

In the format provided by the authors and unedited.

Neanderthal introgression reintroduced functional ancestral alleles lost in Eurasian populations

David C. Rinker¹ , Corinne N. Simonti² , Evonne McArthur³ , Douglas Shaw^{3,4}, Emily Hodges^{3,4} and John A. Capra^{1,3,5}  

¹Department of Biological Sciences, Vanderbilt University, Nashville, TN, USA. ²Department of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA. ³Vanderbilt Genetics Institute, Vanderbilt University, Nashville, TN, USA. ⁴Department of Biochemistry, Vanderbilt University, Nashville, TN, USA. ⁵Departments of Biomedical Informatics and Computer Science, Vanderbilt University, Nashville, TN, USA. ✉e-mail: tony.capra@vanderbilt.edu

SUPPLEMENTARY DATA:

Supplementary Tables

Supplementary Table 1. Simulations suggest that recombination of segregating human alleles onto introgressed haplotypes rarely results in false ascertainment of RAs.

	$f=0.02$	$f=0.04$
False Discovery Rate (FP / (TP + FP))	0.009	0.0165

Supplementary Table 2. Occurrence of RHAs at putatively ancestral CpG sites

	EAS	EUR	SAS
RHA total count per population	61253	41820	66271
<i>Number of RHAs that are T (or A) and are not part of a TpG (or CpA) dinucleotide</i>	28594	19607	30718
<i>Number of RHAs that are T (or A) and are part of a TpG (or CpA) dinucleotide</i>	4185	2890	4501
<i>Percent of RHAs that cover the T (or A) of a TpG (or CpA) dinucleotide</i>	7%	7%	7%
Expected number of FP RHAs due to CpG convergent mutations under upper bound predicted FPR = 0.03	125.55	86.7	135.03
Expected number of FP RHAs at non-CpG sites under upper bound predicted FPR = 0.0003	17.1204	11.679	18.531
Fraction of FP expected among all RHAs	0.23%	0.23%	0.23%

Supplementary Table 3. Counts of simulated ancient allele trajectories into modern Eurasians.

	$f=0.02$		$f=0.04$	
	AVG	SD	AVG	SD
AAs in ModAfr	4924.47	50.45	4925.58	50.41
AAs in ModEurA	4353.89	47.95	4402.27	53.54
<i>Via AMHs only</i>	2536.52	45.17	2531.33	39.78
<i>Via Neand only</i>	44.97	16.35	88.99	23.94
<i>Via AMH & Neand</i>	1772.40	28.84	1781.95	29.52
NDAs in ModEurA	85.13	29.65	167.10	45.04

Definitions:

AAs in ModAfr: ancestral hominin alleles persisting in modern Africans

AAs in ModEurA: total ancestral hominin alleles persisting in modern Eurasians

Via AMHs only: ancestral hominin alleles passed into Eurasians exclusively via AMHs

Via Neand only: ancestral hominin alleles passed into Eurasians exclusively via Neand.

Via AMH/Neand: ancestral hominin alleles passed into Eurasians via AMHs and Neand.

NDAs in ModEurA: Neanderthal derived alleles present in Eurasians

Supplementary Table 4. Genes associated with RA eQTL in LCLs shared between EUR and YRI.

Gene ID	HUGO Symbol of gene associated with eQTL	eQTL RAs (count)
ENSG00000068654	<i>POLR1A</i>	RAA (2)
ENSG00000069998	<i>HDHD5</i> (previously: <i>CECR5</i>) haloacid dehalogenase like hydrolase domain containing 5	RAA (3), RHA (1)
ENSG00000139410	<i>SDSL</i> - Serine dehydratase-like - Homo sapiens	RAA (2), RHA (2)
ENSG00000152926	<i>ZNF117</i> (previously: <i>HPF9</i>)	RHA (1)
ENSG00000160193	<i>WDR-4</i>	RAA (11), RHA (3)
ENSG00000163755	<i>HPS3</i> , biogenesis of lysosomal organelles complex 2 subunit 1	RAA (1), RHA (2)
ENSG00000169609	Chr 15 Open Reading Frame 40	RAA (1*), RHA (1*)
ENSG00000169612	<i>RAMAC</i> (previously: <i>RAMMET</i>), RNA guanine-7 methyltransferase activating subunit	RAA (6 + 4*), RHA (3)
ENSG00000196648	(retired)	

*variant has significant eQTL associations with 2 gene IDs

Supplementary Table 5. Luciferase reporter insert sequences

EUR-EUR Sequence (3' -5')	CTTAAGTGAAGCCGCTAACAGACTGCACAGGATTCAATTCTAAAGCTCGTGCTCAAACCTCTGTCATCCTGCATTCTTTCTTTTCTGCTCTACCGGAAGAGTCACTTGGAGACATTTTCGGGACTCTGCAGAGATGCTAGAGCCAATACAACAGTTATAAATAAGGGCGATATTTCTCTATATTTTATATCCTGACAGTTTGTAGTCCTTTTATCAACATATTCTAATTTCAAACCTCCACCTTGGTCACGCTAGCTATGTGACACTGGCCAAGTCACTCAGCTGCTTTGAACCTTAGCTGCTCCATATTTAAAAATCATAAAAAATAATACAGCTGTTAAGAGCTTAGACTCTGGCACCAGACTACCTGAGTTCCAGATTCTGCCACTTACCAGCTGTGTGCCCTTGGGTAAGCTGCTTAACCTCTCTGTGCCTCTGCTCCATCTATAAAATGGGAAGACTAATAATAGTACTTTCCTCGGAGTTGTTATAAAGATTATACGAATAACTGTGAAGTACTTAGAATAGTGCTGGCACAAGTAAGCACTATGTGTTTTTTTATGCAAGTAATTTGGCCGGGTGCACTGGCTCATGCCTGTAATCTCACCCTCTGGGAGCCAAGATGTGAGGATCATCTGAGGTCAAAAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAAAAATTAGCCGATGTGGTGGCGGGTGCCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGAAGAATCGCTTGAACCCGGGAGGCGGAGTTGTCAGTGAGCAGAGATTGCGCCACTGCACCTCAACCTGGTGACAGAGATGCCGTCTAAAAAATAAATGCAAGGATTACTGTGAAATCCGTATGTTAATGTAAATATTACTTGTGCGTTTAGAAGACAAAGTGATTCTTTTCCAGAAAAGGCAAAACGGGCCAAGGGAGCGTGAGAGCCGTGATCTGACCAACCTGGTTTAGTGTCTGTGCGCTCTCCAGCTGCAGGACCTGAGAAAACTACTTGAAAACTCGTCAAGCTTCGGCTTCCTGACCACACAAGGTCACACCTTCTCAGAAGTTGCGGGGAGGCTCACACATCACTACCGCGCCGGGCACACAGCAGGCGCCGGCTCCAGCCCTCCTGCTCCCGCCCGCGGAGCCTCCAGCGCTCAGTCGAGGTACAGCGAGCTGAAGTGAACCCAGGCCCCGCACAAACCCACAGGCCTTGGGGCGGAGCACCCGAGGCGCGCTCCCGCGCGCGGCCAGTTTCTCCACATGCAGATGAAAAATCACGACCCAAACGTCTCATGGTGGAATCAGAAGACGCGCAGGGAAAAACAGGGACGCGGAACTGCCGGGAAGCGCAGGGGTGACAAGCAGCTGGCCAGGCGCTCCACGAGCGCTCTCCCGGGAGTAGCGTTTCCGAGGCCGCCAGCGAGTCAGAGGAAGGCAGGGCGCATCCGCCCTCCAGCAAGAAGCGGATGCACTCGGGCGCGACGAGGTCCAGGCAGTTCCAGGAGGCTGGGATACAGCCCGGCCGCCCTCTCTCCCGGGCTCCCGCCCCGCTCCGGCCCTGAGTGGCGAGTGGCTCGGCCAGAACCCGGACGCTCTACCTGAGCGGGGCCACAGCATAGCACCTGCAGGCGGGCGGCCCTGGAGCCCCGAGCCGCGCGCGCCCGCCGAGCAAAGCCACGCGCCGCGCCGAGCGCAGCCACAGCCCCACGCAGCCATCCGGCCGTGCGCGTGCACAGTGCACGGCGTGCAGCCCC
----------------------------	---

NDA-EUR Sequence (3' -5')	CTTAAGTGAAGCCGCTAACAGACTGCACAGGATTCAATTCTAAAGCTCGTGCTCAAACCTCTGTATCCTGCATTCTTCTTTTTCTGCCT CTACCGGAAGAGTCACTTGGAGACATTTCTGGGACTCTGCAGAGATGCTAGAGCCAATAAACAGTTATAAATAAGGGCGATATTTCTCT TATATTTTATATCTGACAGTTTGTAAAGTCCTTTTATCAACATATTTCTAATTTCAAACCTTCCACCTTGGTCACTGTCTAGCTATGTGACA CTGGCCAAGTCACTCAGCTGCTTTGAACCTTAGCTGTCCATATTTAAAAATCATAAAAAATAACAGCTGTTAAGAGCTTAGACTCT GGCACCAGACTACCTGAGTTCAGATTCTGCCACTTACCAGCTGTGTGCCCTTGGGTAAGCTGCTTAACCTCTCTGTGCCCTCTGCTCC ATCTATAAAATGGGAAGACTAATAATAGTACTTTCTCGGAGTTGTTATAAAGATTATACGAATAACTGTGAAGTACTTAGAATAGTG CCTGGCACAAAGTAAGCACTATGTGTTTTTTTCATGCAAGTAATTTGGCCGGGTGCACTGGCTCATGCCTGTAATCTCACCACCTCTGG GAGGCCAAGATGTGAGGATCATCTGAGGTCAAAAGTTTCAGACCAGCCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAA AAATTAGCCGGATGTGGTGGCGGGTGCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGAAGAATCGCTTGAACCCGGGAGGCGGAG GTTGCGGTGAGCAGAGATTGCGCCACTGCACCTCAACCTGGTGACAGAGATGCCGTCTAAAAAATAAATGCAAGGATTACTGTGAA ATCCGTATGTTAATGTAAATATTTACTTGTGCGTTTGAAGACAAAGTGATTCTTTTTTTCAGAAAAGGCAAAACGGCCCAAGGGAGC GTGAGAGCCGTGGATCTGACCAACCTGGTTTAGTGCTCTGTGCCGTCTCCAGCTGCAGGACCTGAGAAAACGTACTTGAAACTCGT CAAGCTTCGGCTTCTGTACCACACAAGGTACACCTTCTCAGAAGTTGCGGGGAGGCTCACACATCACTACCGCGCCGGGCACACAGC AGGCGCCGGCTCCAGCCCTCTGCTCCCGCCCGGGAGCCTCCAGCGCTCAGTCGAGGTACAGCGAGCTGAAGTGAACCCAGGGCCC GCACCAAAACCTGAGGACTTGGGGGCGGAGCACCCGAGCGCGGCTCCCGGCGCGCGGCCAGTTTCTTCCACATGCAGATGAAAA TCACGACCCAAACGTCTCATGGTGAAATCAGAAGACGCGCAGGGAACAGGGACGCGGAACTGCCGGGAAGCGCAGGGGCTGAC AAGCAGCTGGCCAGGCGCTCCACGAGCGCTCTCCCGCGGAGTAGCGTTTCCGAGGCGCGCAGCGAGTCCACTGAGCGGGGC CATCCGCCCTCCAGCAAGAACGCGATGCACTCGGGCGGACGACGGTCCAGGCAGTTCCAGGAGGCGGGGATACAGCCCGGCCGCC CCTCTTCCCCGCGGCTCCCGCCCCGCTCCGGCCCTGAGTGGCGAGTGCGTCCGCCAGAACCCTGGACGCTCCTACCTGAGCGGGGC CCACAGCATAGCACCTGCAGGCGGGGCGGCCCTGGAGCCCCGAGCCGCGCGCGCCGCCAGCAAGCCACGCGCCGCGCCGAG CGCAGCCACACAGCCCCACGCAGCCATCCGGCCGTGCGCGTGCGCACGTGCACGGCGTGCGGCCCC
EUR-RA Sequence (3' -5')	CTTAAGTGAAGCCGCTAACAGACTGCACAGGATTCAATTCTAAAGCTCGTGCTCAAACCTCTGTATCCTGCATTCTTCTTTTTCTGCCT CTACCGGAAGAGTCACTTGGAGACATTTCTGGGACTCTGCAGAGATGCTAGAGCCAATAAACAGTTATAAATAAGGGCGATATTTCTCT TATATTTTATATCTGACAGTTTGTAAAGTCCTTTTATCAACATATTTCTAATTTCAAACCTTCCACCTTGGTCACTGTCTAGCTATGTGACA CTGGCCAAGTCACTCAGCTGCTTTGAACCTTAGCTGTCCATATTTAAAAATCATAAAAAATAACAGCTGTTAAGAGCTTAGACTCT GGCACCAGACTACCTGAGTTCAGATTCTGCCACTTACCAGCTGTGTGCCCTTGGGTAAGCTGCTTAACCTCTCTGTGCCCTCTGCTCC ATCTATAAAATGGGAAGACTAATAATAGTACTTTCTCGGAGTTGTTATAAAGATTATACGAATAACTGTGAAGTACTTAGAATAGTG CCTGGCACAAAGTAAGCACTATGTGTTTTTTTCATGCAAGTAATTTGGCCGGGTGCACTGGCTCATGCCTGTAATCTCACCACCTCTGG GAGGCCAAGATGTGAGGATCATCTGAGGTCAAAAGTTTCAGAGACAGCCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAA AAATTAGCCGGATGTGGTGGCGGGTGCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGAAGAATCGCTTGAACCCGGGAGGCGGAG GTTGCGGTGAGCAGAGATTGCGCCACTGCACCTCAACCTGGTGACAGAGATGCCGTCTAAAAAATAAATGCAAGGATTACTGTGAA ATCCGTATGTTAATGTAAATATTTACTTGTGCGTTTGAAGACAAAGTGATTCTTTTTTTCAGACAAGGCAAAACGGCCCAAGGGAGC GTGAGAGCCGTGATCTGACCAACCTGGTTTAGTGCTCTGTGCCGTCTCCAGCTGCAGGACCTGAGAAAACGTACTTGAAGACTTCGT CAAGCTTCGGCTTCTGTACCACACAAGGTACACCTTCTCAGAAGTTGCGGGGAGGCTCACACATCACTACCGCGCCGGGCACACAGC AGGCGCCGGCTCCAGCCCTCTGCTCCCGCCCGGGAGCCTCCAGCGCTCAGTCGAGGTACAGCGAGCTGAAGTGAACCCAGGGCCC GCACCAAAACCTGAGGACTTGGGGGCGGAGCACCCGAGCGCGGCTCCCGGCGCGCGGCCAGTTTCTTCCACATGCAGATGAAAA TCACGACCCAAACGTCTCATGGTGAAATCAGAAGACGCGCAGGGAACAGGGACGCGGAACTGCCGGGAAGCGCAGGGGCTGAC AAGCAGCTGGCCAGGCGCTCCACGAGCGCTCTCCCGCGGAGTAGCGTTTCCGAGGCGCGCAGCGAGTCCACTGAGCGGGGC CATCCGCCCTCCAGCAAGAACGCGATGCACTCGGGCGGACGACGGTCCAGGCAGTTCCAGGAGGCGGGGATACAGCCCGGCCGCC CCTCTTCCCCGCGGCTCCCGCCCCGCTCCGGCCCTGAGTGGCGAGTGCGTCCGCCAGAACCCTGGACGCTCCTACCTGAGCGGGGC CCACAGCATAGCACCTGCAGGCGGGGCGGCCCTGGAGCCCCGAGCCGCGCGCGCCGCCAGCAAGCCACGCGCCGCGCCGAG CGCAGCCACACAGCCCCACGCAGCCATCCGGCCGTGCGCGTGCGCACGTGCACGGCGTGCGGCCCC
NDA-RA Sequence (3' -5')	CTTAAGTGAAGCCGCTAACAGACTGCACAGGATTCAATTCTAAAGCTCGTGCTCAAACCTCTGTATCCTGCATTCTTCTTTTTCTGCCT CTACCGGAAGAGTCACTTGGAGACATTTCTGGGACTCTGCAGAGATGCTAGAGCCAATAAACAGTTATAAATAAGGGCGATATTTCTCT TATATTTTATATCTGACAGTTTGTAAAGTCCTTTTATCAACATATTTCTAATTTCAAACCTTCCACCTTGGTCACTGTCTAGCTATGTGACA CTGGCCAAGTCACTCAGCTGCTTTGAACCTTAGCTGTCCATATTTAAAAATCATAAAAAATAACAGCTGTTAAGAGCTTAGACTCT GGCACCAGACTACCTGAGTTCAGATTCTGCCACTTACCAGCTGTGTGCCCTTGGGTAAGCTGCTTAACCTCTCTGTGCCCTCTGCTCC ATCTATAAAATGGGAAGACTAATAATAGTACTTTCTCGGAGTTGTTATAAAGATTATACGAATAACTGTGAAGTACTTAGAATAGTG CCTGGCACAAAGTAAGCACTATGTGTTTTTTTCATGCAAGTAATTTGGCCGGGTGCACTGGCTCATGCCTGTAATCTCACCACCTCTGG GAGGCCAAGATGTGAGGATCATCTGAGGTCAAAAGTTTCAGACCAGCCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAA AAATTAGCCGGATGTGGTGGCGGGTGCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGAAGAATCGCTTGAACCCGGGAGGCGGAG GTTGCGGTGAGCAGAGATTGCGCCACTGCACCTCAACCTGGTGACAGAGATGCCGTCTAAAAAATAAATGCAAGGATTACTGTGAA ATCCGTATGTTAATGTAAATATTTACTTGTGCGTTTGAAGACAAAGTGATTCTTTTTTTCAGACAAGGCAAAACGGCCCAAGGGAGC GTGAGAGCCGTGATCTGACCAACCTGGTTTAGTGCTCTGTGCCGTCTCCAGCTGCAGGACCTGAGAAAACGTACTTGAAGACTTCGT CAAGCTTCGGCTTCTGTACCACACAAGGTACACCTTCTCAGAAGTTGCGGGGAGGCTCACACATCACTACCGCGCCGGGCACACAGC AGGCGCCGGCTCCAGCCCTCTGCTCCCGCCCGGGAGCCTCCAGCGCTCAGTCGAGGTACAGCGAGCTGAAGTGAACCCAGGGCCC GCACCAAAACCTGAGGACTTGGGGGCGGAGCACCCGAGCGCGGCTCCCGGCGCGCGGCCAGTTTCTTCCACATGCAGATGAAAA TCACGACCCAAACGTCTCATGGTGAAATCAGAAGACGCGCAGGGAACAGGGACGCGGAACTGCCGGGAAGCGCAGGGGCTGAC AAGCAGCTGGCCAGGCGCTCCACGAGCGCTCTCCCGCGGAGTAGCGTTTCCGAGGCGCGCAGCGAGTCCACTGAGCGGGGC CATCCGCCCTCCAGCAAGAACGCGATGCACTCGGGCGGACGACGGTCCAGGCAGTTCCAGGAGGCGGGGATACAGCCCGGCCGCC CCTCTTCCCCGCGGCTCCCGCCCCGCTCCGGCCCTGAGTGGCGAGTGCGTCCGCCAGAACCCTGGACGCTCCTACCTGAGCGGGGC CCACAGCATAGCACCTGCAGGCGGGGCGGCCCTGGAGCCCCGAGCCGCGCGCGCCGCCAGCAAGCCACGCGCCGCGCCGAG CGCAGCCACACAGCCCCACGCAGCCATCCGGCCGTGCGCGTGCGCACGTGCACGGCGTGCGGCCCC

b1-EUR (3' -5)	CTTAAGTGAAGCCGCTAACAGACTGCACAGGATTCAATTCTAAAGCTCGTGCTCAAACCTCTGTCATCCTGCATTCTTCTTTTTCTGCTCTACCGGAAGAGTCACTTGGAGACATTTCTGGGACTCTGCAGAGATGCTAGAGCCAATACAACAGTTATAAATAAGGGCGATATTTCCCTTATATTTATATCCTGACAGTTTGTAAAGTCCTTTTATCAACATATTCTAATTTCAAACCTCCACCTTGGTCACGTCTAGCTATGTGACACTGGCCAAGTCACTCAGCTGCTTTGAACCTTAGCTGCTCCATATTTAAAAATCATAAAAAATAACAGCTGTTAAGAGCTTAGACTCTGGCACCAGACTACCTGAGTTCCAGATTCTGCCACTTACCAGCTGTGTGCCCTTGGGTAAAGCTGCTTAACCTCTCTGTGCTCTGCTCCATCTATAAAATGGGAAGACTAATAATAGTACTTTCCTCGGAGTTGTTATAAAGATTATACGAATAACTGTGAAGTACTTAGAATAGTGCTGGCACAAAGTAAGCACTATGTGTTTTTTTCATGCAAGTAATTTGG
b1_NDA(3' -5)	CTTAAGTGAAGCCGCTAACAGACTGCACAGGATTCAATTCTAAAGCTCGTGCTCAAACCTCTGTCATCCTGCATTCTTCTTTTTCTGCTCTACCGGAAGAGTCACTTGGAGACATTTCTGGGACTCTGCAGAGATGCTAGAGCCAATAAAACAGTTATAAATAAGGGCGATATTTCCCTTATATTTATATCCTGACAGTTTGTAAAGTCCTTTTATCAACATATTCTAATTTCAAACCTCCACCTTGGTCACGTCTAGCTATGTGACACTGGCCAAGTCACTCAGCTGCTTTGAACCTTAGCTGCTCCATATTTAAAAATCATAAAAAATAACAGCTGTTAAGAGCTTAGACTCTGGCACCAGACTACCTGAGTTCCAGATTCTGCCACTTACCAGCTGTGTGCCCTTGGGTAAAGCTGCTTAACCTCTCTGTGCTCTGCTCCATCTATAAAATGGGAAGACTAATAATAGTACTTTCCTCGGAGTTGTTATAAAGATTATACGAATAACTGTGAAGTACTTAGAATAGTGCTGGCACAAAGTAAGCACTATGTGTTTTTTTCATGCAAGTAATTTGG
b2-EUR(3' -5')	TTTTTTTCATGCAAGTAATTTGGCCGGGTGCACTGGCTCATGCCTGTAATCTCACCCTCTGGGAGGCCAAGATGTGAGGATCATCTGAGGTCAAAGTTTCGAGACCAGCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAAAAATTAGCCGGATGTGGTGGCGGGTGCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGAAGATCGCTTGAACCCGGGAGGCGGAGGTTGCAGTGAGCAGAGATTGCGCCA CTGCACTCCAACCTGGTGACAGAGATGCCGTCTAAAAAAGGATTAAGTGTGAAATCCGTATGTTAATGTAATAATATTA CTTGTGCGTTTAGAAGACAAAGTGATTCTTTTTCCAGAAAAGGCAAAACGGCCCAAGGGAGCGTGAGAGCCGTGGATCTGACCAACC TGGTTTAGTGCTGTGCCGTCTCCAGCTGCAAGGACCTGAGAAAACGTACTTGAAAACCTCGTCAAGCTTCGGCTTCCTGACCACACA AGGTCACACCTTCTCAGAAGTTGCGGGGAGGCTCACACATCTACTACCGCGCCGGGCACACAGCAGGCGCCGGCTCCAGCCCTCTGTCT CCCGCCCCGCGGAGCCTCCAGCGCTCAGTCGAGGTCACAGCGAGCTGAACTGAACCCAGGCCCGCACCAACCCACAGGCACTTGGGG GCGGAGCACCCGAGGCGCGGCTCCCGGCGCGGCGCCAGTTTCTCCACATGCAGATGAAAATCACGACCCAAACGTCTCATGGTG GAAATCAGAAGACGCGCAGGGAAAACAGGGACGCGGAAACTGCCGGGAAGCGCAGGGGCTGACAAGCAGCCTGGCCAGGCCGTCCCA CGAGCGCTCTCCCGCGGGAGTAGCGTTTCCGAGGCCGCGAGCTCAGAGGAAGGCGAGGCGCATCCGCCCTCCAGCAAGACGCGA TGCACTCGGGCGCGACGACGGTCCAGGCAGTTCCAGAGGCTGAGGATACAGCCCGCGCCCTCCTTCCCGCGGCTCCCGCCCC CGCCTCCGGCCCTGAGTGGCGAGTGGCTCGGCCAGAACCAGGAGCTCCTCACCTGAGCGGGGCCACAGCATAGCACCTGCAGGCGGG GCGGCCCTGGAGCCCCGAGCCGCGCGCGCCCGCCAGCAAGCCACGCGCCGCGCCGAGCGCAGCCACACAGCCCCACGCGAGCC ATCCGGCCGTGCGCGTGCACAGTGCACGGCGTGCGGCCCC
b2-RA(3' -5)	TTTTTTTCATGCAAGTAATTTGGCCGGGTGCACTGGCTCATGCCTGTAATCTCACCCTCTGGGAGGCCAAGATGTGAGGATCATCTGAGGTCAAAGTTTCGAGACCAGCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAAAAATTAGCCGGATGTGGTGGCGGGT GCCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGAAGATCGCTTGAACCCGGGAGGCGGAGGTTGCCGTGAGCAGAGATTGCGCCA CTGCACTCCAACCTGGTGACAGAGATGCCGTCTAAAAAAGGATTAAGTGTGAAATCCGTATGTTAATGTAATAATATTA CTTGTGCGTTTAGAAGACAAAGTGATTCTTTTTCCAGACAAGGCAAAACGGCCCAAGGGAGCGTGAGAGCCGTGGATCTGACCAACC TGGTTTAGTGCTGTGCCGTCTCCAGCTGCAAGGACCTGAGAAAACGTACTTGAAAACCTCGTCAAGCTTCGGCTTCCTGACCACACA AGGTCACACCTTCTCAGAAGTTGCGGGGAGGCTCACACATCTACTACCGCGCCGGGCACACAGCAGGCGCCGGCTCCAGCCCTCTGTCT CCCGCCCCGCGGAGCCTCCAGCGCTCAGTCGAGGTCACAGCGAGCTGAACTGAACCCAGGCCCGCACCAACCCACAGGCACTTGGGG GCGGAGCACCCGAGGCGCGGCTCCCGGCGCGCGGCCAGTTTCTCCACATGCAGATGAAAATCACGACCCAAACGTCTCATGGTG GAAATCAGAAGACGCGCAGGGAAAACAGGGACGCGGAAACTGCCGGGAAGCGCAGGGGCTGACAAGCAGCCTGGCCAGGCCGTCCCA CGAGCGCTCTCCCGCGGGAGTAGCGTTTCCGAGGCCGCGAGCTCAGGGGAAGGCGAGGCGCATCCGCCCTCCAGCAAGAACGCGA TGCACTCGGGCGGACGACGGTCCAGGCAGTTCCAGAGGCGGGGATACAGCCCGCGCCCTCCTTCCCGCGGCTCCCGCCCC CGCCTCCGGCCCTGAGTGGCGAGTGGCTCGGCCAGAACCAGGAGCTCCTCACCTGAGCGGGGCCACAGCATAGCACCTGCAGGCGGG GCGGCCCTGGAGCCCCGAGCCGCGCGCGCCCGCCAGCAAGCCACGCGCCGCGCCGAGCGCAGCCACACAGCCCCACGCGAGCC ATCCGGCCGTGCGCGTGCACAGTGCACGGCGTGCGGCCCC

Supplementary Table 6 Luciferase primer sequences

	Primer	Sequence (5'-3')
Primers for Sanger Sequencing	pG4.27_seq_FP1	CAGGTGCCAGAACATTTCTC
	pGL4.27_seq_FP2	CCTCTAGTGTCTAAGCTTGG
	pGL4.27_seq_FP3	CGCGTCTTCTGATTTCCACC
	pGL4.27_seq_R	CTAAACCAGGTTGGTCAGATC
Primers to produced b2-EUR sub-regions	B2.1-EUR-F	GCAGTACTTTTTTTCATGCAAGTAATTTGGCCGG
	B2.1-EUR-R	CTCTGCTCACTGCAACCTCCG
	B2.2-EUR-F	GCGGAGGTTGCAGTGAGCAGAGATTG
	B2.2-EUR-R	GGCCGTTTTGCCTTTTCTGGAAAAAGG
	B2.3-EUR-F	CCTTTTTCCAGAAAAGGCAAAACGGCC
	B2.3-EUR-R	CCTGCCTTCCTCTGACTCGCTG
	B2.4-EUR-F	CAGCGAGTCAGAGGAAGGCAGGG
	B2.4-EUR-R	CTGGTATCCCAGCCTCCTGGGAAC
	B2.5-EUR-F	GTTCCCAGGAGGCTGGGATACCAGC
	B2.5-EUR-R	GAATCTGAGCTAGTGGGGCCGCAC
Primers to create restriction overhangs on b2-EUR sub regions	B2.1-EURwOH	TCGAGCGATCGGAGCTCCTAGCAGTACTTTTTTTCAT GCAAGTAATTTGGCCGGGTGC
	B2.5-EURwOH	GGCTCCGGTCTAGAACTAGAGCTAGTGGGGCCGCAC
Primers to create NheI restriction site on b2-EUR and b2-RA	B2-EUR/RAwOH-F	GCAGTACTTTTTTTCATGCAAGTAATTTGGCCGGGTG CACT
	B2-EUR/RAwOH-R	CTGGCCGGTACCTGAGCTCGGAATCTGAGCTAGTGGG GGC
Primers to create XhoI restriction site on b1-NDA and b1-EUR	B1-EUR/NDawOH-F	GAGGCCAGATCTTGATATCCCTTAAGTGAAGCCGCTA ACAG
	B1-EUR/NDawOH-R	CCAAATTACTTGTCATGAAAAAACACATAGTGCTTAC TTTGTGCCAG
Primers used to amplify b1-NDA and b1-EUR	B1-EUR/NDA-F	CTTAAGTGAAGCCGCTAACAG
	B1-EUR/NDA-R	CCAAATTACTTGTCATGAAAAAACAC

Supplementary Table 7. European introgressed variants with significant MPRA evidence of modulating expression in LCLs.

Chr	Loc (hg19)	Introgressed class	rsID	nearest TSS	distance from TSS	HUGO name
chr2	68490970	NDA	rs12713637	NM_000945	11318	<i>PPP3R1</i>
chr2	121044922	NDA	rs79742700	NM_002881	34508	<i>RALB</i>
chr3	119188213	NDA	rs75416321	NM_152305	428	<i>POGLUT1</i>
chr4	38805942	NDA	rs5743566	NM_003263	470	<i>TLR1</i>
chr4	38807328	NDA	rs45588337	NM_003263	915	<i>TLR1</i>
chr7	64448291	RHA	rs11972247	NM_015852	3123	<i>ZNF117</i>
chr9	101969304	RAA	rs77521170	NM_033087	14942	<i>ALG2</i>
chr12	113364471	NDA	rs4767034	NM_006187	11777	<i>OAS3</i>
chr12	132569521	RHA	rs77330556	NR_003290	693	<i>EP400NL</i>
chr19	41209256	RAA	rs116796128	NM_001142555	11755	<i>ADCK4</i>
chr22	17639918	RAA	rs71312076	NM_033070	251	<i>HDHD5</i>

Supplementary Table 8. MPRA activity of introgressed Eurasian variants.

Number of tested NDAs that are >400bp from any RA, and tested RAs that are >400 bp from any NDA			EAS	EUR	SAS	
		RA	27208	14290	23888	
		NDA	19434	19953	22129	
Number of tested introgressed variants showing significantly different activity levels (SuRE scores) between REF and ALT alleles						
maxSuRE > 1	Total	RA	10129	5298	8960	
		NDA	6093	6420	7050	
		Sig. diff*	RA	484	218	411
			NDA	211	209	237
	RA:NDA enrichment					
		vs all tested	FET p	6.15E-10	0.000112	3.14E-09
	OR†		1.65	1.46	1.62	
	vs all with SuRE > 1	FET p	5.17E-05	0.01514	8.76E-05	
		OR	1.40	1.28	1.38	
	maxSuRE > 2	Total	RA	2437	1310	2209
NDA			1653	1763	1956	
Sig. diff *			RA	353	169	310
			NDA	197	194	213
RA:NDA enrichment						
		vs all tested	FET p	0.005326	0.06133	0.0006945
OR			1.28	1.22	1.35	
vs all with SuRE > 2		FET p	0.01949	0.1136	0.002314	
		OR	1.25	1.20	1.34	
maxSuRE > 4		Total	RA	478	279	393
	NDA		425	459	506	
	Sig. diff *		RA	136	78	128
			NDA	75	83	88
	RA:NDA enrichment					
		vs all tested	FET p	0.07997	0.09236	0.03415
	OR		1.30	1.31	1.35	
	vs all with SuRE > 4	FET p	0.000149	0.002348	1.75E-07	
		OR	1.85	1.76	2.29	

*Significant differences in the activity levels of the REF and ALT alleles is determined using a permutation-based FDR of 5% that is determined for each maxSuRE threshold (Methods).
 $OR = ((R/N)/(R'/N'))$ where R is the # of significant RAs, N is the # of significant NDAs, R' is the # of non-significant tested RAs, and N' is the # of non-significant tested NDAs

Supplementary Table 9. MPRA activity among RA subclasses

RA subclass	MPRA status	Population		
		EAS	EUR	SAS
RAA	Tested	8080	3972	6872
	Sig. diff*	229	94	189
RHA	Tested	9726	5366	8822
	Sig. diff	255	124	222
	<i>p</i> -value (FET)	0.4048	0.8898	7.88E-09
	RAA:RHA activity (OR _†)	1.08334	1.0247	0.7158527
RAA _{AFR+}	Tested	7258	3024	5869
	Sig. diff	207	73	162
RAA _{AFR-}	Tested	323	377	414
	Sig. diff	13	10	14
	<i>p</i> -value (FET)	0.232	0.724	0.44
	RAA _{AFR+} : RAA _{AFR-} activity (OR)	0.70011	0.907918	0.81106

*Significant differences in the activity levels of the REF and ALT alleles is determined using a permutation-based FDR of 5% that is determined at a maxSuRE threshold of 1 (Methods).

†OR of activity compares the number of significantly different sites of the first subclass to those of the second subclass.

Supplementary Table 10. RA and NDA content of high frequency introgressed haplotypes

	EAS	EUR	SAS
NDA	882	994	1047
RAA	172	282	283
RHA	136	191	115
Total	1196	1467	1445
RA fraction of high freq. introgressed haplotypes*	0.258	0.322	0.275
RA fraction of POP overall	0.392	0.315	0.347
<i>p</i> -value (FET)	< 2.2e-16	0.5353	7.884e-09
OR	0.540	1.04	0.716
Total high freq. haplotypes in POP	44	45	38
High freq. haplotypes having RA fraction > Overall POP	7 (16%)	17 (38%)	9 (24%)

*Regions bearing evidence for positive selection within the respective Eurasian populations from Gittelman et al. 2016

Supplementary Table 11. RA and NDA content of genomic regions under recent positive selection

	EAS	EUR	SAS
NDA	976	887	1552
RAA	901	756	1220
RHA	76	56	83
Total	1953	1699	2855
RA fraction of introgressed regions corresponding to regions under positive selection in AFR*	0.500	0.478	0.456
RA fraction in POP overall	0.392	0.315	0.347
<i>p</i> -value (FET)	< 2.2e-16	< 2.2e-17	< 2.2e-18

*Regions referred to here are from set "S2" from Peyrégne et al. 2017. These regions represent regions with evidence for ancient selective sweeps in both the African-American and the deCode recombination maps. Results for the less stringently defined set "S1" were similar to those reported here.