Supplementary Methods

Targeting of nucleotide kinases using siRNA

Nucleotide kinases were knocked down using siGENOME siRNA (Dharmacon, GE Healthcare Life Sciences, Lafayette, CO). PBMC and tissues transfected with non-targeting siRNA were used as controls. For transfection of PBMC, a Neon™ Transfection System (Life Technologies, Fredrick, MD) was used. Electroporation conditions were as follows: pulse voltage 2100 V, pulse width 15 ms, 1 pulse, 1 x 10^6 cells, and 500 nM siRNA. For tissue electroporation, a total of 5 mg of tissue was used for a single electroporation. The tissues were electroporated in 0.4 cm cuvettes (Bio-Rad, Hercules, CA) using a Gene Pulser Xcell™ electroporater (Bio-Rad). A square waveform (500 V and 10 ms) and 500 nM of siRNA was used.

Immunoblotting of nucleotide kinases

Following electroporation, tissues were cultured for 24 h and PBMC for 48 h in DMEM supplemented with 10% FBS prior to homogenization. For immunoblots, 10 µg of homogenized cells and tissues were resolved by SDS-PAGE gel electrophoresis. Proteins were transferred onto a nitrocellulose membrane and blotted with AK2, CKM, PKM, PKLR, and GUK1 antibodies (Thermo Fisher Scientific, Waltham, MA). Anti-β-actin was used for normalization (Cell Signaling, Danvers, MA).

Detection of TFV, TFV-MP, and TFV-DP using ultra-high performance liquid chromatography-tandem mass spectrometry

TFV (10 µM; NIH AIDS Reagent Program) was added to the culture medium 24 h (for vaginal and colorectal tissues) or 48 h (for PBMC) after electroporation with siRNA. Following 12 h of incubation with TFV, the tissues and cells were harvested and homogenized in 70% methanol. Samples were centrifuged for 10 min at 1,500 x g at 4ºC and the supernatant was dried under vacuum. An ultra-high performance liquid chromatography-tandem mass spectrometry (uHPLC-MS/MS) assay was developed for the quantification of TFV, TFV-MP, and TFV-DP using a Dionex Ultimate 3000 uHPLC system coupled to a TSQ Vantage Triple Stage Quadrupole mass spectrometer (Thermo Fisher Scientific). Analytes were separated using a Hypersil GOLD-C18 column (3 µm, 100 mm x 1 mm, Thermo Fisher Scientific) at a flow rate of 0.05 mL/min. Solvent A was 2 mM ammonium phosphate (Thermo Fisher Scientific) with 3 mM hexylamine (Thermo Fisher Scientific) in water, pH 9.2, and solvent B was acetonitrile (Thermo Fisher Scientific). The gradient used is as follows: 9% B from 0 to 0.5 min, 9% B to 60% B from 0.5 to 15.5 min, 60% B to 9% B from 15.5 to 15.6 min, and held at 9% B until 29.6 min. In selected reaction monitoring mode, fragment ions were detected by positive ionization using the following transitions (Q1 → Q3): TFV (*m/z* 288 → 176), TFV-MP (*m/z* 368 → 270), and TFV-DP (*m/z* 448 → 270). Dried cell and tissue extracts were reconstituted in 100 µL mobile phase A for uHLPC-MS/MS analysis.

Sample preparation for Next-generation sequencing

Samples were prepared following the TSCA library preparation guide using 50 ng of template DNA per reaction. Agencourt AMPure XP beads (Beckman Coulter, Inc., Brea, CA) were used for PCR clean-up and library normalization was performed according to the TSCA protocol. The final pooled DNA library (6 µL) was diluted in 594 µL HT1 buffer and spiked with 1% PhiX. One technical control was included per sample batch and runs were sequenced using an Illumina MiSeq sequencing platform generating 150 bp paired-end reads.

Next-generation sequencing data analysis

Secondary analysis of the base calls and Phred-like quality score (Qscore) generated by Real Time Analysis software was performed using on-instrument MiSeq Reporter software. Reads were mapped to the GRCh37 (hg19) reference assembly using a banded Smith-Waterman algorithm and variant calling was carried out using the Genome Analysis Toolkit. Variant call format files were annotated using Illumina VariantStudio software. Raw variant calls were filtered applying a coverage threshold > 30X, a minimum base call Qscore of 30, and an alternate variant frequency > 20%. Variants were cross-referenced with the National Center for Biotechnology Information database of Single Nucleotide Polymorphisms. The phenotypic consequence of missense variants was assigned using SIFT (sorts intolerant from tolerant substitutions; J. Craig Venter Institute online tool) and PolyPhen (polymorphism phenotyping; Harvard University online tool) in silico prediction tools where amino acid substitutions were scored.[1, 2] A SIFT score < 0·05 was suggestive of a damaging amino acid substitution and > 0·05 a tolerated substitution, whereas a PolyPhen score > 0·908 was suggestive of a probably damaging, 0·447-0·908 a possibly damaging, or < 0·447 a benign amino acid substitution.

References

1. Ng PC, Henikoff S. Predicting deleterious amino acid substitutions. Genome Res. 2001; **11**(5): 863-74.
2. Ramensky V, Bork P, Sunyaev S. Human non-synonymous SNPs: server and survey. Nucleic Acids Res. 2002; **30**(17): 3894-900.

Supplementary Table 1

Target	Chr	Start Coordinate	Stop Coordinate	Length	Padding Per Exon	Amplicons	Avoid SNPs	SNP Count	Coverage	Score	Added	Labels
AK2_Exon_2123580	1	33480113	33480205	93	10	1	Yes	2	100	96	6/4/2014	
AK2_Exon_2123827	1	33473531	33476444	2914	10	21	Yes	30	100	79	6/4/2014	
AK2_Exon_2124084	1	33490033	33490178	146	10	1	Yes	0	100	96	6/4/2014	
AK2_Exon_2126005	1	33502327	33502522	196	10	2	Yes	0	100	60	6/4/2014	
AK2_Exon_2297408	1	33497135	33497272	138	10	1	Yes	0	100	96	6/4/2014	
AK2 + AK2	1	33476816	33479013	2198	0	13	Yes	8	79	90	6/4/2014	Merged
AK2 + AK2 + AK2	1	33486958	33487314	357	0	3	Yes	6	100	66	6/4/2014	Merged
PKM2 + PKM2	15	72499059	72499628	570	0	5	Yes	4	100	79	6/4/2014	Merged
PKM2 + PKM2	15	72523231	72523694	464	0	4	Yes	10	100	60	6/4/2014	Merged
pklr + pklr	1	155262958	155263391	434	0	4	Yes	2	100	70	6/4/2014	Merged
pklr + pklr	1	155270662	155271235	574	0	5	Yes	0	100	75	6/4/2014	Merged
pklr + pklr	1	155264016	155264553	538	0	3	Yes	0	89	66	6/4/2014	Merged
pklr + pklr + pklr	1	155264897	155265557	661	0	5	Yes	0	100	64	6/4/2014	Merged
PKM2_Exon_2133147	15	72502004	72502210	207	10	2	Yes	0	100	96	6/4/2014	
PKM2_Exon_2133145	15	72491360	72492107	748	10	6	Yes	10	100	69	6/4/2014	
PKM2_Exon_2132671	15	72502678	72502829	152	10	1	Yes	0	100	80	6/4/2014	
PKM2_Exon_2130832	15	72509740	72509851	112	10	1	Yes	2	100	95	6/4/2014	
PKM2_Exon_2130918	15	72511275	72511461	187	10	1	Yes	0	100	96	6/4/2014	
PKM2_Exon_2129898	15	72494785	72494971	187	10	1	Yes	0	100	80	6/4/2014	
PKM2_Exon_2130917	15	72492805	72493006	202	10	2	Yes	6	100	60	6/4/2014	
PKM2_Exon_2132670	15	72500952	72501242	291	10	3	Yes	4	100	85	6/4/2014	
PKM2_Exon_2256281	15	72495353	72495539	187	10	2	Yes	0	100	60	6/4/2014	
PKLR_Exon_2008276	1	155259074	155260479	1406	10	0	Yes	0	0	0	6/4/2014	
PKLR_Exon_2010448	1	155261537	155261738	202	10	1	Yes	0	100	96	6/4/2014	
PKLR_Exon_2008350	1	155269879	155270081	203	10	1	Yes	0	100	60	6/4/2014	
CKM_Exon_2256677	19	45809661	45810196	536	10	4	Yes	8	100	74	6/4/2014	
CKM_Exon_2256845	19	45814997	45815188	192	10	2	Yes	2	100	70	6/4/2014	
CKM_Exon_2258427	19	45811657	45811800	144	10	1	Yes	0	100	80	6/4/2014	
CKM_Exon_2257753	19	45826069	45826243	175	10	1	Yes	0	100	60	6/4/2014	
CKM_Exon_2256678	19	45818713	45818865	153	10	1	Yes	0	100	60	6/4/2014	
CKM_Exon_2256846	19	45822769	45822999	231	10	1	Yes	0	47	96	6/4/2014	
CKM_Exon_2258262	19	45810709	45810918	210	10	2	Yes	0	100	70	6/4/2014	
CKM_Exon_2259371	19	45821073	45821247	175	10	1	Yes	0	100	60	6/4/2014	

Supplementary Table 2

Amplicon	Chr	Start Coordinate	Stop Coordinate	Target	Length	Strand	Avoid SNPs	SNP Count	Score
Amplicon (45486902)	19	45818686	45818958	Exon_2256678	273	REVERSE	Yes	0	60
Amplicon (45486904)	19	45810584	45810821	Exon_2258262	238	REVERSE	Yes	0	80
Amplicon (45486905)	19	45810768	45810992	Exon_2258262	225	FORWARD	Yes	0	60
Amplicon (45486903)	19	45822644	45822903	Exon_2256846	260	FORWARD	Yes	0	96
Amplicon (45486923)	15	72498932	72499156	UserDefined_0	225	REVERSE	Yes	2	60
Amplicon (45486924)	15	72499072	72499297	UserDefined_0	226	FORWARD	Yes	0	80
Amplicon (45486925)	15	72499214	72499439	UserDefined_0	226	REVERSE	Yes	0	80
Amplicon (45486926)	15	72499358	72499587	UserDefined_0	230	FORWARD	Yes	2	80
Amplicon (45486927)	15	72499538	72499763	UserDefined_0	226	REVERSE	Yes	0	96
Amplicon (45486928)	15	72523108	72523334	UserDefined_0	227	REVERSE	Yes	2	60
Amplicon (45486929)	15	72523258	72523503	UserDefined_0	246	FORWARD	Yes	0	60
Amplicon (45486930)	15	72523448	72523721	UserDefined_0	274	REVERSE	Yes	0	60
Amplicon (45486931)	15	72523668	72523897	UserDefined_0	230	FORWARD	Yes	8	60
Amplicon (45486906)	19	45821042	45821281	Exon_2259371	240	REVERSE	Yes	0	60
Amplicon (45486989)	15	72500827	72501053	Exon_2132670	227	REVERSE	Yes	0	96
Amplicon (45486990)	15	72500973	72501242	Exon_2132670	270	FORWARD	Yes	0	80
Amplicon (45486991)	15	72501189	72501415	Exon_2132670	227	REVERSE	Yes	4	80
Amplicon (45486992)	15	72495230	72495454	Exon_2256281	225	FORWARD	Yes	0	60
Amplicon (45486993)	15	72495408	72495634	Exon_2256281	227	REVERSE	Yes	0	60
Amplicon (45486987)	15	72492678	72492910	Exon_2130917	233	REVERSE	Yes	2	60
Amplicon (45486988)	15	72492862	72493088	Exon_2130917	227	FORWARD	Yes	4	60
Amplicon (45486907)	1	33476691	33476916	UserDefined_0	226	FORWARD	Yes	0	96
Amplicon (45486908)	1	33476831	33477057	UserDefined_0	227	REVERSE	Yes	0	80
Amplicon (45486909)	1	33476979	33477207	UserDefined_0	229	FORWARD	Yes	0	96
Amplicon (45486910)	1	33477123	33477348	UserDefined_0	226	REVERSE	Yes	0	96
Amplicon (45486911)	1	33477265	33477490	UserDefined_0	226	FORWARD	Yes	0	60
Amplicon (45486912)	1	33477403	33477627	UserDefined_0	225	REVERSE	Yes	0	98
Amplicon (45486913)	1	33477541	33477766	UserDefined_0	226	FORWARD	Yes	0	95
Amplicon (45486914)	1	33477679	33477907	UserDefined_0	229	REVERSE	Yes	0	98
Amplicon (45486915)	1	33477823	33478048	UserDefined_0	226	FORWARD	Yes	0	96
Amplicon (45486916)	1	33477967	33478213	UserDefined_0	247	REVERSE	Yes	0	98
Amplicon (45486917)	1	33478615	33478839	UserDefined_0	225	REVERSE	Yes	4	98
Amplicon (45486918)	1	33478757	33478996	UserDefined_0	240	FORWARD	Yes	2	80
Amplicon (45486919)	1	33478945	33479171	UserDefined_0	227	REVERSE	Yes	2	80
Amplicon (45486944)	1	155264768	155264993	UserDefined_0	226	REVERSE	Yes	0	60
Amplicon (45486945)	1	155264916	155265143	UserDefined_0	228	FORWARD	Yes	0	60
Amplicon (45486946)	1	155265068	155265293	UserDefined_0	226	REVERSE	Yes	0	60
Amplicon (45486947)	1	155265212	155265439	UserDefined_0	228	FORWARD	Yes	0	60
Amplicon (45486948)	1	155265392	155265617	UserDefined_0	226	REVERSE	Yes	0	80
Amplicon (45486941)	1	155264049	155264277	UserDefined_0	229	REVERSE	Yes	0	60
Amplicon (45486942)	1	155264193	155264428	UserDefined_0	236	FORWARD	Yes	0	60
Amplicon (45486943)	1	155264375	155264599	UserDefined_0	225	REVERSE	Yes	0	80
Amplicon (45486932)	1	155262831	155263057	UserDefined_0	227	REVERSE	Yes	0	80
Amplicon (45486933)	1	155262977	155263206	UserDefined_0	230	FORWARD	Yes	2	60
Amplicon (45486934)	1	155263123	155263349	UserDefined_0	227	REVERSE	Yes	0	60
Amplicon (45486935)	1	155263295	155263520	UserDefined_0	226	FORWARD	Yes	0	80
Amplicon (45486936)	1	155270537	155270771	UserDefined_0	235	FORWARD	Yes	0	60
Amplicon (45486937)	1	155270693	155270918	UserDefined_0	226	REVERSE	Yes	0	80
Amplicon (45486938)	1	155270843	155271067	UserDefined_0	225	FORWARD	Yes	0	80
Amplicon (45486939)	1	155270981	155271206	UserDefined_0	226	REVERSE	Yes	0	60
Amplicon (45486940)	1	155271157	155271417	UserDefined_0	261	FORWARD	Yes	0	96
Amplicon (45486920)	1	33486831	33487061	UserDefined_0	231	REVERSE	Yes	2	60
Amplicon (45486921)	1	33486989	33487214	UserDefined_0	226	FORWARD	Yes	2	60
Amplicon (45486922)	1	33487163	33487388	UserDefined_0	226	REVERSE	Yes	2	80
Amplicon (45486972)	1	33502204	33502431	Exon_2126005	228	REVERSE	Yes	0	60
Amplicon (45486973)	1	33502378	33502603	Exon_2126005	226	FORWARD	Yes	0	60
Amplicon (45486950)	1	33473404	33473668	Exon_2123827	265	REVERSE	Yes	0	98
Amplicon (45486951)	1	33473582	33473808	Exon_2123827	227	FORWARD	Yes	0	60
Amplicon (45486952)	1	33473724	33473948	Exon_2123827	225	REVERSE	Yes	0	80
Amplicon (45486953)	1	33473868	33474092	Exon_2123827	225	FORWARD	Yes	0	96
Amplicon (45486954)	1	33474010	33474238	Exon_2123827	229	REVERSE	Yes	0	80
Amplicon (45486955)	1	33474154	33474378	Exon_2123827	225	FORWARD	Yes	0	96
Amplicon (45486956)	1	33474300	33474524	Exon_2123827	225	REVERSE	Yes	0	80
Amplicon (45486957)	1	33474444	33474668	Exon_2123827	225	FORWARD	Yes	0	96
Amplicon (45486958)	1	33474582	33474809	Exon_2123827	228	REVERSE	Yes	0	60
Amplicon (45486959)	1	33474726	33474953	Exon_2123827	228	FORWARD	Yes	0	80
Amplicon (45486960)	1	33474868	33475092	Exon_2123827	225	REVERSE	Yes	0	98
Amplicon (45486961)	1	33475012	33475237	Exon_2123827	226	FORWARD	Yes	2	98
Amplicon (45486962)	1	33475152	33475382	Exon_2123827	231	REVERSE	Yes	0	60
Amplicon (45486963)	1	33475298	33475524	Exon_2123827	227	FORWARD	Yes	0	80
Amplicon (45486964)	1	33475446	33475671	Exon_2123827	226	REVERSE	Yes	2	95
Amplicon (45486965)	1	33475586	33475811	Exon_2123827	226	FORWARD	Yes	4	60
Amplicon (45486966)	1	33475726	33475950	Exon_2123827	225	REVERSE	Yes	2	80
Amplicon (45486967)	1	33475876	33476100	Exon_2123827	225	FORWARD	Yes	6	80
Amplicon (45486968)	1	33476018	33476243	Exon_2123827	226	REVERSE	Yes	8	60
Amplicon (45486969)	1	33476154	33476402	Exon_2123827	249	FORWARD	Yes	4	60
Amplicon (45486970)	1	33476352	33476577	Exon_2123827	226	REVERSE	Yes	2	80
Amplicon (45486971)	1	33490004	33490274	Exon_2124084	271	REVERSE	Yes	0	96
Amplicon (45486994)	1	155261502	155261768	Exon_2010448	267	REVERSE	Yes	0	96
Amplicon (45486949)	1	33480078	33480338	Exon_2123580	261	REVERSE	Yes	2	96
Amplicon (45486900)	19	45811626	45811869	Exon_2258427	244	REVERSE	Yes	0	80
Amplicon (45486901)	19	45826034	45826287	Exon_2257753	254	REVERSE	Yes	0	60
Amplicon (45486974)	1	33497104	33497342	Exon_2297408	239	REVERSE	Yes	0	96
Amplicon (45486894)	19	45809534	45809758	Exon_2256677	225	REVERSE	Yes	2	80
Amplicon (45486895)	19	45809676	45809900	Exon_2256677	225	FORWARD	Yes	4	60
Amplicon (45486896)	19	45809822	45810070	Exon_2256677	249	REVERSE	Yes	0	96
Amplicon (45486897)	19	45810018	45810243	Exon_2256677	226	FORWARD	Yes	2	60
Amplicon (45486898)	19	45814870	45815100	Exon_2256845	231	REVERSE	Yes	0	80
Amplicon (45486899)	19	45815048	45815274	Exon_2256845	227	FORWARD	Yes	2	60
Amplicon (45486995)	1	155269852	155270123	Exon_2008350	272	REVERSE	Yes	0	60
Amplicon (45486975)	15	72501875	72502100	Exon_2133147	226	REVERSE	Yes	0	96
Amplicon (45486976)	15	72502047	72502273	Exon_2133147	227	FORWARD	Yes	0	96
Amplicon (45486977)	15	72491237	72491461	Exon_2133145	225	REVERSE	Yes	0	60
Amplicon (45486978)	15	72491381	72491605	Exon_2133145	225	FORWARD	Yes	0	96
Amplicon (45486979)	15	72491523	72491751	Exon_2133145	229	REVERSE	Yes	6	60
Amplicon (45486980)	15	72491667	72491896	Exon_2133145	230	FORWARD	Yes	4	60
Amplicon (45486981)	15	72491815	72492045	Exon_2133145	231	REVERSE	Yes	0	80
Amplicon (45486982)	15	72491999	72492224	Exon_2133145	226	FORWARD	Yes	0	60
Amplicon (45486985)	15	72511234	72511496	Exon_2130918	263	REVERSE	Yes	0	96
Amplicon (45486984)	15	72509717	72509967	Exon_2130832	251	REVERSE	Yes	2	95
Amplicon (45486986)	15	72494760	72495030	Exon_2129898	271	REVERSE	Yes	0	80
Amplicon (45486983)	15	72502647	72502877	Exon_2132671	231	REVERSE	Yes	0	80

Supplementary Table 3

Study Site	Ethnicity	Gene	Consequence	Variant (Ref.>Alt.)	Chr	Coordinate	Genotype	Read Depth	Quality	Alt. Variant Frequency	cDNA Position	Coding DNA Sequence Position	Protein Position	Amino Acid (Ref.>Alt.)	Exon	Intron	SIFT Prediction	PolyPhen Prediction
USA	Multiracial	AK2	Splice Region Variant	C>T	1	33502337	Het	84	377.81	28.6	176	93	31	Q	1/6			
USA	African American	AK2	Missense Variant	A>G	1	33490096	Het	114	100	21.93	249	166	56	S>P	2/6		Deleterious (0.02)	Probably Damaging (0.95)
UGA	African	AK2	Deletion	AC>A	1	33490041	Het	100	93	20.43	0	0	0			2/5		
USA	African American	AK2	Stop Gained	T>A	1	33487271	Het	209	100	44.98	336	253	85	K>*	3/6			
SA	African	AK2	Splice Region Variant	C>G	1	33487190	Het	43	292.96	25.6	0	0	0			3/5		
USA	European American	AK2	Missense Variant	T>C	1	33487025	Het	44	411.37	31.8	451	368	123	D>G	4/6		Deleterious (0)	Possibly Damaging (0.452)
USA	African American	AK2	Splice Region Variant	G>A	1	33480194	Het	35	95.01	22.9	510	427	143	L	5/6			
SA	African	AK2	Missense Variant	A>G	1	33480193	Het	146	411.68	22.1	511	428	143	L>P	5/6		Deleterious (0)	Probably Damaging (1)
SA	African	AK2	Missense Variant	G>A	1	33480188	Het	83	618.48	27.7	516	433	145	H>Y	5/6		Deleterious (0)	Probably Damaging (1)
USA	African American	AK2	Missense Variant	A>G	1	33479002	Het	34	472.36	44.1	583	500	167	I>T	6/6		Deleterious (0.03)	Possibly Damaging (0.632)
UGA	African	AK2	Missense Variant	T>A	1	33478963	Het	56	100	32.14	622	539	180	E>V	6/6		Tolerated (0.27)	Benign (0.009)
UGA	African	AK2	Missense Variant	G>T	1	33478842	Het	61	100	26.23	743	660	220	F>L	6/6		Tolerated (0.08)	Benign (0.079)

Supplementary Table 4

Study Site	Ethnicity	Gene	Consequence	Ref. SNP	Variant (Ref.>Alt.)	Chr	Coordinate	Genotype	Read Depth	Quality	Alt. Variant Frequency	cDNA Position	Coding DNA Sequence Position	Protein Position	Amino Acid (Ref.>Alt.)	Exon	SIFT Prediction	PolyPhen Prediction
SA	Multiracial	CKM	Stop Gained		T>A	19	45822839	Het	33	195.69	24.2	308	133	45	K>*	2/8		
USA	European American	CKM	Missense Variant		A>G	19	45821187	Het	111	1172.15	54.1	419	244	82	Y>H	3/8	Deleterious (0.02)	Possibly Damaging (0.474)
USA	European American	CKM	Missense Variant	rs11559024	T>C	19	45821183	Het	246	2698.31	55.7	423	248	83	E>G	3/8	Deleterious (0.01)	Possibly Damaging (0.467)
USA	African American	CKM	Missense Variant		T>C	19	45821171	Het	40	178.01	30	435	260	87	E>G	3/8	Deleterious (0.04)	Possibly Damaging (0.467)
SA	African	CKM	Missense Variant		C>T	19	45821144	Het	75	298.11	24.3	462	287	96	R>H	3/8	Tolerated (0.07)	Probably Damaging (0.976)
UGA	African	CKM	Missense Variant		G>A	19	45821142	Het	87	100	33.33	464	289	97	H>Y	3/8	Deleterious (0)	Probably Damaging (0.985)
UGA	African	CKM	Missense Variant		C>T	19	45818815	Het	69	100	36.23	564	389	130	R>H	4/8	Deleterious (0)	Probably Damaging (0.966)
UGA	African	CKM	Deletion		TC>T	19	45818725	Het	87	100	29.89	653	478	160		4/8		
USA	European American	CKM	Missense Variant	rs17357122	G>A	19	45815163	Het	1222	12543.15	52.3	672	497	166	T>M	5/8	Deleterious (0.03)	Possibly Damaging (0.56)
USA	European American	CKM	Missense Variant		C>T	19	45815161	Het	135	453.95	21.5	674	499	167	G>S	5/8	Deleterious (0.01)	Benign (0.307)
SA	African	CKM	Missense Variant		A>G	19	45815155	Het	85	359.74	29.4	680	505	169	F>L	5/8	Tolerated (1)	Benign (0.003)
USA	African American	CKM	Missense Variant		A>G	19	45815143	Het	74	306.33	27	692	517	173	Y>H	5/8	Deleterious (0)	Possibly Damaging (0.725)
USA	Hispanic	CKM	Missense Variant		C>T	19	45815077	Het	45	648.34	44.4	758	583	195	D>N	5/8	Tolerated (0.06)	Benign (0.099)
UGA	African	CKM	Missense Variant		G>C	19	45815056	Het	64	100	51.56	779	604	202	L>V	5/8	Deleterious (0.03)	Possibly Damaging (0.878)
SA	African	CKM	Missense Variant	rs17875625	C>A	19	45811716	Het	149	1742.6	36.2	903	728	243	G/V	6/8	Deleterious (0)	Probably Damaging (0.949)
UGA	African	CKM	Missense Variant		T>A	19	45810892	Het	228	100	29.39	969	794	265	K>M	7/8	Deleterious (0)	Possibly Damaging (0.799)
USA	African American	CKM	Missense Variant		T>C	19	45810880	Het	73	203.8	23.6	981	806	269	H>R	7/8	Tolerated (0.27)	Benign (0.002)
SA	African	CKM	Stop Gained		T>A	19	45810794	Het	67	344.42	20.9	1067	892	298	K>*	7/8		
SA	African	CKM	Missense Variant		A>T	19	45810781	Het	36	275.73	28.6	1080	905	302	L>Q	7/8	Deleterious (0)	Probably Damaging (0.919)
USA	African American	CKM	Missense Variant		A>G	19	45810736	Het	37	100	81.08	1125	950	317	L>P	7/8	Deleterious (0)	Probably Damaging (0.999)
USA	European American	CKM	Missense Variant		T>C	19	45810049	Het	43	747.67	51.2	1280	1105	369	K>E	8/8	Tolerated (0.1)	Benign (0.001)

Supplementary Table 5

Study Site	Ethnicity	Gene	Consequence	Ref. SNP	Variant (Ref.>Alt.)	Chr	Coordinate	Genotype	Read Depth	Quality	Alt. Variant Frequency	cDNA Position	Coding DNA Sequence Position	Protein Position	Amino Acid (Ref.>Alt.)	Exon	Intron
USA	European American	PKM	Stop Gained	rs180716407	G>G	15	72523315	Het	98	2517.56	70.4	413	14	5	S>*	1/12	
USA	African American	PKM	Missense Variant		C>T	15	72511417	Het	69	1786.01	72.5	643	244	82	A>T	3/12	
USA	Asian	PKM	Missense Variant		G>C	15	72511307	Het	41	220.69	22.5	753	354	118	N>K	3/12	
SA	African	PKM	Missense Variant		T>A	15	72511306	Het	51	310.69	23.5	754	355	119	T>S	3/12	
USA	African American	PKM	Splice Region Variant		G>T	15	72509849	Het	53	229.65	28.3	0	0	0			3/11
USA	European American	PKM	Splice Region Variant		G>T	15	72509849	Hom	68	1526.7	100	0	0	0			3/11
USA	European American	PKM	Missense Variant	rs147939689	C>A	15	72509829	Het	92	719.87	42.2	788	389	130	R>L	4/12	
USA	European American	PKM	Missense Variant		A>T	15	72502768	Het	146	690.44	28.8	919	520	174	S>T	5/12	
USA	African American	PKM	Deletion		AT>A	15	72502154	Het	116	795.61	25.9	1045	646	216		6/12	
SA	African	PKM	Missense Variant		A>T	15	72502148	Het	71	387.61	31	1052	653	218	L>Q	6/12	
UGA	African	PKM	Missense Variant		T>C	15	72502097	Het	32	73	21.88	1103	704	235	Y>C	6/12	
SA	African	PKM	Splice Region Variant		C>T	15	72502009	Het	135	1609.82	58.6	0	0	0			6/11
UGA	African	PKM	Missense Variant		C>A	15	72499593	Het	104	100	29.81	1483	1084	362	D>Y	8/12	
USA	Multiracial	PKM	Missense Variant		T>C	15	72499587	Het	37	229.14	24.3	1489	1090	364	I>V	8/12	
UGA	African	PKM	Missense Variant		C>T	15	72499476	Het	98	100	46.94	1600	1201	401	A>T	8/12	
UGA	African	PKM	Missense Variant		T>C	15	72499202	Het	162	100	23.46	1628	1229	410	K>R	9/12	
USA	African American	PKM	Missense Variant		T>G	15	72499188	Het	43	309.72	42.9	1642	1243	415	T>P	9/12	
USA	African American	PKM	Stop Gained	rs151078084	G>A	15	72499077	Het	53	636.2	60.4	1753	1354	452	Q>*	9/12	
SA	African	PKM	Splice Donor Variant		C>A	15	72499068	Het	35	130.68	28.6	0	0	0			9/11
USA	European American	PKM	Splice Acceptor Variant		T>A	15	72495531	Het	118	464.01	25.4	0	0	0			9/11
SA	Asian	PKM	Missense Variant		C>T	15	72495471	Het	192	1360.88	25	1820	1421	474	R>Q	10/12	
UGA	African	PKM	Missense Variant		C>T	15	72495394	Het	37	100	51.35	1897	1498	500	A>T	10/12	
USA	European American	PKM	Missense Variant		T>C	15	72492094	Het	78	909.97	59	2114	1715	572	K>R	12/12	

Supplementary Table 6

Study Site	Ethnicity	Gene	Consequence	Ref. SNP	Variant (Ref.>Alt.)	Chr	Coordinate	Genotype	Read Depth	Quality	Alt. Variant Frequency	cDNA Position	Coding DNA Sequence Position	Protein Position	Amino Acid (Ref.>Alt.)	Exon	Intron	SIFT Prediction	PolyPhen Prediction
USA	African American	PKLR	Stop Gained		C>T	1	155271142	Het	36	520.77	44.4	84	45	15	W>*	1/11			
SA	African	PKLR	Missense Variant		C>T	1	155271098	Het	237	933.85	25.3	128	89	30	G>E	1/11		Deleterious (0.01)	Probably Damaging (0.995)
SA	African	PKLR	Missense Variant		A>T	1	155270005	Het	46	178.21	21.7	206	167	56	F>Y	2/11		Tolerated (0.29)	Benign (0.075)
USA	African American	PKLR	Missense Variant		T>A	1	155269960	Het	79	555.01	25.3	251	212	71	E>V	2/11		Deleterious (0)	Probably Damaging (0.919)
USA	African American	PKLR	Missense Variant		A>T	1	155269934	Het	40	1090.01	77.5	277	238	80	S>T	2/11		Tolerated (0.19)	Benign (0.087)
UGA	African	PKLR	Missense Variant		A>G	1	155269924	Het	46	100	54.35	287	248	83	V>A	2/11		Tolerated (0.97)	Benign (0.001)
USA	African American	PKLR	Splice Donor Variant		A>G	1	155269887	Het	61	730.01	37.7	0	0	0			2/10		
USA	African American	PKLR	Missense Variant		A>T	1	155265533	Het	150	544.01	24	337	298	100	S>T	3/11		Tolerated (0.06)	Benign (0.32)
USA	European American	PKLR	Missense Variant		C>T	1	155265484	Het	49	245.01	30.6	386	347	116	R>Q	3/11		Deleterious (0)	Probably Damaging (0.996)
USA	Hispanic	PKLR	Missense Variant		G>A	1	155264966	Het	73	648.55	30.1	674	635	212	P>L	5/11		Deleterious (0.03)	Benign (0.094)
USA	African American	PKLR	Missense Variant		T>C	1	155264910	Het	31	180.37	32.3	730	691	231	I>V	5/11		Tolerated (0.86)	Benign (0.002)
USA	Multiracial	PKLR	Splice Acceptor Variant		T>A	1	155264545	Het	48	353.18	27.1	0	0	0			5/10		
USA	African American	PKLR	Missense Variant		C>T	1	155264463	Het	51	418.89	47.1	814	775	259	V>M	6/11		Deleterious (0.03)	Possibly Damaging (0.892)
SA	African	PKLR	Missense Variant	rs147689373	C>T	1	155264409	Het	49	772.63	47.9	868	829	277	E>K	6/11		Tolerated (0.36)	Possibly Damaging (0.742)
UGA	African	PKLR	Missense Variant		T>C	1	155264369	Het	124	100	20.16	908	869	290	K>R	6/11		Tolerated (0.24)	Possibly Damaging (0.879)
USA	European American	PKLR	Missense Variant		G>T	1	155264287	Het	88	240.49	20.5	990	951	317	H>Q	6/11		Tolerated (0.98)	Possibly Damaging (0.577)
USA	African American	PKLR	Missense Variant		C>T	1	155264115	Het	117	1141.01	31.6	1066	1027	343	E>K	7/11		Deleterious (0)	Probably Damaging (0.992)
USA	European American	PKLR	Splice Region Variant		G>A	1	155263221	Het	42	544.16	59.5	0	0	0			8/10		
UGA	African	PKLR	Deletion		AT>A	1	155263133	Het	40	100	47.5	1309	1270	424			9/11		
USA	African American	PKLR	Stop Gained		G>A	1	155263098	Het	100	100	60	1345	1306	436	Q>*	9/11			
USA	European American	PKLR	Missense Variant		T>C	1	155263097	Het	61	190.09	23	1346	1307	436	Q>R	9/11		Tolerated (0.27)	Benign (0.423)
SA	African	PKLR	Missense Variant		C>T	1	155263086	Het	38	568.78	78.9	1357	1318	440	E>K	9/11		Deleterious (0.05)	Possibly Damaging (0.858)
SA	African	PKLR	Stop Gained		C>A	1	155263086	Het	63	228.29	24.2	1357	1318	440	E>*	9/11			