome assembly tasks. R.A.D. performed RNA-seq sample processing and analysis. D.L.S. analysed TLR-4 functional data. K.W. and J.R. supervised the assembly and analysis of the genome. C.-B.S. and S.M.S. analysed and interpreted genetic data of ICAM-2. G.W.C.T. and M.W.H. analysed gene family evolution. N.B.P. collected samples and conducted RNA-seq experiments. L.P. and C.E.M. sequenced and assembled RNA-seq transcripts. D.S. designed and analysed TLR-4 experiments. J.R. conceived the study, designed experiments and analysed genomic data. G.S. conceived, designed and led the study. D.P., S.E.B., J.R. and G.S. wrote the manuscript with input from all authors.

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