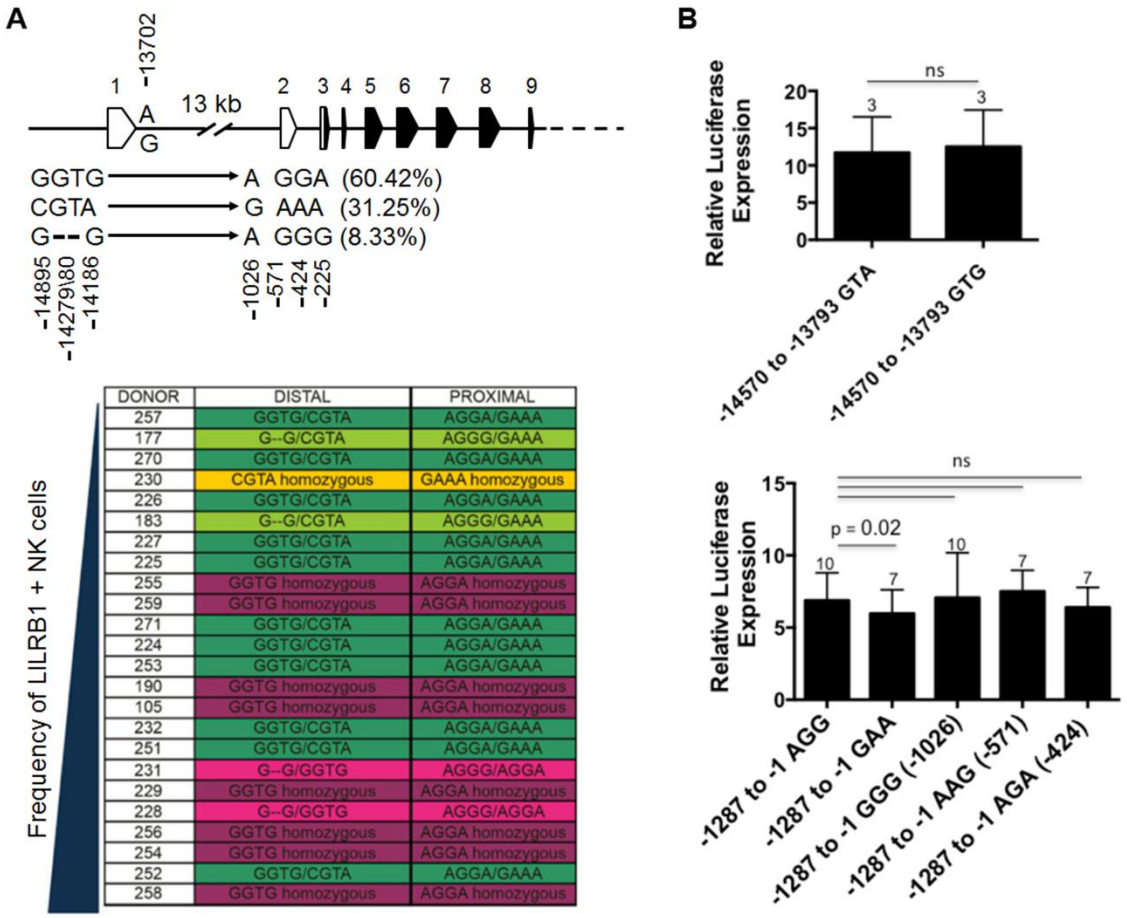
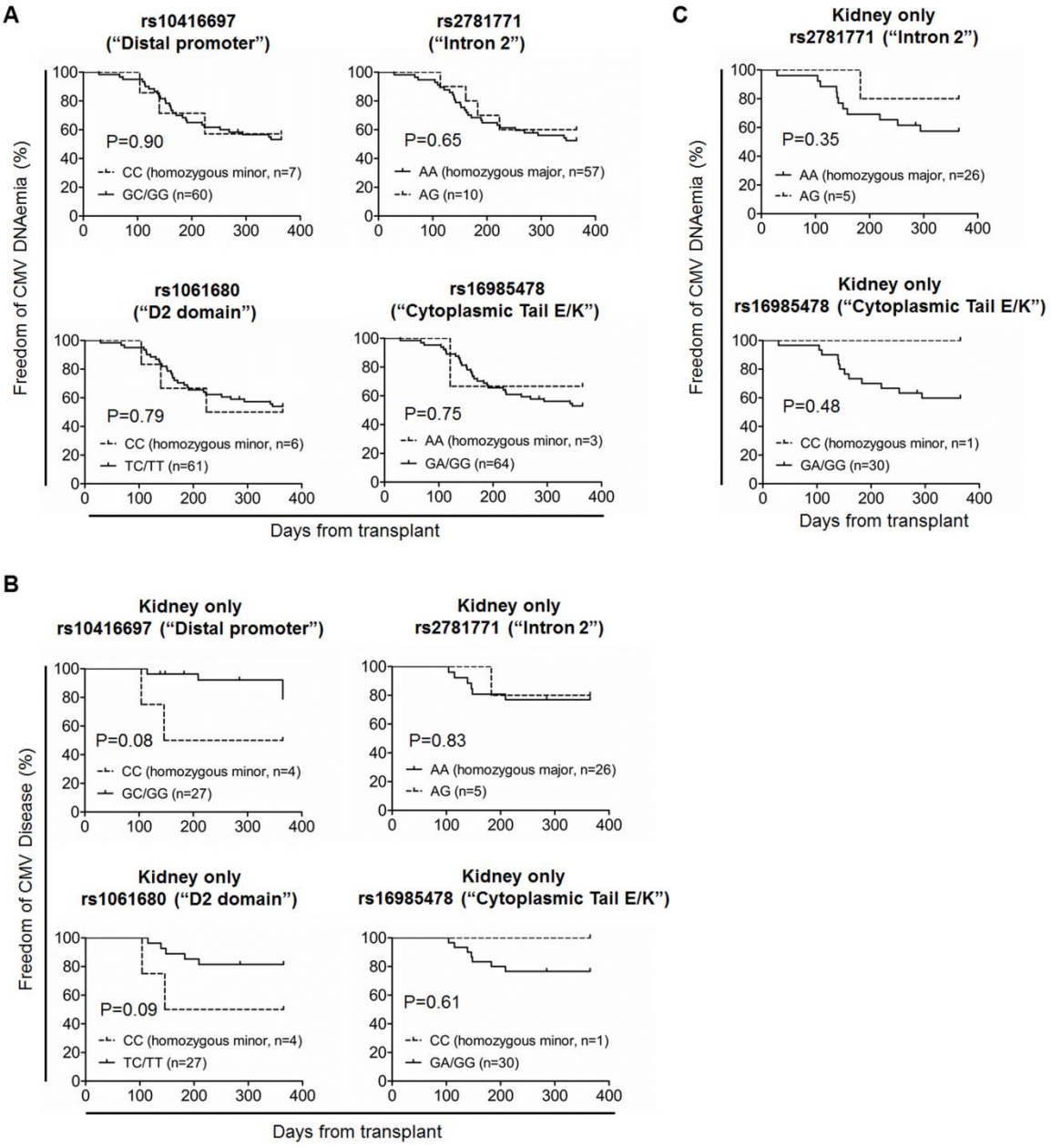
Supplementary Materials

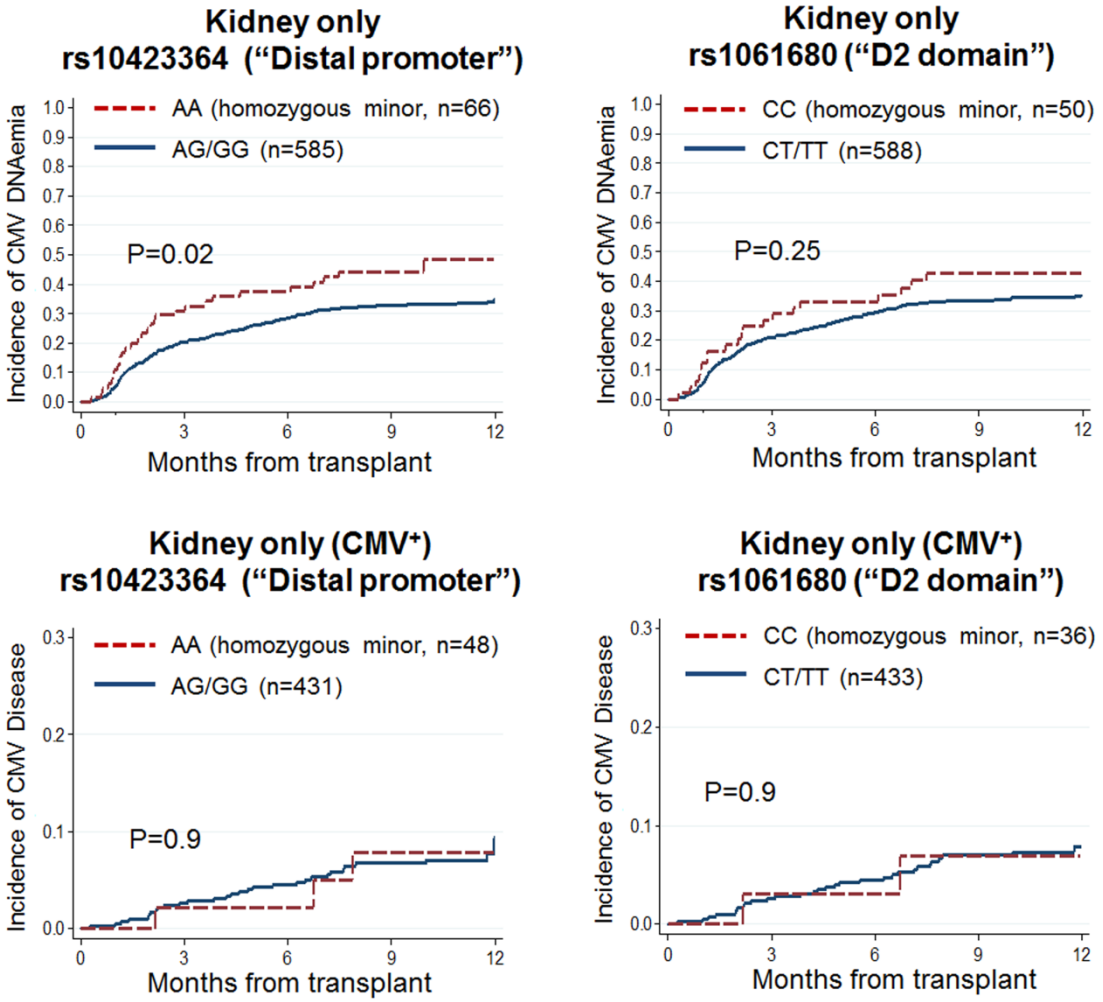


Supplemental Figure 1. Polymorphism of the distal and proximal promoter.

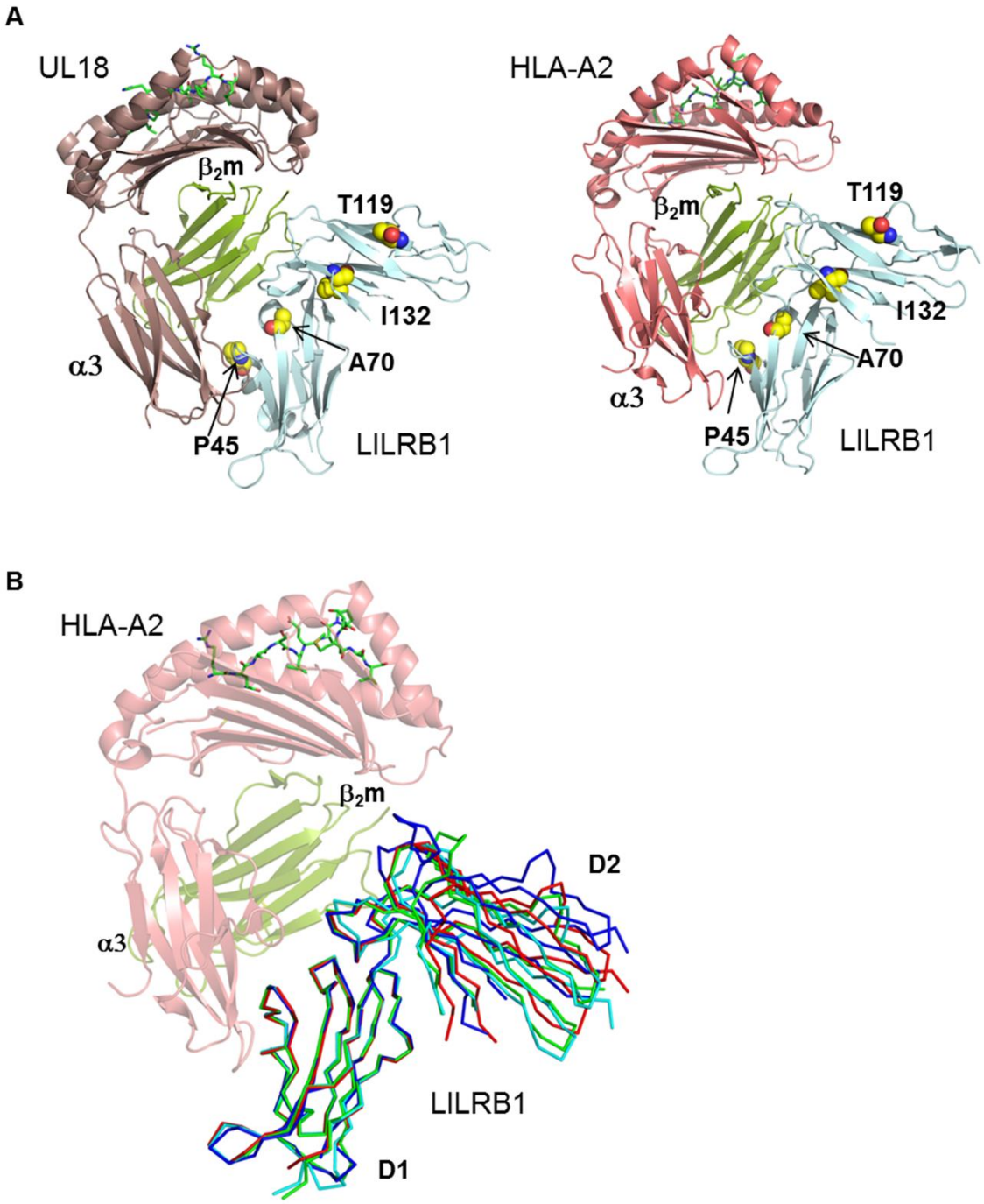
(A) Deduced regulatory region genotypes and LILRB1 expression on NK cells. Three haplotypes and their frequencies within 24 individuals are illustrated for the distal and proximal promoter regions. The numbers underneath indicate the positions relative to the translational start. The lower portion shows distal promoter haplotype for donors listed in ascending order according to LILRB1 expression on NK with each compound genotype coded by color. The LILRB1 expression and proximal promoter genotypes are derived from Davidson et al (1). (B) Transcriptional activity of the two major distal (top) and proximal (bottom) promoter regions in NK92 cells. For each the fragments tested include three of the four SNPs shown in A that are within the active promoter regions. The bottom panel includes three point mutations at the indicated positions. The number of independent experimental tests for each is indicated above the error bar.



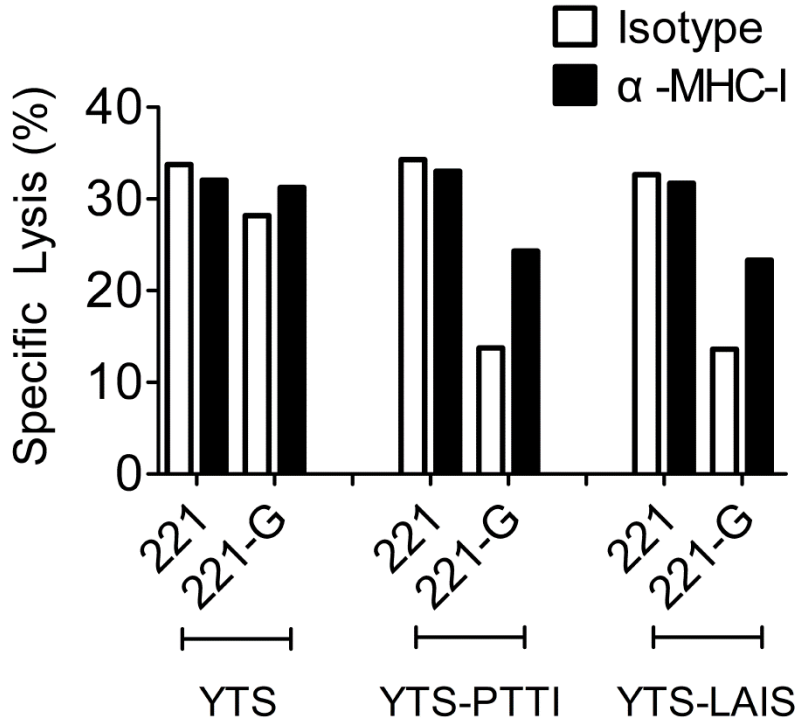
Supplemental Figure 2. LILRB1 polymorphisms and HCMV in Canadian transplant patients.
(A) Incidence of HCMV infection in all post-transplant patients grouped by LILRB1 genotype. (B) Incidence of HCMV disease in post-kidney transplant patients grouped by LILRB1 genotype. (C) Incidence of HCMV infection in post-kidney transplant patients grouped by the genotype of *rs2781771* and *rs16985478*.



Supplemental Figure 3. The association of the HCMV infection or disease (only in the case of D+/R or R+) incidence with different LILRB1 haplotype alleles in kidney transplant patients from STCS.

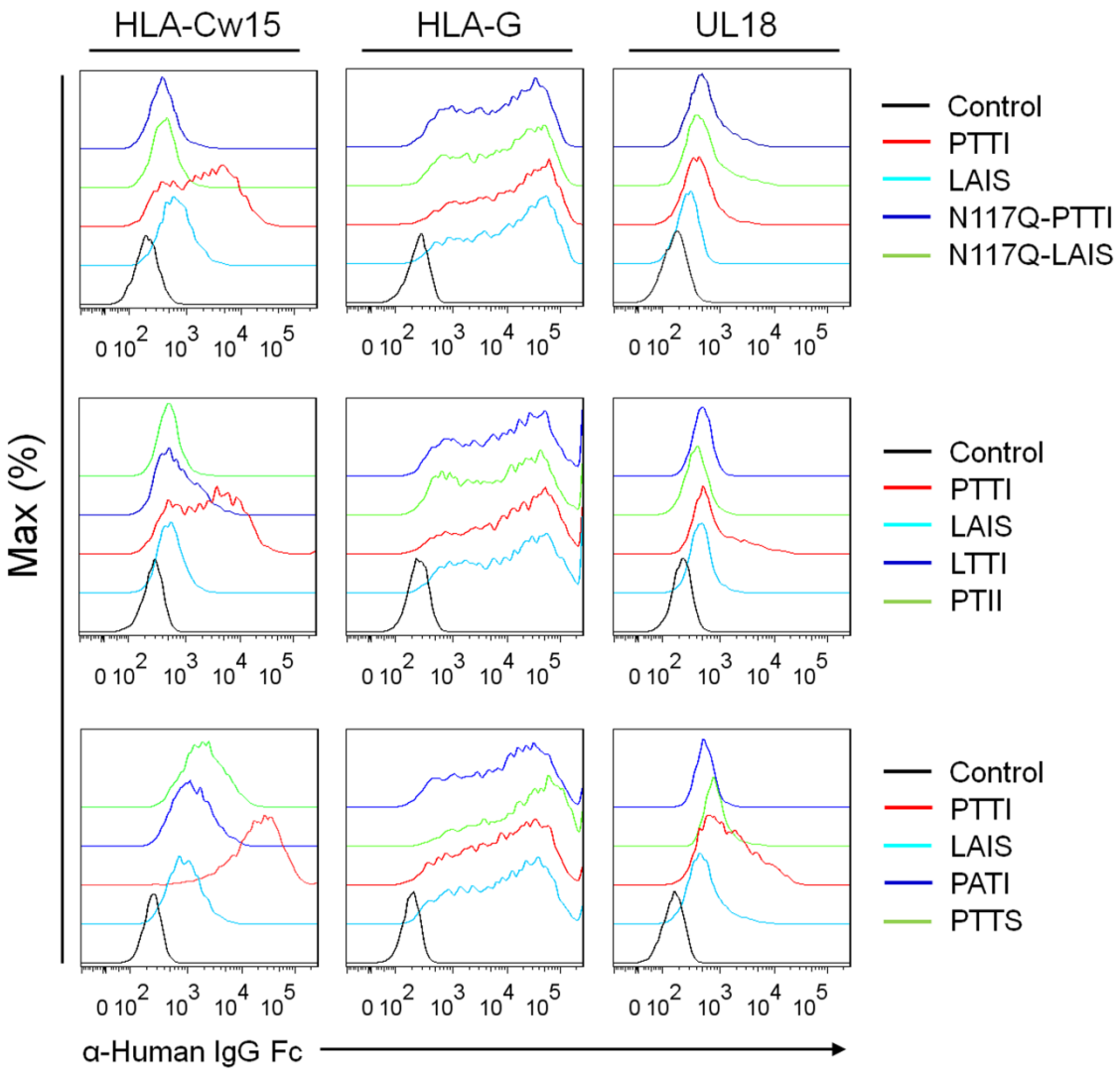


Supplemental Figure 4. Similarities and differences in LILRB1 binding with ligands.
(A) The crystal structures of the LILRB1/UL18 (PDB code 3D2U) and LILRB1/HLA-A2 (PDB code 4NO0) complexes reveal significant overall similarities. The positions of the four LILRB1 variable residues Pro45, Ala70, Thr119 and Ile132 are indicated. (B) Superposition of the D1 domain of the four crystal structures of LILRB1 reveals a significant flexibility in the angle formed between the D1 and D2 domains. The free LILRB1-PATI (PDB code 1G0X), free LILRB1-PTTI (PDB code 1UGN), free LILRB1-LAIS (PDB code 1VDG) and the LILRB1-PATI/HLA-A2 complex (PDB code 4NO0) are colored in red, cyan, green and blue, respectively.

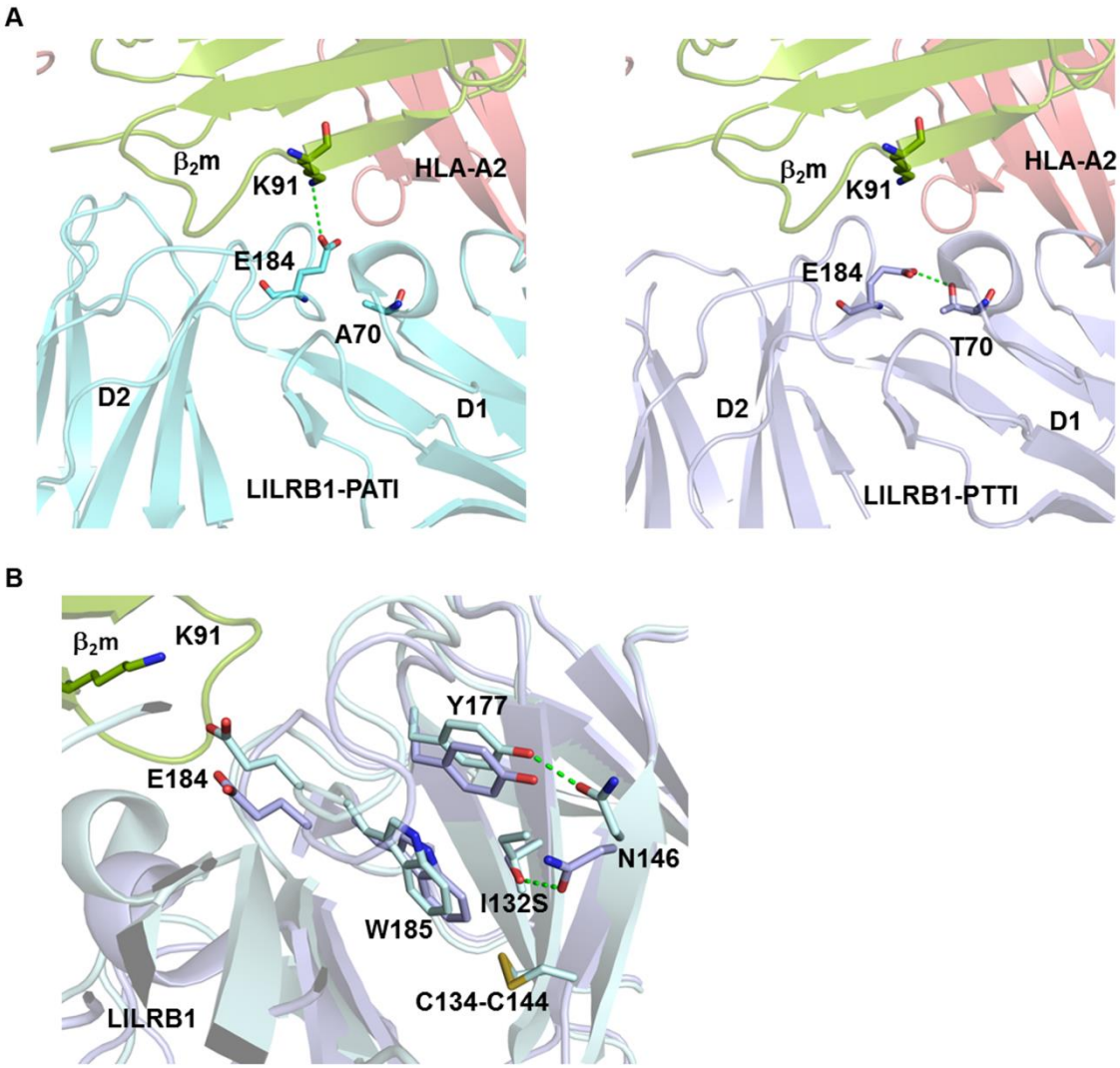


Supplemental Figure 5. Anti-MHC-I blocking of the killing of 721.221 cells expressing HLA-G by YTS cells expressing LILRB1 variants.

Lysis was determined in the presence of 10μg/ml α-MHC-I (W6/32) or isotype control at an E:T of 10:1. Figure shows the representative result of 3 independent tests.



Supplemental Figure 6. FACs data of the LILRB1 mutants binding with HLA-Cw15, HLA-G and UL18.
FACs data shown is the representative data of LILRB1 mutants at one same concentration. The binding with HLA-Cw15, HLA-G was using LILRB1 mutants at 50μg/ml, and the binding with UL18 was using LILRB1 mutants at 100μg/ml.



Supplemental Figure 7. LILRB1 residues 70 and 132 impact indirectly on MHC binding.
(A) The indirect effect of the A70T polymorphism, shown for the HLA-A2/LILRB1 complex, is due to the conformation modification of the side chain of residue E184 and the removal of a salt bridge formed with residue K91 in β2m. (B) The S132I modification abrogates the hydrogen bond formed between the side chain of S132 and the HLA residue N146. As a result of this modification, the side chains of the HLA residues Y177 and W185 are also affected, changing the shape of the section of LILRB1 that connects the D1 and D2 domains and thus the interface that contacts LILRB1. Furthermore, the S132I modification results in a movement of residue E184, which is localized closer to the β2m subunit, resulting in favorable interactions.

	Total N=67	CMV Disease (N=17)	No CMV Disease	p-value
Age, y, mean (SD)	48.1 (14.4)	47.7 (14.6)	49.3 (14.2)	0.829
Sex, M/F, No.	50/17	13/4	37/13	1.000
Type of transplant				
Kidney	31 (46.3)	7 (41.2)	34 (48.0)	0.197
Kidney-pancreas	8 (11.9)	1 (5.9)	7 (14.0)	
Liver	15 (22.4)	5 (29.4)	10 (20.0)	
Lung	7 (10.4)	2 (11.8)	5 (10.0)	
Heart	3 (4.5)	0	3 (6.0)	
Other	3 (4.5)	2 (11.8)	1 (2.0)	
Antiviral Prophylaxis				
Intravenous Ganciclovir	10 (14.9)	3 (17.6)	7 (14.0)	0.709
Valganciclovir	65 (97.0)	17 (100.0)	48 (96.0)	1.000
Oral ganciclovir	2 (3.0)	0	2 (4.0)	1.000
Duration of prophylaxis, d,	98 (96-150)	98 (96-125)	98 (92-153)	0.988
Induction therapy				0.973
None	4 (6.0)	1 (5.9)	3 (6.0)	
Basiliximab	37 (55.2)	9 (52.9)	28 (56.0)	
Thymoglobulin	26 (38.8)	7 (41.2)	19 (38.0)	
Alemtuzumab	0			
Maintenance				
Steroids	57 (85.1)	15 (88.2)	42 (84.0)	1.000
Tacrolimus	58 (86.6)	14 (82.4)	44 (88.0)	0.682
Cyclosporin	6 (9.0)	3 (17.6)	3 (6.0)	0.166
MMF/MPA	58 (86.6)	13 (76.5)	45 (90.0)	0.216
Azathioprine	1 (1.5)	0	1 (2.0)	1.000
mTOR inhibitors	5 (7.5)	3 (17.6)	2 (4.0)	0.099
Other	1 (1.5)	1 (5.9)	0	0.254
rs16985478				0.796
AA	3 (4.5)	1 (5.9)	2 (4.0)	
GA	24 (35.8)	7 (41.2)	17 (34.0)	
GG	40 (59.7)	9 (52.9)	31 (62.0)	
rs10416697				0.532
CC	7 (10.4)	3 (17.6)	4 (8.0)	
GC	26 (38.8)	6 (35.3)	20 (40.0)	
GG	34 (50.7)	8 (47.1)	26 (52.0)	
rs1004443				0.532
AA	34 (50.7)	8 (47.1)	26 (52.0)	
AG	26 (38.8)	6 (35.3)	20 (40.0)	
GG	7 (10.4)	3 (17.6)	4 (8.0)	
rs2781771				0.706
AA	57 (85.1)	14 (82.4)	43 (86.0)	
AG	10 (14.9)	3 (17.6)	7 (14.0)	
GG	0			
rs1061680				0.348
CC	6 (9.0)	3 (17.6)	3 (6.0)	
TC	26 (38.8)	6 (35.3)	20 (40.0)	
TT	35 (52.2)	8 (47.1)	27 (54.0)	

Supplemental Table 1. Canadian Patients Characteristics

Abbreviations: CMV, Cytomegalovirus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin

SNP	All organs		Kidney	
	Any CMV constellation N=1018	Only D+ or/and R+ N=776	Any CMV constellation N=651	Only D+ or/and R+ N=479
CMV infection				
LILRB1 rs1061680[A]	P=0.4	P=0.4	P=0.25	P=0.06[B]
LILRB1 rs10423364[A]	P=0.2	P=0.2	P=0.02	P=0.005
CMV disease				
LILRB1 rs1061680[A]	P=0.8	P=0.9	0.6	0.9
LILRB1 rs10423364[A]	P=1.0	P=0.7	0.8	0.9

Supplemental Table 2. Univariate analysis of the association between LILRB1 SNPs and CMV infection in STCS.

[A] P values assessed by log-rank test, recessive mode

[B] P=0.2 when all the patients with rs1061680 (N=1118)

	CMV infection in kidney CMV D+/R- or R+					
	Univariate analysis			Multivariate analysis		
Variable	HR	(95%CI)	P value [A]	HR	(95%CI)	P value [A]
LILRB genotypes available						
Recipient male sex	0.93	(0.70-1.22)	0.6	-	-	-
Recipient age (per year)	1.02	(1.01-1.03)	**0.0003**	1.02	(1.01-1.03)	**<0.00001**
LILRB1 genotypes						
rs10423364 AA vs. GG/GA	1.74	(1.18-2.58)	**0.005**	1.69	(1.13-2.54)	**0.01**
rs1061680 CC vs. TT/TC	1.56	(0.98-2.47)	0.06	-	-	-
CMV serostatus						
D+/R-	reference					
D-/R+	0.87	(0.59-1.29)	0.5	-	-	-
D+/R+	1.50	(1.07-2.10)	**0.02**	0.59	(0.43-0.81)	**0.001**
Corticosteroids	2.25	(1.11-4.58)	**0.03**	2.17	(1.06-4.46)	**0.03**
Ciclosporine	2.33	(1.73-3.12)	**<0.00001**	2.00	(1.46-2.76)	**0.00002**
Tacrolimus	0.47	(0.35-0.63)	**<0.00001**	-	-	-
Rejection episodes	1.46	(1.05-2.05)	**0.03**	1.94	(1.37-2.75)	**0.0002**
Exposure to antiviral drugs	0.27	(0.19-0.39)	**<0.00001**	0.25	(0.17-0.36)	**<0.00001**
LILRB and KIR genotypes available (N=263)						
Recipient male sex	0.71	(0.45-1.12)	0.14	-	-	-
Recipient age (per year)	1.02	(1.00-1.03)	**0.05**	1.02	(1.00-1.04)	**0.02**
LILRB1 genotypes						
rs10423364 AA vs. GG/GA	2.13	(1.15-3.95)	**0.02**	2.10	(1.11-3.98)	**0.02**
rs1061680 CC vs. TT/TC	1.64	(0.79-3.43)	0.18	-	-	-
KIR haplotype B [B]	1.40	(0.82-2.40)	0.2	-	-	-
KIR gene *KIR2DS4*	0.69	(0.42-1.13)	0.14	0.68	(0.40-1.13)	0.14
CMV serostatus						
D+/R-	reference					
D-/R+	0.60	(0.29-1.20)	0.15	0.44	(0.25-0.76)	**0.004**
D+/R+	1.33	(0.74-2.38)				
Corticosteroids	2.76	(1.00-7.58)	**0.05**	3.16	(1.12-8.87)	**0.03**
Ciclosporine	3.18	(1.94-5.21)	**<0.00001**	2.48	(1.46-4.19)	**0.001**
Tacrolimus	0.37	(0.22-0.60)	**0.00006**	-	-	-
Rejection episodes	1.25	(0.71-2.22)	0.4	-	-	-
Exposure to antiviral drugs	0.33	(0.18-0.61)	**0.0004**	0.36	(0.19-0.68)	**0.002**

Supplemental Table 3. Multivariate analysis in kidney HCMV D+/R- or R+ transplant recipients in STCS.

[A] P value assessed by multivariate Cox regression model.

[B] KIR haplotype B was defined by the presence of one or more of the following genes: KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5 and KIR3DS1 (2, 3).

Reference

1. **Davidson, C.L., Li, N.L., and Burshtyn, D.N. 2010. LILRB1 polymorphism and surface phenotypes of natural killer cells. *Human immunology* 71:942-949.**
2. **Gonzalez, A., Schmitter, K., Hirsch, H., Garzoni, C., Van Delden, C., Boggian, K., Mueller, N., Berger, C., Villard, J., and Manuel, O. 2014. KIR-associated protection from CMV replication requires pre-existing immunity: a prospective study in solid organ transplant recipients. *Genes and immunity* 15:495-499.**
3. **Robinson, J., Waller, M.J., Stoehr, P., and Marsh, S.G. 2005. IPD—the immuno polymorphism database. *Nucleic acids research* 33:D523-D526.**

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