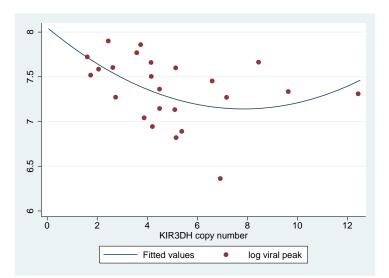
## **Supporting Information**

**Figure S1.** Alignment of predicted amino acid sequences of *KIR3DH* alleles identified in 8 unrelated rhesus monkeys. *KIR3DH* alleles, expressed by CD14<sup>-</sup>CD16<sup>+</sup> NK cells that were isolated from 8 selected rhesus monkeys that differed in their *KIR3DH* copy numbers (range 1–10 copies pdg), were sequenced. The predicted amino acid residues of *MmKIR3DH* genes were aligned. Leader peptide sequences of newly identified KIRs are incomplete due to primer binding. Amino acid residues that are identical to the consensus are indicated by a period. Absent residues are indicated by a dash. The consensus sequence shows the residues that are represented in >50% of the aligned KIRs. A position where no residue is represented in >50% of the different alleles is indicated by a dash. Translation stop sites are indicated by an asterisk.

Lador popting 14.0000 10000000000000000000000000000000		
100123201		MSLMVLSLACVGLFLVQRACP 21
165:1300		
100122327		
106123295		
165:1329:1		
10512398		
JN6123331       HELLIVLGVACVOFTUL         D0       Accessing         D1       Accessing         D1 <t< th=""><th></th><th></th></t<>		
1016.12399 001.12302       HELITYLEJACYGLIV		
001121201 00112202       MELIVAGUACUUELV		
10112223       HELTULGYNALYNFFLANDON         00       Accel 1         01       <		
GU112262     RELIVUS/VACMOPUL/CHI/G/INFIDE/LINDE/SINFIFUSALOTE/COSTPOSTEDSALODE/LI/VT 121       D0 dosin		
0         domain         HIGODOSTI-LABREAUVERCONVIL/CHTR./G/INSTRUT_INDOSING IFFISERIC/SPLADGTER.RESTRUEAGETER.REST		
JM613296       N L O N.F V O N M	GU112262	MSLIVLSVACVGFFLV
JM613296       N L O N.F V O N M		
JM613296       N D N. P V D N. M	D0 domain	
JH613294       N. L. O. O. R.F.       V. O. N. D. N. H.       N. J.		
JH613300		
JN613297		
JN613295		
JN613292		
JN613296		
JN613291      , P, R. Y. D. L, E, M       M         JN613293      , P, R. Y. D. L, E, R       M         J0112303      , P, R. Y. D. L, E, R       M         J0112303      , P, R. Y. D. L, E, R       M         J0112303      , P, R. Y. D. L, E, R       M         J0112302      , N. N. P, R       R, P. N         J0112303      , M. N. P, R       R, R         J0112304      , M       M       P. N         J0112303      , M       M       M         J0112304      , M       M       M       M         J0112303      , M       M       M       M       M         J0112304      , M       M.		
NN613299		
0U12301      DF		
NN6.12233		
CU12262      , N P, R, C. P,, R, R, P. N, R         P1 domain       OVERPELLANCELVESSEVPENTE/FLUXUELMOGSQAWISINGTISATISALACTINE/USYNSPPLIUTT 221         7N613296		
D1         downin         GUMMAPSILAL-POPLVKSGETVTLQCSSDVF0HFLMSEVTE/MLUVGLHGGGGANTSINSTSDLAGTTRCTGSVTHSPVLSAPSDPLDIVIT         221           101         1<		
JN612296		
JN612296		
JNK113294		
JW13300		
NN112257		
JVN112251	JN613300	
NN112291		
JN612291		
JNB12291		
NN613299		
CU112301		
JN613293      K		
GU112262      KFF		
D2 domain JN613296         GLYEKPSLSAQPGPTVQAGENVTLSCSSR/SFDMYHLSREGEARELSLSAVPSVNGTP(JDFLGPATHGGTTRCPGSFRT/PYKMS/PSDPLPVSVT 319           JN613296         K.         C.         I.         A.         T.         D.         N.K.           JN613294         K.         C.         I.         A.         T.         D.         N.K.           JN613291         M.         C.         I.         A.         T.         D.         K.K.           JN613292         D.         OI         K.         SA.O.D.         B.K.           JN613292         D.         OI         K.         SA.O.D.         B.K.           JN613291         D.         C.         R.         G.         A.         B.H.         B.H.           JN613291         M.         C.         R.         G.         A.         H.H.         M.H.		
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NN613296       .K.       .K.		
NN613296       .K.       .K.	D2 domain	GLVERDSLSAOPGDEVUDAGENUTLSCSSE/SEDMUHLSBEGEARELSLSAUDSUNGTEO/DEPLGDATHCGTVRCFGSERT/DVKWS/DSDDLDVSUT 319
NN613294       .K.		
NN613290       K.       C.       I.       A.       T.       D.       K.         NN613295       D.       OI       G.       Q.       K.       SA. Q. D.       S.         NN613295       D.       OI       G.       Q.       K.       SA. Q. D.       S.         NN613292       D.       OI       K.       A.       SA. Q. D.       HI.         NN613293       C.       R.       A.       SA. Q. D.       HI.         NN613293       C.       R.       A.       SA. Q. D.       HI.         NN613293       C.       R.       G.       A.       H.       HI.         N1613293       C.       R.       G.       A.       H.       HI.         N1613293       R.       C.       R.       G.       A.       H.       H.         GU112262       R.       C.       R.       G.       A.       H.       H. <t< th=""><th></th><th></th></t<>		
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NN613292	JN613300	.K
JN613298	JN613300 JN613297	.KA
JN613299	JN613300 JN613297 JN613295	.K
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JN613293	JN613300 JN613297 JN613295 JN613292 JN613298	.K
GU112262	JN613300 JN613297 JN613295 JN613292 JN613298 JN613291	.K.       .C.       .I.       .A.       .T.       .D.       .K.
Stem         GNPSSSWPSPTEPSCKTSITRHLP         345           JN613294	JN613300 JN613297 JN613295 JN613295 JN613292 JN613298 JN613291 JN613299	.K.       .C.       .I.       .A.       .T.       .D.       .K.         .QN       .G.       .Q.       .A.       .A.       .Q.       .D.       .K.         .D.       .QI       .A.       .A.       .SA.       .Q.       .D.       .HI         .D.       .QI       .A.       .SA.       .Q.       .D.       .HI         .C.       .R.       .G.       .A.       .H.          .C.       .R.       .G.       .A.       .H. <td< th=""></td<>
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JN613296	JN613300 JN613297 JN613295 JN613292 JN613298 JN613291 JN613291 JN613291 JN613293	.K.       .C.       .I.       .A.       .T.       .D.       .K.         .QN.       .G.       .Q.       .A.       .A.       .Q.
JN613296	JN613300 JN613297 JN613295 JN613292 JN613298 JN613291 JN613291 JN613291 JN613293	.K.       .C.       .I.       .A.       .T.       .D.       .K.         .QN.       .G.       .Q.       .A.       .A.       .Q.
JN613294	JN613300 JN613297 JN613295 JN613292 JN613298 JN613291 JN613291 JN613299 GU112301 JN613293 GU112262	.K.       .C.       .I       .A.       .T.       .D.       .K.
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JN613295      R.          JN613292      R.          JN613298          JN613299      G.       NSG.         JN613293      R.       S.G.         JN613293      R.       S.G.         GUI12301	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613299 GU112301 JN613293 GU112262 Stem JN613296 JN613294	.K.
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JN613298	JN613300 JN613297 JN613295 JN613292 JN613292 JN613291 JN613291 JN613293 GU112262 Stem JN613296 JN613296 JN613294 JN613297	.K.       .C.       .I.       .A.       .T.       .D.       .K.         .QN.       .G.       .Q.       .A.       .A.       .Q.       .S.         .D.       .QI       .A.       .SA.       .Q.       .S.         .D.       .QI       .A.       .SA.       .Q. <t< th=""></t<>
JN613291	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613299 GU112262 Stem JN613296 JN613294 JN613294 JN613294 JN613295	.K.
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GU112301	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613299 GU112301 JN613293 GU112262 Stem JN613294 JN613294 JN613294 JN613297 JN613297 JN613297 JN613295 JN613292	.K.
JN613293      RS.G         GU112262      RS.G         Transmembrane domain       IVIRYSVATIIFTILLFFLL 365       Cytoplasmic tail       RRWCSDKKRL*       387         JN613296	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 GU112301 JN613299 GU12201 JN613293 GU12262 Stem JN613294 JN613294 JN613294 JN613295 JN613295 JN613295 JN613292 JN613291	.K.
GU112262      RS.GYLQV.         Transmembrane domain       IVIRYSVATIIFTILLFFLL 365       Cytoplasmic tail       RRWCSDKKRL*       387         JN613296	JN613300 JN613297 JN613295 JN613292 JN613291 JN613291 JN613291 JN613291 GU112301 JN613293 GU112262 Stem JN613296 JN613296 JN613294 JN613297 JN613295 JN613292 JN613292 JN613291 JN613299	.K.
Transmembrane domain       IVIRYSVATIIFTILLFFLL 365       Cytoplasmic tail       RRWCSDKKRL*       387         JN613296       *       *       *       *       *       *         JN613294       H.       *       *       *       *       *         JN613294       H.       *	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613293 GU112262 Stem JN613296 JN613294 JN613294 JN613294 JN613295 JN613295 JN613295 JN613295 JN613298 JN613298 JN613298 JN613299 GU112301	.K.
JN613296       *         JN613294      *         JN613300      *         JN613297      *         JN613295      *         JN613295      *         JN613298      *         JN613291      *         JN613299      *         JN613293      *         JN613293      *	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613293 GU112262 Stem JN613296 JN613296 JN613294 JN613295 JN613295 JN613295 JN613295 JN613295 JN613291 JN613291 JN613291 JN613291 JN613291 JN613291 JN613291	.K.
JN613296       *         JN613294      *         JN613300      *         JN613297      *         JN613295      *         JN613295      *         JN613298      *         JN613291      *         JN613299      *         JN613293      *         JN613293      *	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613293 GU112262 Stem JN613296 JN613296 JN613294 JN613295 JN613295 JN613295 JN613295 JN613295 JN613291 JN613291 JN613291 JN613291 JN613291 JN613291 JN613291	.K.
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JN613300	JN613300 JN613297 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613293 GU112262 <b>Stem</b> JN613296 JN613294 JN613294 JN613295 JN613295 JN613295 JN613295 JN613299 JN613299 GU112301 JN613299 GU112301 JN613293 GU112262 <b>Transmembrane domain</b>	.K.
JN613297     H.     *       JN613295     *     *       JN613292     *     *       JN613298     *     *       JN613291     *     *       JN613299     *     *       JN613293     *     *	JN613300 JN613297 JN613295 JN613295 JN613292 JN613298 JN613299 GU112301 JN613293 GU112262 Stem JN613294 JN613294 JN613294 JN613295 JN613295 JN613295 JN613295 JN613295 JN613291 JN613291 JN613293 GU112301 JN613293 GU112262 Transmembrane domain JN613296	.K.
JN613295 ************************************	JN613300 JN613297 JN613295 JN613295 JN613292 JN613298 JN613298 JN613299 GU112301 JN613293 GU112262 <b>Stem</b> JN613294 JN613294 JN613297 JN613297 JN613299 GU12301 JN613299 GU12301 JN613299 GU12301 JN613293 GU112262	.K.
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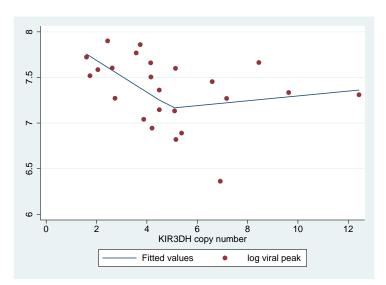
**Figure S2**. High *KIR3DH* copy numbers associate with low peak plasma SIV RNA levels in *Mamu-A\*01<sup>-</sup>*, *TRIM5* 1-5 homozygous rhesus monkeys. The cohort of monkeys was divided into *Mamu-A\*01<sup>-</sup>* and *Mamu-A\*01<sup>+</sup>* monkeys and then further subdivided into two groups: one of monkeys that expressed only the *TRIM5* alleles 1-5 and one of monkeys that expressed at least one of the permissive *TRIM5* alleles 6-11. The association of *KIR3DH* copy number on peak viral load in these subgroups of monkeys was fitted to two models: a parabola and a linear spline with a fixed knot at a *KIR3DH* copy number of 5. The parabola (A) and the linear spline (B) for the *Mamu-A\*01<sup>-</sup>* monkeys that express only the restrictive *TRIM5* alleles 1-5 are shown. A comparison of the coefficients ( $\beta$ ) and significance of *KIR3DH* copy number in monkeys expressing various combinations of *Mamu-A\*01* and *TRIM5* alleles is shown in the tables below.

Α



Groups				Copy nu	mber	Copy number squared	
Model	MHC class I	TRIM5	n	β	P value	β	P value
Parabola	Mamu-A*01 <sup>−</sup>	1-5	24	- 0.23	0.015	0.015	0.074
	Mamu-A*01 <sup>−</sup>	6-11	19	- 0.26	0.036	0.036	0.078
	Mamu-A*01 <sup>+</sup>	1-5	9	0.14	0.83	-0.007	0.92
	Mamu-A*01 <sup>+</sup>	6-11	5	- 2.84	0.081	0.316	0.07

 $\beta$  and *P* values are documented for *KIR3DH* copy number.



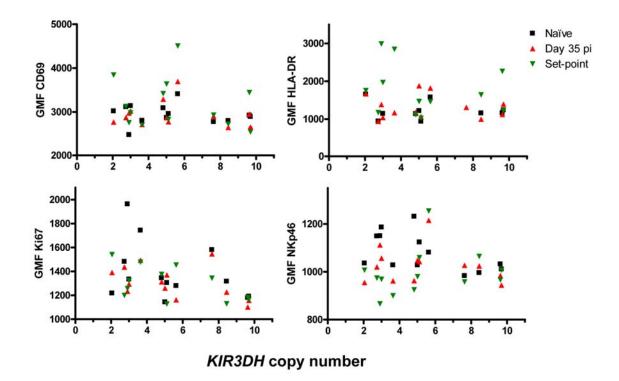
	Groups			Spline 1	slope	Spline 2	2 slope
Model	MHC class I	TRIM5	n	β	Ρ	β	Р
					value		value
Linear spline with	Mamu-A*01 <sup>-</sup>	1-5	24	- 0.17	0.016	0.03	0.53
fixed knot at 5	Mamu-A*01 <sup>-</sup>	6-11	19	- 0.07	0.26	0.25	0.12
	Mamu-A*01 <sup>+</sup>	1-5	9	0.03	0.92	0.13	0.70
	Mamu-A*01 <sup>+</sup>	6-11	5	- 0.29	0.44	0.86	0.14

 $\beta$  and *P* values are documented for *KIR3DH* copy number.

Based on previous reports that an individual NK cells usually expressed 3-5 KIRs that are randomly selected on their surface [58], we hypothesized that *KIR3DH* copy numbers above 5 might not result in a linear increase in surface expression of *KIR3DH* molecules, and so the effects of *KIR3DH* on peak viral load might not decline in a linear fashion for large copy numbers. Therefore we fit two types of models that allow for this non-linearity: a parabola and linear splines with a fixed knot (at a KIR3DH copy number of 5). In both models we observed a statistically significant association between *KIR3DH* copy numbers and peak plasma SIV RNA levels in *Mamu-A\*01<sup>-</sup>* rhesus monkeys expressing only the *TRIM5* alleles 1-5 (parabola model coefficient of copy number of -0.23 with *P* = 0.015 and coefficient of squared copy number of 0.015 with *P* = 0.074; linear spline model: slope of line for copy number  $\leq 5$  of -0.17 with *P* = 0.016 and slope of line for copy number >5 of 0.03 with *P* = 0.53). In the *Mamu-A\*01<sup>-</sup>* monkeys that expressed at least one of the permissive *TRIM5* alleles 6-11, the association between *KIR3DH* copy number

and *in vivo* SIV replication during primary infection was also significant in the parabolic model (linear term coefficient of -0.26 with P = 0.036 and squared term coefficient of 0.036 with P = 0.078). However, this association did not reach statistical significance in the linear spline model. In the other subgroups of monkeys defined on the basis of their *Mamu-A\*01* and *TRIM5* status, no significant relationship between *KIR3DH* copy number and peak viral load was observed; in some cases, coefficient values were in the opposite direction to what was found in *Mamu-A\*01<sup>-</sup>* rhesus monkeys expressing only the *TRIM5* alleles 1-5.

**Figure S3.** Phenotypic analysis of CD16<sup>+</sup> NK cells during primary infection in monkeys differing in their *KIR3DH* copy number. A cohort of rhesus monkeys was sampled pre-infection (naïve) and twice during primary infection: on day 35 post-infection (pi) and between days 70 and 96 pi (set-point). Surface expression of CD69, HLA-DR and NKp46, as well as intracellular levels of Ki67 in the CD16<sup>+</sup> NK cell subset were measured using monoclonal antibody staining and flow cytometric analysis. The geometric means of the fluorescence intensities (GMF) of these stainings are shown.



The level of NK cell activation was assessed by measuring the surface expression of CD69, HLA-DR and NKp46 and by evaluating the intracellular levels of Ki67 in CD16<sup>+</sup> NK cells (Figure S3). All of these molecules were expressed in CD16<sup>+</sup> NK cells of naïve monkeys and their expression levels changed post-SIV-infection. Importantly, *KIR3DH* copy number was not associated with the expression levels of any of the molecules at any of the timepoints we investigated. Similarly, no association between *KIR3DH* copy number and levels of NK cell activation molecules was observed in the other NK cell subsets in rhesus monkeys: DN and CD56<sup>+</sup> NK cells (data not shown).

## Table S1. MLPA probe sequences

Probe sets for CREBBP (XM\_001095225) and EP300 (XM\_001102844) were designed as internal controls. The hybridization sequences do not include the FAM-labeled universal primer binding sequences located at the 5' end of each LHS (5'-GGGTTCCCTAAGGGTTGGA-3') and the 3' end of each RHS (5'-TCTAGATTGGATCTTGCTGGCAC-3'). They contribute a total of 42bp to the product size.

Probe	Left (LHS) and right hybridization sequences (RHS) 5'-3'	Size of MLPA	
		product	
KIR3DH	LHS: GTATCACCAGACACCTGCCTATTGTG	98	
	RHS: ATTAGGTACTCGGTGGCCACCATCATCTTC		
EP300_set1	LHS: GTTGCTGCTGCTGTTGCATCATCTGTTG	102	
	RHS: TCGTCTCAAGATGTCTCGGAATTGTGAAGGCA		
EP300_set2	LHS: CAGCAGGAAGTGAAGGCTGTACTTGTTGG	104	
	RHS: GGAAGTTGTGTTGTTGGTGGTGTAGGTGTCTGC		
CREBBP	LHS: CTCGGTACTGTGGATTCATACTCGCCATGTTGG	110	
	RHS: GGTTGTGTCCTGGGTTCATGATGTTCAAGGCCTGG		