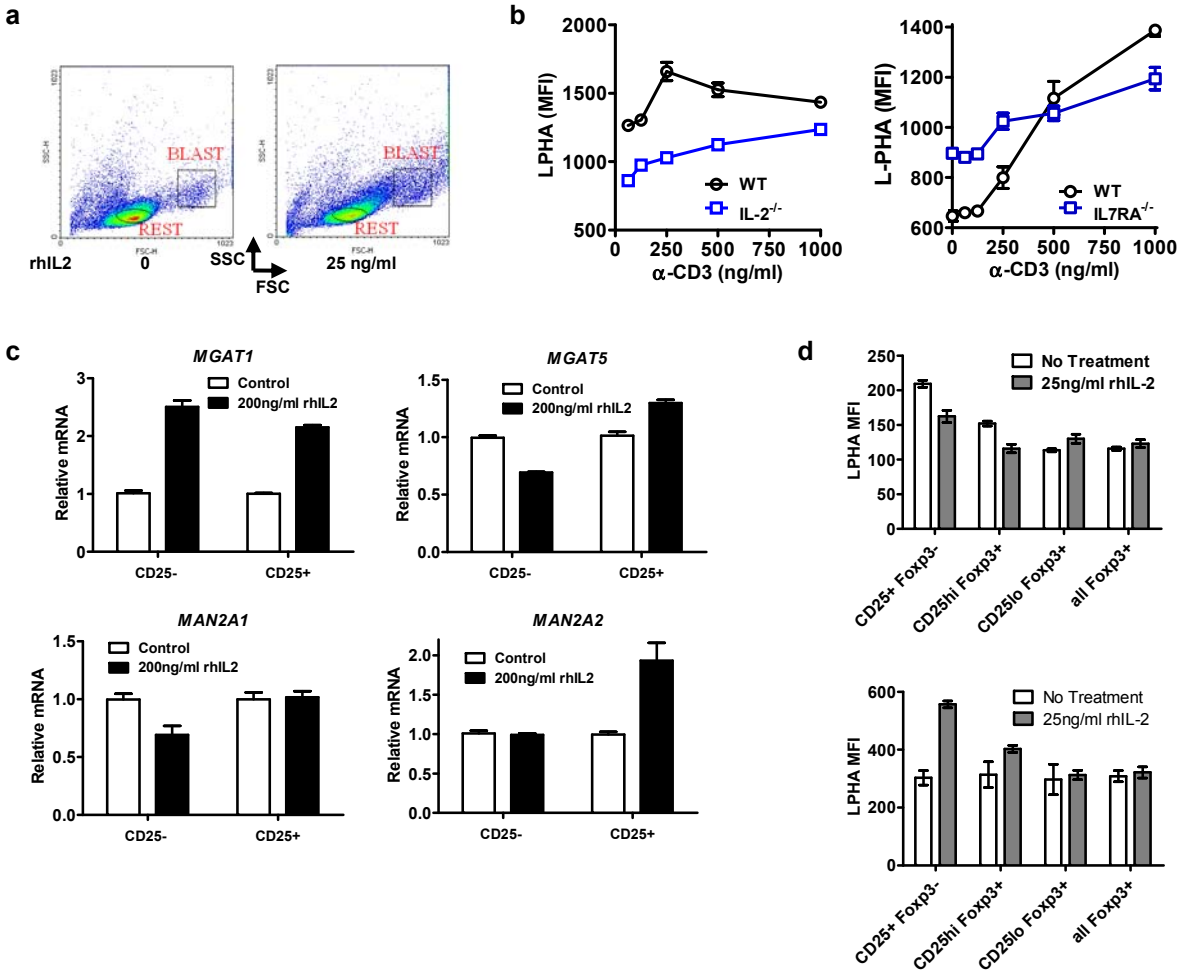
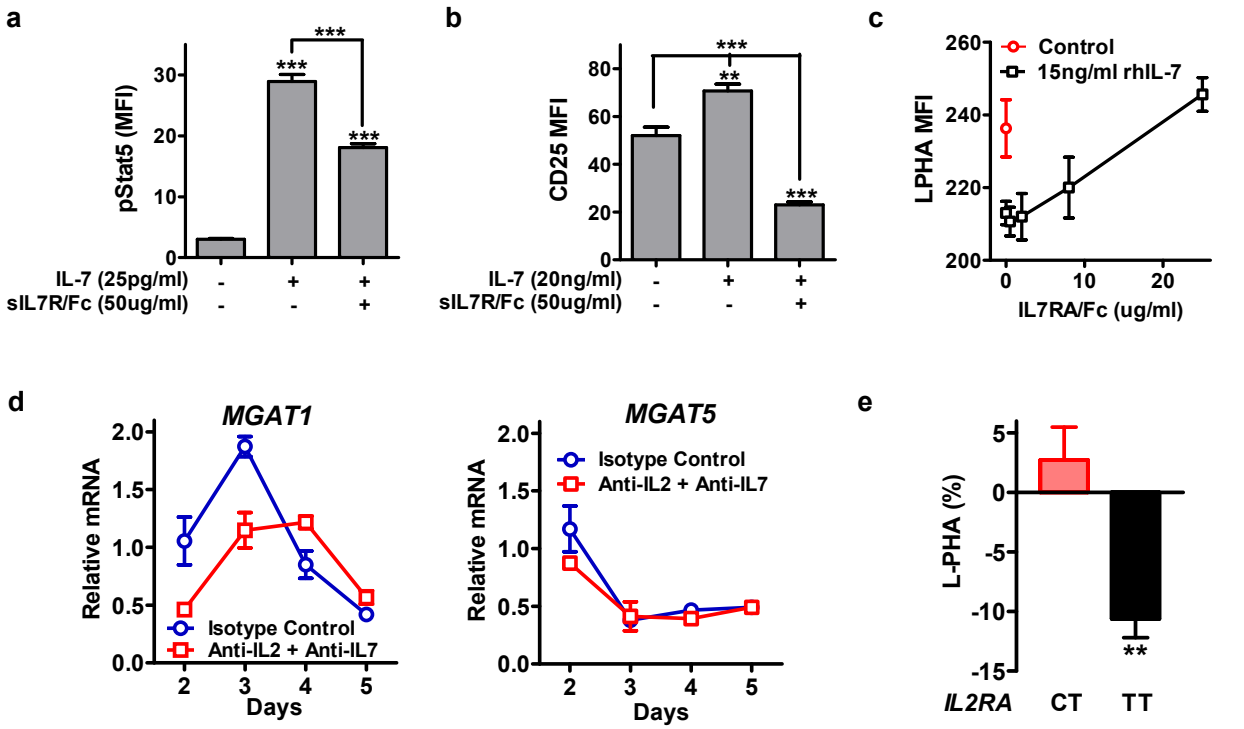


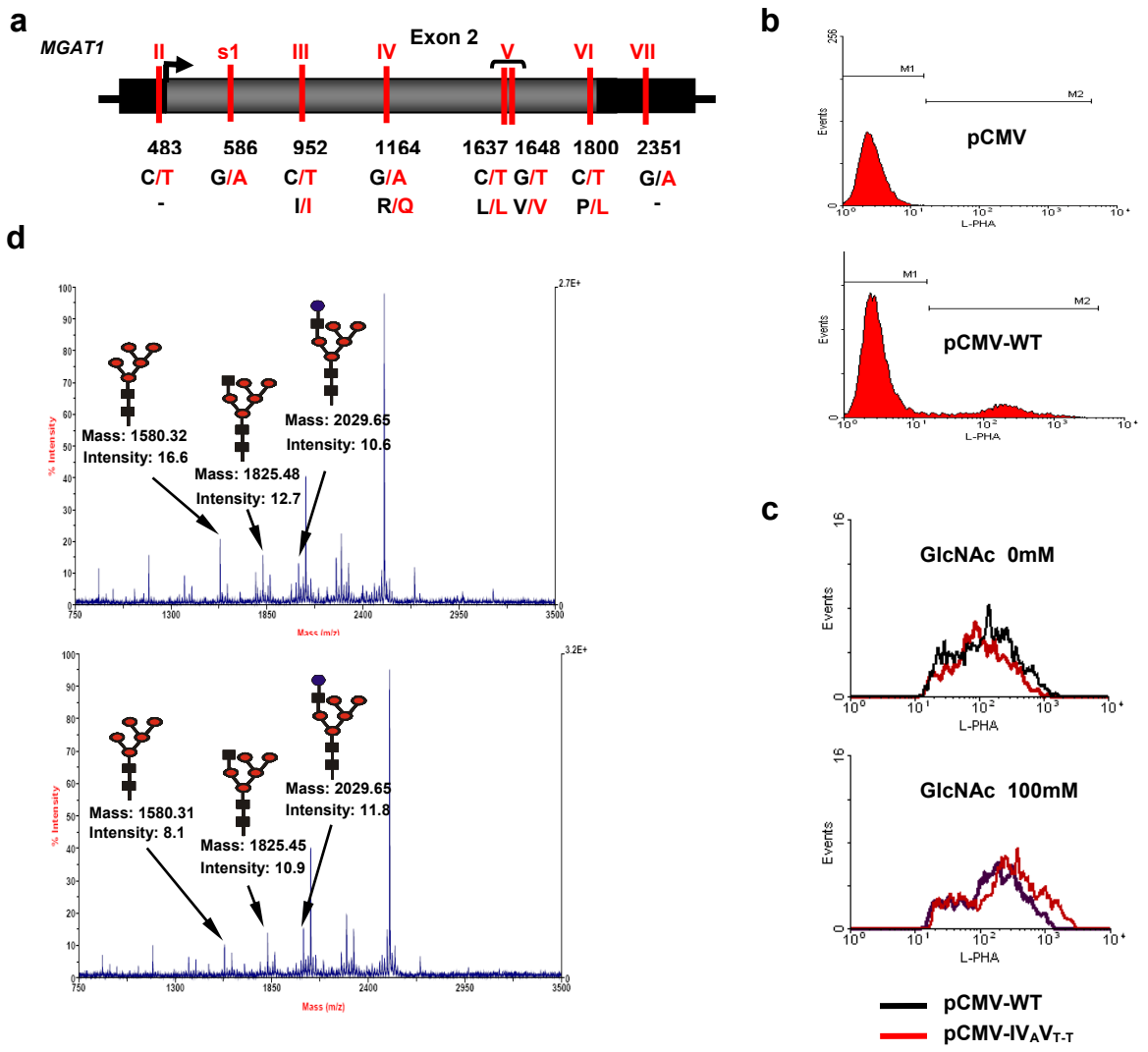
Supplementary Figure S1. N-glycan branching by IL-2 and IL-7

(a) Human $CD3^+$ T cells treated with the indicated concentrations of rhIL-2 for four days. The gated regions indicate cells considered at rest or blasting. FCS – forward scatter, SSC – side scatter. **(b)** Mouse splenocytes of the indicated genotypes were stimulated with anti-CD3 for 5 days (right panel) or 3 days (left panel). $CD25^+CD4^+$ T cell blasts were analyzed by FACS for L-PHA binding. **(c)** Quantitative RT-PCR on cDNA derived from human T cells (*IL2RA**CT and *IL7RA**CT). Purified $CD3^+$ T cells were stimulated with plate bound anti-CD3 (1ug/ml) for 2 days in the presence of 10ug/ml anti-IL2 to induce CD25 expression in the absence of IL-2 signaling. $CD25^+$ and $CD25^-$ cells were then isolated by the EasySep human CD25 positive selection kit and treated with rhIL2 (200ng/ml) for 12 hours prior to isolation of RNA. **(d)** L-PHA FACS analysis of the indicated T cell subsets (*IL2RA**CT and *IL7RA**CC) with and without rhIL2 treatment for four days, gated on resting (top) or blasting (bottom) cells as shown in (a). MFI = mean fluorescence intensity.

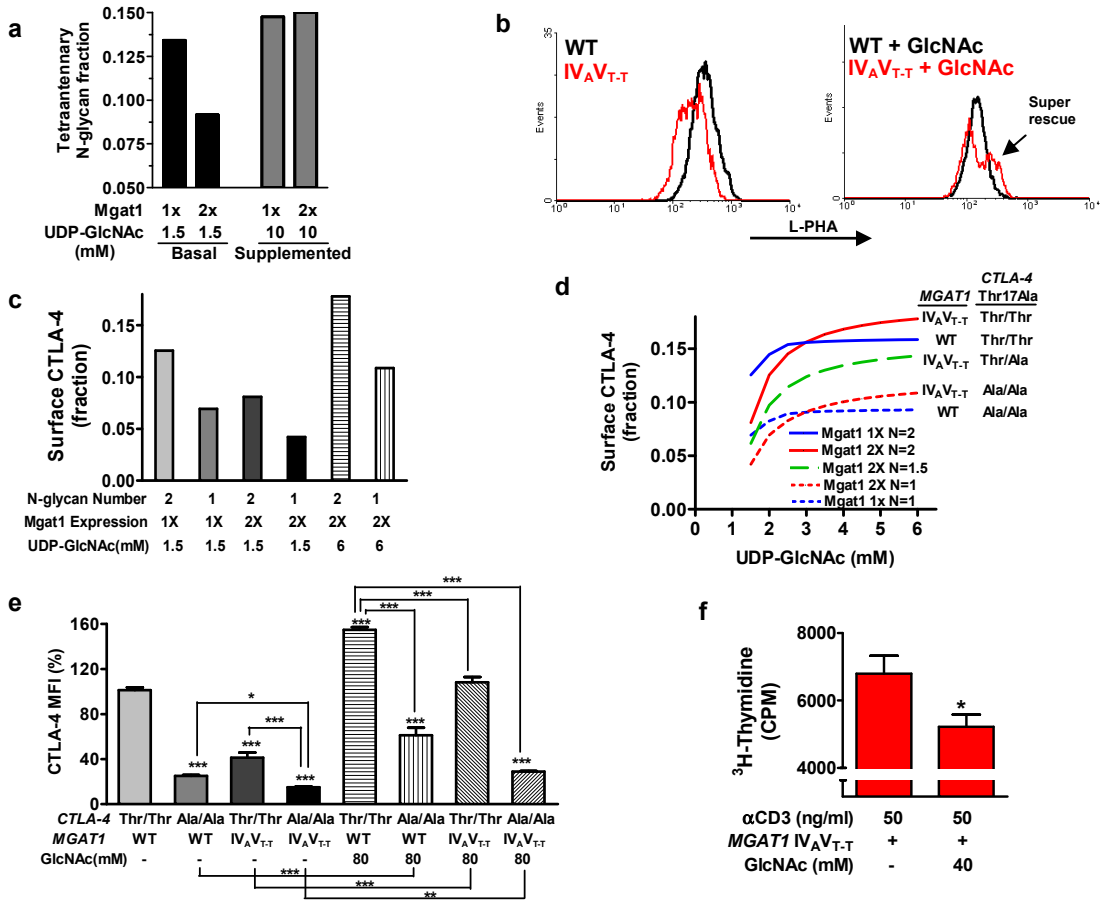


Supplementary Figure S2. sIL7RA-Fc antagonizes IL-7 signaling

(a) Resting human CD3$^+$ T cells (*IL2RA**CT and *IL7RA**CC) were treated in triplicate as indicated for 15 minutes, then fixed and analyzed for intracellular Stat5 phosphorylation by FACS, gating on CD4$^+$ cells. P-values by ANOVA and Newman-Keuls Multiple Comparison Test. **(b)** Human CD3$^+$ T cells (*IL2RA**CT and *IL7RA**CT) were stimulated with plate bound anti-CD3 (400ng/ml) and treated as indicated for 5 days. CD25 expression in CD4$^+$ T cells were analyzed by FACS. P-values by ANOVA and Newman-Keuls Multiple Comparison Test. **(c)** L-PHA FACS analysis of resting human CD3$^+$ T cells (*IL2RA**CT and *IL7RA**CT) treated as indicated for 3 days. Data are gated on CD4$^+$ T cells. **(d)** Quantitative RT-PCR on cDNA derived from human T cells (*IL2RA**CT and *IL7RA**CT). Purified CD4$^+$ T cells were stimulated with plate bound anti-CD3 for the indicated times in the presence or absence of anti-IL-2 + anti-IL-7 neutralizing antibody. CD25$^+$ cells were used to isolate RNA. Relative mRNA levels were normalized to actin. **(e)** Human CD3$^+$ T cells of the indicated genotypes (n=1 for each genotype) and matched for *IL7RA* (CC) and *MGAT1* (common variant) were stimulated in triplicate with anti-CD3 (4ug/ml) for 6 days and analyzed for L-PHA staining by FACS. CD25$^+$CD4$^+$ T cell blasts were gated based on forward vs. side scatter. Error bars are standard error of three biological replicates. P-value by T test (one sided). **p<0.01, ***p<0.001 in all panels. Error bars are standard error of triplicate or greater values in all panels unless otherwise stated. MFI = mean fluorescence intensity.

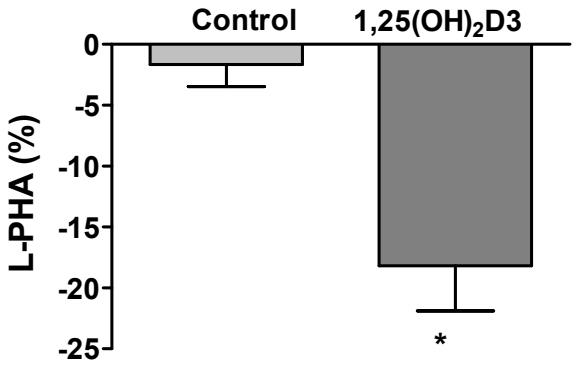


Supplementary Figure S3. *MGAT1* haplotypes reduce N-glycan branching
(a) SNPs in *MGAT1* identified by sequencing 42 MS patients. II – ss104807085, III - ss104807087, IV - rs7726005, V – rs2070924 and rs2070925, VI – rs634501, VII - ss104807088 and s1-ss104807086. **(b)** Examples of L-PHA FACS histograms used to generate data for Lec1 transfection experiments measuring L-PHA binding. Mgat1-deficient Lec1 cells transiently transfected in triplicate with empty vector (pCMV) or various *MGAT1* haplotypes were stained with L-PHA and analyzed by FACS. The M2 gait, representing all transfected cells, was used to determine MFI for all data, with error bars representing standard error of triplicate values. **(c)** Examples of L-PHA FACS histograms used to generate data for GlcNAc supplementation experiments with transfected Lec1 cells. **(d)** Examples of two spectra from donors with the *MGAT1* common (top) or IVAVT-T (bottom) haplotype used to calculate the ratio of mono-antennary (i.e. (Gal)GlcNAc1Man5GlcNAc2) to Man5GlcNAc2. To normalize the data, the peak intensities of mass ion 1825 (GlcNAc1Man5GlcNAc2) and 2029 (Gal1GlcNAc1Man5GlcNAc2) were added together and divided by the peak intensity of mass ion 1580 (Man5GlcNAc2). This ratio was obtained from spectra of 6 individuals with and 6 individuals without the *MGAT1* IVAVT-T haplotype (i.e. 12 samples in total) and analyzed by t-test.



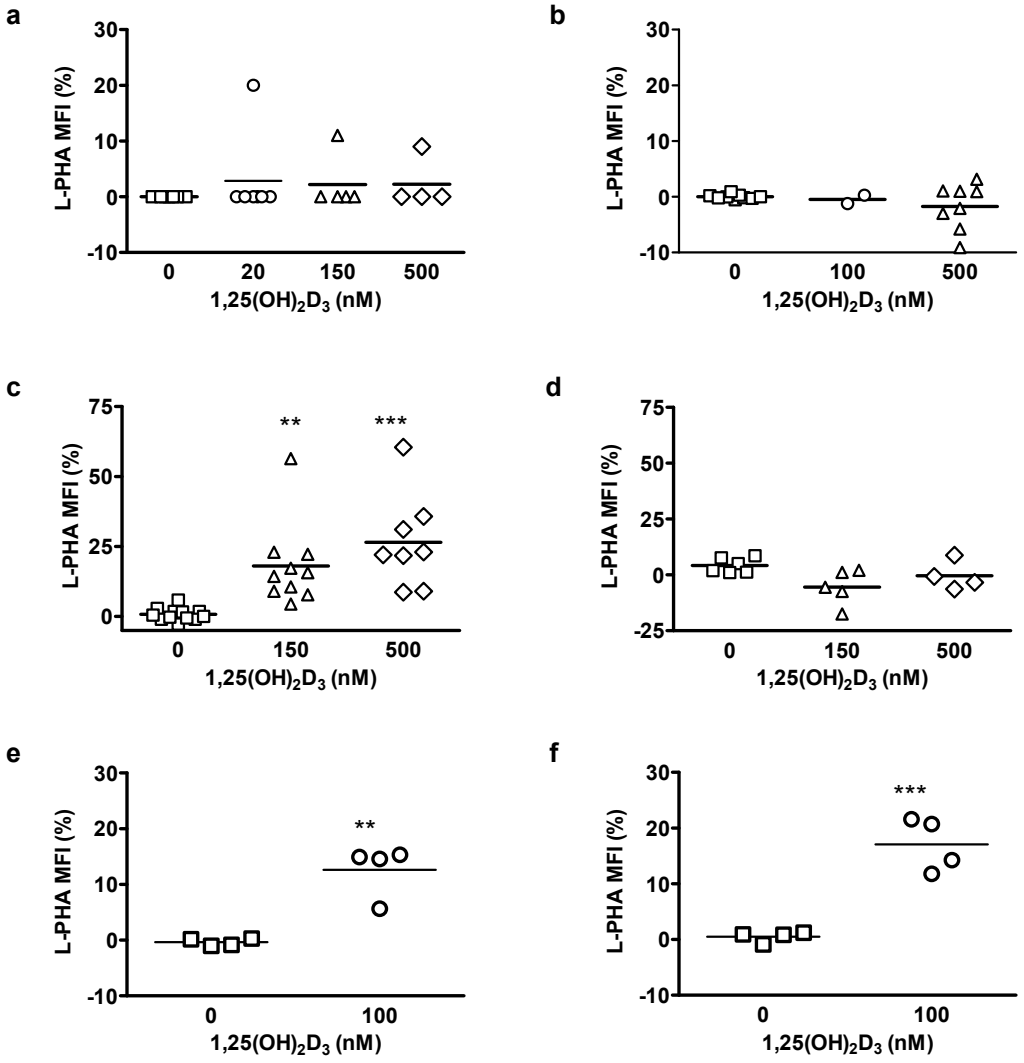
Supplementary Figure S4. Conditional regulation of N-glycan branching and T cell growth by *MGAT1* IV_AV_{T-T}

(a) Ordinary Differential Equation (ODE) model of medial Golgi enzyme reactions and the galectin lattice showing predicted alterations in β1,6GlcNAc branching. Mgat1, 2 and 5 activities were modeled with measurements made in 129/Sv mouse T cells. **(b)** Human PBMCs of the indicated genotypes were rested with or without GlcNAc and examined by FACS for L-PHA binding in $CD4^+$ T cells at day 3. Subjects (n=2) were homozygous for the common alleles of *CTLA-4*, *IL2RA**T and *IL7RA**C. **(c)** ODE model showing predicted alterations in surface retention of CTLA-4 under varying conditions (i.e. number of N-glycans attached to CTLA-4, increases in Mgat1 activity and UDP-GlcNAc levels). **(d)** ODE model showing predicted alterations in surface retention of CTLA-4 in the indicated genotypes as UDP-GlcNAc levels change. **(e)** Human PBMCs of the indicated genotypes were stimulated with or without GlcNAc and examined by FACS at day 5. CTLA-4 MFI was assessed in $CD4^+$ T cell blasts with background subtracted from resting cells and normalized to cells homozygous for both common variants. n=2 for Ala/Ala+WT and Ala/Ala+IV_AV_{T-T}; n=1 for Thr/Thr+WT and Thr/Thr+IV_AV_{T-T}; subjects are carriers for *IL2RA**T and *IL7RA**C except one Ala/Ala+IV_AV_{T-T} subject with unknown genotype. P-values by ANOVA and the Newman-Keuls Multiple Comparison Test. *p<0.05, ***p<0.001. **(f)** Human PBMCs with the *MGAT1* IV_AV_{T-T} haplotype were stimulated with anti-CD3 with or without GlcNAc and examined for proliferation at day 2. P values by t-test. *p<0.05. Error bars are standard error of triplicate or greater values. MFI = mean fluorescence intensity.



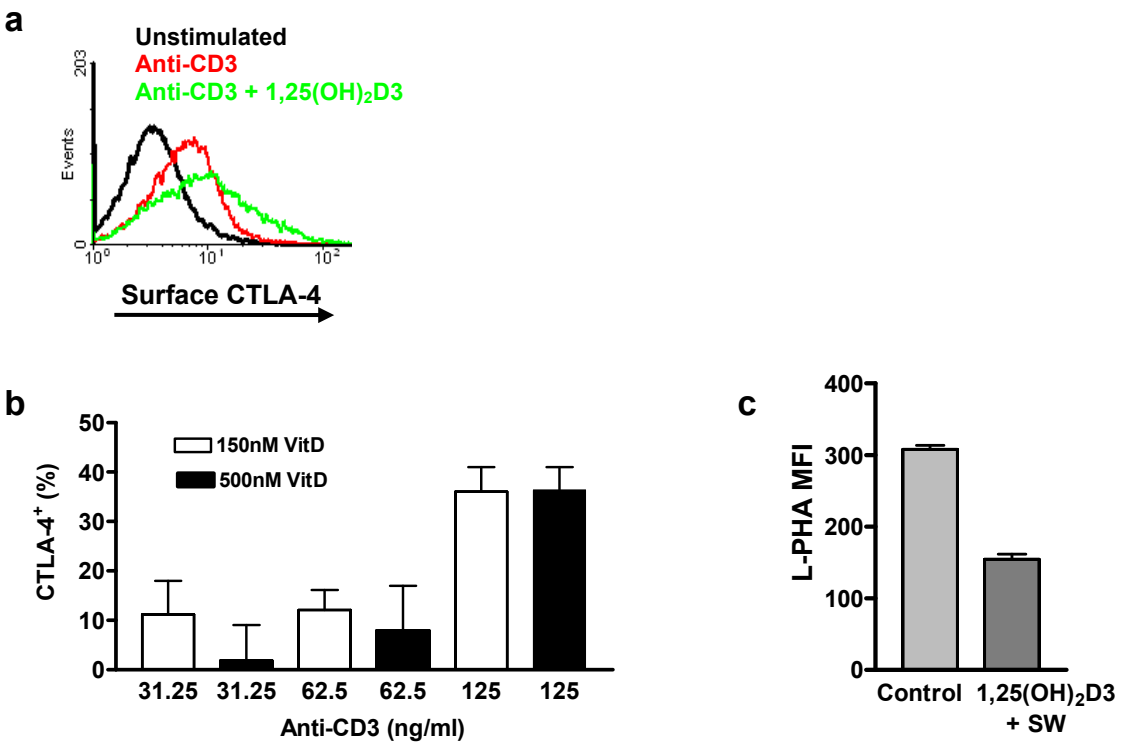
Supplementary Figure S5. *IL2RAC and *IL7RA**T with Vitamin D3 in N-glycan branching**

Purified human $CD3^+$ T cells homozygous for both protective *IL2RA**C and *IL7RA**T alleles were pre-stimulated with plate-bound anti-CD3 for 2 days (400ng/ml) and then treated with 100nM $1,25(OH)_2D_3$ for 3 days. L-PHA binding was analyzed by FACS in $CD4^+$ T cell blasts. P-value was determined by t-test. *$p<0.05$. MFI = mean fluorescence intensity. Error bars are standard error of triplicate values.



Supplementary Figure S6. Vitamin D3 regulates N-glycan branching in activated mouse and human CD4$^+$ T cells

(a) Resting mouse or **(b)** resting human CD3$^+$ T cells were cultured with the indicated concentrations of 1,25$(OH)_2D_3$, stained with L-PHA in triplicate, and analyzed by FACS (gated on CD4$^+$ T cells). **(c)** Male or **(d)** female mouse CD3$^+$ T cells were pre-stimulated with plate bound anti-CD3 for 2 days then treated with 1,25$(OH)_2D_3$ for 3 days as indicated, stained with L-PHA in triplicate, and analyzed by FACS (gated on CD4$^+$ T cells). P-values by ANOVA and the Newman-Keuls Multiple Comparison Test. **p<0.01, ***p<0.001. **(e)** Male or **(f)** female human CD3$^+$ T cells were stimulated, treated, and analyzed as in (c). P-values by t-test in (e) and (f). **p<0.01, ***p<0.001. Horizontal bars represent the average MFI (mean fluorescence intensity) of each treatment group in all panels.



Supplementary Figure S7. Vitamin D3 regulates CTLA-4 surface expression and N-glycan branching

(a) Purified mouse $CD3^+$ T cells were stimulated with plate-bound anti-CD3 (0 or 250ng/ml) with or without $1,25(OH)_2D_3$ (150nM) for 5 days and analyzed by FACS for cell surface CTLA-4 expression in $CD4^+$ T cells. **(b)** Purified mouse $CD3^+$ T cells were stimulated and treated with or without $1,25(OH)_2D_3$ as indicated for 5 days. CTLA-4 surface expression was analyzed as in (a). Shown is the percentage increase in CTLA-4 relative to cells not treated with $1,25(OH)_2D_3$. Error bars are standard error of triplicate values **(c)** Splenocytes from female mice immunized with 100ug MBP+CFA to induce EAE were stained with L-PHA and analyzed by FACS to assess for effectiveness of SW in reducing N-glycan branching in $CD4^+$ T cells. n=1 mouse for control and n=2 mice for $1,25(OH)_2D_3$ + SW, with each mouse stained in triplicate. Error bars represent the range of values. MFI = mean fluorescence intensity.

Supplementary Table S1. Association analysis of single variants in Multiple Sclerosis

		Variant Frequency			
		Control (n)	Disease (n)	p-value	Odds Ratio [95% CI]
***IL2RA**T (rs2104286)**	Cohort 1	0.745 (1484)	0.770 (1196)	1.95×10^{-2}	1.14 [1.01-1.30]
	Cohort 2	0.729 (5023)	0.771 (1972)	3.81×10^{-5}	1.19 [1.09-1.30]
	Combined Data	**0.740 (6507)**	**0.770 (3168)**	$\mathbf{2.44 \times 10^{-6}}$	**1.18 [1.10-1.26]**
	Combined p-values			$\mathbf{1.12 \times 10^{-5}}$	
***IL7RA**C (rs6897932)**	Cohort 1	0.737 (1485)	0.762 (1200)	1.66×10^{-2}	1.15 [1.01-1.30]
	Cohort 2	0.750 (5024)	0.771 (1972)	5.67×10^{-3}	1.12 [1.03-1.22]
	Combined Data	**0.747 (6509)**	**0.767 (3172)**	$\mathbf{1.05 \times 10^{-3}}$	**1.12 [1.04-1.20]**
	Combined p-values			$\mathbf{9.67 \times 10^{-4}}$	
***CTLA-4**Thr17 (rs237155)**	Cohort 1	0.611 (1489)	0.629 (1200)	9.75×10^{-2}	1.08 [0.96-1.20]
	Cohort 2	0.614 (5017)	0.614 (1973)	4.66×10^{-1}	1.00 [0.93-1.08]
	Combined Data	**0.613 (6506)**	**0.620 (3173)**	$\mathbf{1.84 \times 10^{-1}}$	**1.03 [0.97-1.09]**
	Combined p-values			$\mathbf{1.86 \times 10^{-1}}$	
MGAT1 $\mathbf{IV_AV_{T\text{-}T}}$	Cohort 1	0.0673 (1501)	0.0947 (1204)	4.43×10^{-3}	1.45 [1.10-1.92]
	Cohort 2	0.0721 (7056)	0.0939 (2076)	5.33×10^{-4}	1.33 [1.12-1.59]
	Combined Data	**0.0713 (8557)**	**0.0942 (3280)**	$\mathbf{1.52 \times 10^{-5}}$	**1.36 [1.17-1.56]**
	Combined p-values			$\mathbf{3.30 \times 10^{-5}}$	
MGAT1 $\mathbf{IV_A}$	Cohort 1	0.161 (1490)	0.187 (1202)	3.74×10^{-2}	1.20 [0.98-1.47]
	Cohort 2	0.162 (5697)	0.174 (2077)	1.11×10^{-1}	1.09 [0.95-1.24]
	Combined Data	**0.162 (7187)**	**0.179 (3279)**	$\mathbf{1.66 \times 10^{-2}}$	**1.13 [1.01-1.26]**
	Combined p-values			$\mathbf{2.69 \times 10^{-2}}$	
MGAT1 $\mathbf{V_{T\text{-}T}}$	Cohort 1	0.0725 (1489)	0.101 (1196)	4.14×10^{-3}	1.44 [1.10-1.89]
	Cohort 2	0.0805 (7085)	0.0987 (2077)	4.29×10^{-3}	1.25 [1.06-1.48]
	Combined Data	**0.0791 (8574)**	**0.0996 (3273)**	$\mathbf{1.67 \times 10^{-4}}$	**1.29 [1.12-1.48]**
	Combined p-values			$\mathbf{2.12 \times 10^{-4}}$	

Variant frequency in non-latino Caucasians with MS and controls from North America. Reported is one-sided p-value computed using the Cochran-Armitage test with the *MGAT1* $IV_AV_{T\text{-}T}$ haplotype (rs7726005, rs2070924 and rs2070925), the *MGAT1* IV_A polymorphism (rs7726005) and the *MGAT1* $V_{T\text{-}T}$ polymorphisms (rs2070924 and rs2070925) coded 0 or 1 for carrier status and *IL2RAT (rs2104286), *IL7RA**C (rs6897932) and *CTLA-4* Thr17 (rs231775) coded as 0, 1 or 2 for the number of alleles. For 1387 controls in cohort 2, the *MGAT1* IV_A polymorphism was genotyped only in those positive for the *MGAT1* $V_{T\text{-}T}$ polymorphisms; therefore frequencies of the former are not reported for these samples. Combined p-values by Fishers method. OR = Odds Ratio; 95% CI = 95% Confidence Intervals. All control cohorts are in HWE.**

Supplementary Table S2. Stratified analysis of *MGAT1* IV_AV_{T-T} in Multiple Sclerosis

			***MGAT1* IV_AV_{T-T} Frequency**			
			Control (n)	**Disease (n)**	**p-value**	**Odds Ratio [95% CI]**
***IL2RA**T + *IL7RA**C**	**< 4**	Cohort 1	0.0619 (1017)	0.1041 (788)	$5.47x10^{-4}$	1.76 [1.25-2.48]
		Cohort 2	0.0734 (3474)	0.0965 (1296)	$4.46x10^{-3}$	1.35 [1.08-1.69]
		Combined Data	**0.0708 (4491)**	**0.0993 (2084)**	**$3.60x10^{-5}$**	**1.45 [1.21-1.74]**
		Combined p-values			**$3.40x10^{-5}$**	
	= 4	Cohort 1	0.0799 (463)	0.0760 (408)	$4.15x10^{-1}$	0.95 [0.58-1.56]
		Cohort 2	0.0728 (1552)	0.0874 (675)	$1.18x10^{-1}$	1.22 [0.88-1.69]
		Combined Data	**0.0744 (2015)**	**0.0831 (1083)**	**$1.95x10^{-1}$**	**1.13 [0.86-1.48]**
		Combined p-values			**$1.97x10^{-1}$**	
***CTLA-4**Thr17**	**< 2**	Cohort 1	0.0634 (931)	0.109 (714)	$4.22x10^{-4}$	1.81 [1.27-2.58]
		Cohort 2	0.0729 (3100)	0.101 (1226)	$1.07x10^{-3}$	1.43 [1.14-1.80]
		Combined Data	**0.0707 (4031)**	**0.104 (1940)**	**$4.95x10^{-6}$**	**1.53 [1.26-1.85]**
		Combined p-values			**$7.05x10^{-6}$**	
	= 2	Cohort 1	0.0764 (550)	0.0742 (485)	$4.48x10^{-1}$	0.97 [0.61-1.54]
		Cohort 2	0.0742 (1915)	0.0817 (747)	$2.56x10^{-1}$	1.11 [0.81-1.52]
		Combined Data	**0.0746 (2465)**	**0.0787 (1232)**	**$3.29x10^{-1}$**	**1.06 [0.82-1.37]**
		Combined p-values			**$3.63x10^{-1}$**	
***IL2RA**T + *IL7RA**C + *CTLA-4**Thr17**	**< 6**	Cohort 1	0.0641 (1310)	0.101 (1039)	$5.42x10^{-4}$	1.64 [1.22-2.21]
		Cohort 2	0.0733 (4422)	0.100 (1715)	$2.45x10^{-4}$	1.41 [1.16-1.71]
		Combined Data	**0.0712 (5732)**	**0.101 (2754)**	**$1.62x10^{-6}$**	**1.46 [1.24-1.71]**
		Combined p-values			**$2.24x10^{-6}$**	
	= 6	Cohort 1	0.0941 (170)	0.0552 (163)	$8.90x10^{-2}$	0.56 [0.24-1.31]
		Cohort 2	0.0749 (601)	0.0504 (258)	$9.49x10^{-2}$	0.66 [0.35-1.24]
		Combined Data	**0.0791 (771)**	**0.0523 (421)**	**$4.08x10^{-2}$**	**0.64 [0.39-1.06]**
		Combined p-values			**$4.88x10^{-2}$**	

Stratified analysis in 2 independent North American Caucasian case-control MS cohorts. Reported is one-sided p-value computed using the Cochran-Armitage test with *MGAT1* IV_AV_{T-T}(rs7726005, rs2070924 and rs2070925) coded 0 or 1 for carrier status and *IL2RAT (rs2104286), *IL7RA**C (rs6897932) and *CTLA-4* Thr17 (rs231775) coded as 0, 1 or 2 for the number of alleles. OR = Odds Ratio; 95% CI = 95% Confidence Intervals. All control cohorts are in HWE.**