

Supplemental Data

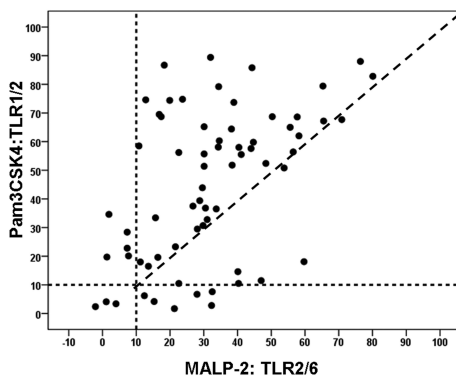
Distinct Innate Immunity Pathways to Activation and Tolerance in Subgroups of Chronic Lymphocytic Leukemia with Distinct Immunoglobulin Receptors

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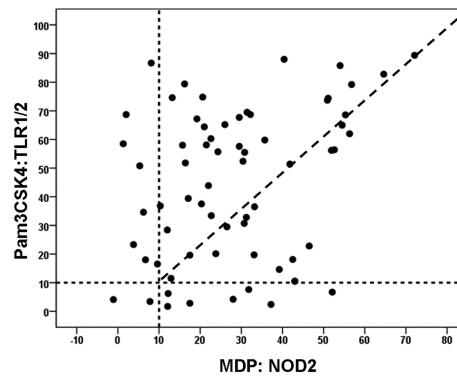
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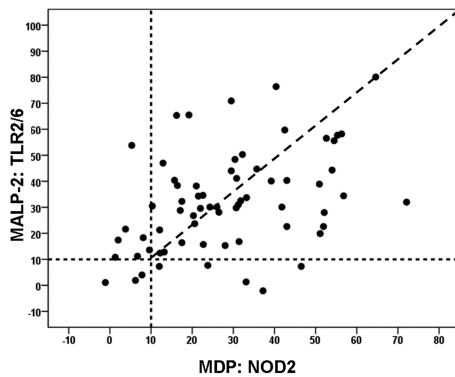
Supplemental Figure 1A



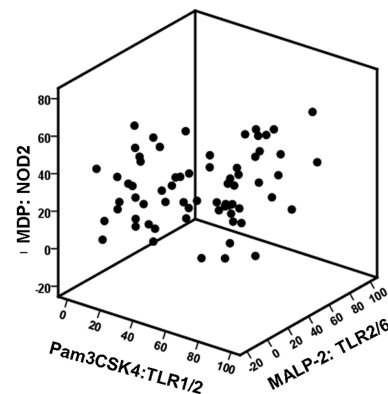
Supplemental Figure 1B



Supplemental Figure 1C

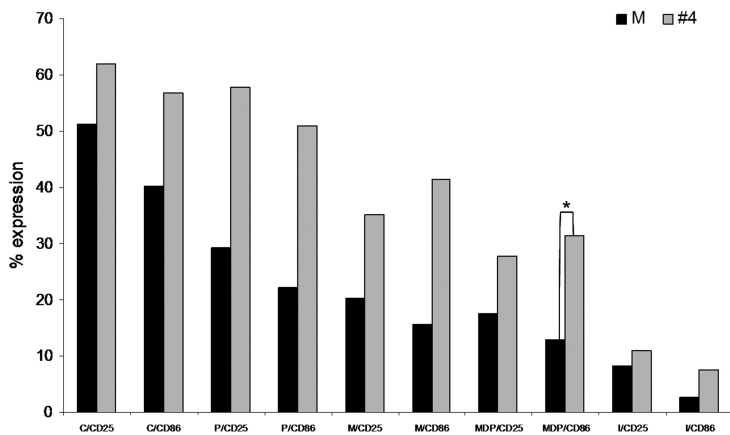


Supplemental Figure 1D

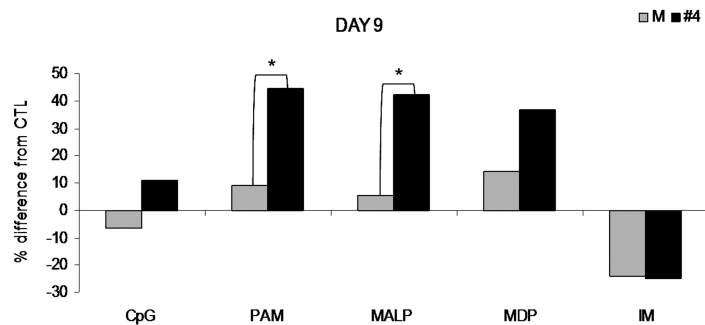


**Supplementary Figure S1.** CLL cells exhibit concordant patterns of response to stimulation of TLR1/2, TLR2/6 and NOD2 with the appropriate ligands. From the pairs of CD25 and CD86 values for each stimulation experiment with Pam3CSK4, MALP-2 and MDP, the maximum value was selected as the representative value of responsiveness. Spearman correlation test revealed that (i) 53/58 cases (91%) showed qualitatively similar responses after TLR1/2 and TLR2/6 stimulation ( $p < 0.001$ ,  $R = 0.46$ ); (ii) 50/57 (88%) and 52/57 (91%) cases responsive to NOD2 were also responsive to TLR1/2 and TLR2/6, respectively ( $p < 0.05$ ,  $R = 0.26$  and  $p < 0.001$ ,  $R = 0.42$ ); and, (iii) 46/65 (71%) cases had concordant patterns of response to stimulation of TLR1/2, TLR2/6 and NOD2 with their respective ligands ( $p < 0.05$ ). Pairwise scatter plots showing the distribution of the pairs of the new "max" variables indicate concordant patterns of response in independent stimulation of (A) TLR1/2 and TLR2/6; (B) TLR1/2 and NOD-2; (C) TLR2/6 and NOD-2; and, (D) all the above receptors.

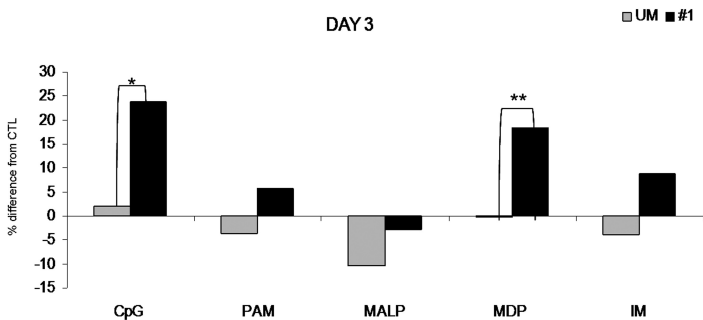
Supplemental Figure 2A



Supplemental Figure 2B

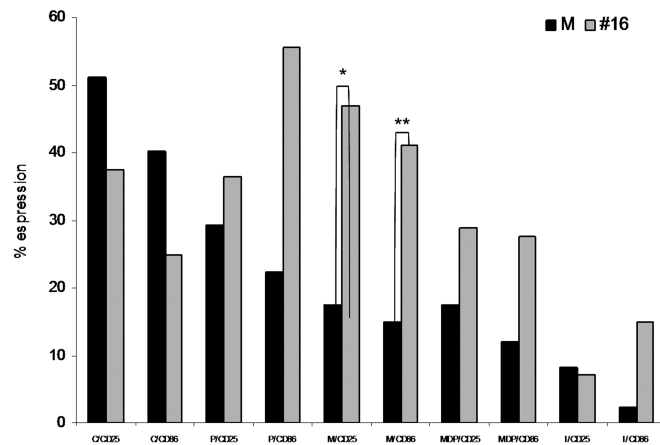


Supplemental Figure 2C

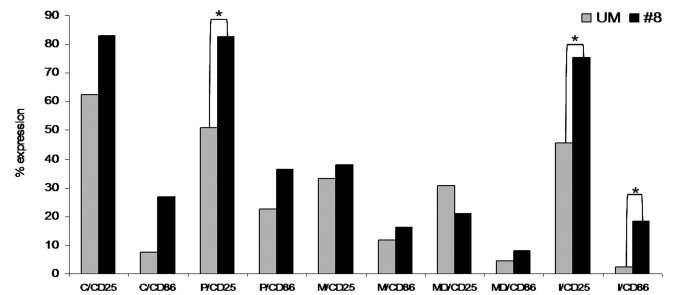


**Supplementary Figure S2.** Distinct innate immunity responses in stereotyped CLL subsets are independent of mutational status. (A) Differences in CD25 and CD86 expression after stimulation of TLRs and NOD2 in M-CLL vs subset #4. (B) Differences in CLL cell viability after stimulation of TLRs and NOD2 in M-CLL vs subset #4. (C) Differences in CLL cell viability after stimulation of TLRs and NOD2 in U-CLL vs subset #1. Prior to statistical analysis values were normalized to the unstimulated controls. C: CpG ODN, P: Pam3CSK4, M: MALP-2, MD:MDP, I:Imiquimod, \*  $p < 0.05$ , \*\*  $p < 0.005$ .

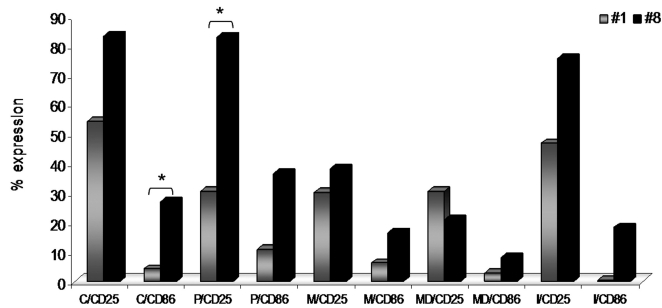
Supplemental Figure 3A



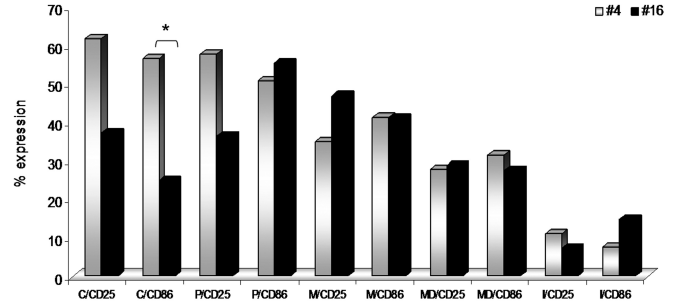
Supplemental Figure 3B



Supplemental Figure 3C



Supplemental Figure 3D



**Supplemental Figure S3.** Differential responses to TLR and NOD2 stimulation in the 'minor' subsets of CLL cases with stereotyped BcRs, irrespective of *IGHV* gene mutational status. (A) Differences in CD25 and CD86 expression after stimulation of TLRs and NOD2 in M-CLL vs subset #16. (B) Differences in CD25 and CD86 expression after stimulation of TLRs and NOD2 in UM-CLL vs subset #8. (C) Comparison of unmutated subset #1 versus unmutated subset #8 revealed statistically significant differences in the induction of CD25 and CD86 after TLR1/2 stimulation with Pam3CSK4. (D) Comparison of mutated subset #4 vs mutated subset #16 revealed statistically significant differences in the induction of CD86 after TLR9 stimulation with CpG. The graphs are based on median values (before statistical analysis values were normalized to the unstimulated controls). C: CpG ODN, P: Pam3CSK4, M: MALP-2, MD:MDP, I:Imiquimod, \*  $p < 0.05$ .

**Supplementary Table S1.** Demographic, biological and clinical data of CLL patients included in the study.

sIGH: surface Ig heavy isotype; sIGL: surface Ig light isotype; sCD38: surface CD38; cZAP-70: cytoplasmic ZAP-70.

Lab Identifier	Sex	Age of Diagnosis	Rai	Binet	Disease Progression	Last Follow-Up	Current status	sIGH	sIGL	sCD38	cZAP-70	Karyotype	FISH
P4699	F	76	0	A	YES	5/12/09	ALIVE	MD	kappa	33.5	73		Trisomy 12
P3506	M	71	0	A	YES	12/15/09	ALIVE	MD	kappa	31.1	49	47,XX,+12	Trisomy 12
P3870	M	68	0	A	NO	11/2/09	ALIVE	MD	kappa			46,XY	
P4295	F	57	0	A	NO	10/12/09	ALIVE	MD	lambda	0.3	33	46,XX	Del13q
P2355	M	54	II	A	YES	1/22/10	ALIVE	MD	kappa	4.5	47	46,XY	normal
P2685	F	67	0	A	NO	12/15/09	ALIVE	MD	lambda	0.5	12		normal
P3073	F	38	IV	C	YES	4/15/09	DEAD	MD	kappa	40	65	46,XX,del(6)(q21q27)	normal
P8805	F	70	I	A	YES	1/20/10	ALIVE	MD	kappa	7.4	37	46,XX,t(2:13)(p23;q14)[2]/46,XX[24]	Del13q+Del11q
P9320	M	47	I	A	NO	5/19/10	ALIVE	MD	kappa	43.6	24		normal
P1697	M	60	II	A	YES	1/14/10	ALIVE	MD	kappa	0.3		46,XY	
P571	M	47	0	A	YES	7/20/07	ALIVE	MD	kappa	7.8		47,XY,+12	
P8762	M	62	I	A	YES	1/14/10	ALIVE	MD	lambda	67.3	55	46,XY (20)	normal
P1618	M	62	0	A	NO	11/10/09	ALIVE	MD	lambda	1.1	3	46,XY	normal
P1156	F	63	II	A	YES	2/23/10	DEAD	M	kappa	66.4	68.9	47,XX,inv(9)(p13q22),+12/47,XX,t(1:13)(p12;q12),inv(9)(p13q22),+12	
P5283	M	61	I	A	NO	11/23/09	ALIVE	MD	lambda	91.7	60.5	46,XY	
P511	M	63	II	B	YES	12/21/09	ALIVE	MD	lambda	16.9			
P2329	F	57	0	A	NO	10/7/09	ALIVE	MD	lambda	15	12.5	46,XX	normal
P7155	M	50	0	A	NO	10/5/09	ALIVE	MD	lambda	20.8	54.1	46,XY (25)	Del11q
P2618	F	78	0	A	NO	9/7/09	ALIVE	MD	kappa	1.8			
P8192	M	54	I	A	NO	11/9/09	ALIVE	MD	kappa	1.9	18.3	46,XY(10)	normal
P7794	F	76	0	A	NO	9/7/09	ALIVE	G	kappa	34	0.5	47,XX,+12	Trisomy 12
P6124	M	68	0	A	NO	12/1/09	ALIVE	MD	lambda	2.5	10.3	46,XY	normal
P9940	M	33	I	A	NO		ALIVE	G	kappa	0.2	1.4		
P4383	F	69	0	A	NO	12/1/09	ALIVE	G	kappa	0	6.3	46,XX	
P6460	M	69	0	A	NO	11/23/09	ALIVE	MD	lambda	0.9	5.1	46,XY (15)	normal
P1894	M	52	0	A	NO	9/7/09	ALIVE	M	kappa	5.3		46,XY	Del13q+Del13q
P427	M	53	0	A	NO	9/7/09	ALIVE	MD	kappa	0.6			
P2577	M	37	0	A	NO	11/27/09	ALIVE	MD	lambda	1.2	6	46,XY,inv(9)(p13q21)	normal
P2548	M	69	I	A	YES	12/10/09	ALIVE	MD	kappa	28.2		46,X,t(Y;11)(q12;q23),del(13)(q12q14)/46,XY,t(3;5)(q29;q23)	
P5231	M	57	II	B	YES	11/25/09	ALIVE	MD	kappa	91.5	17.8	46,XY	normal
P5728	M	53	I	A	NO	6/15/09	ALIVE	MD	lambda	32.5	2.4	46,XY	normal
P5949	M	50	0	A	NO	11/11/09	ALIVE	MD	kappa	0.5	5.5	46,XY	normal
P4875	F	72	0	A	NO	10/20/09	ALIVE	MD	kappa	1.4	13.4	46,XX	Del13q
P7961	F							MD	kappa	4.4	28.6	46,XX,der(4)t(4;17)(p11;q11),-17+mar(11) / 44,X,-X,der(4)t(4;17)(p11;q11),-13,add(15)(p13),-17,+mar1,+dmin (7) / 46,XY(8)	
P5017	F	70	0	A	YES	12/7/09	ALIVE	MD	kappa	12.2	40		Del13q+Del17p

Continued

Supplementary Table S1. Continued.

P6068	F	76	0	A	NO	9/29/09	ALIVE	MD	kappa	0.6	14				
P1055	F	48	I	A	NO	11/25/09	ALIVE	MD	kappa	2.2	28	Not determined			
P1188	M	58	I	B	NO	12/1/09	ALIVE	MD	lambda	4.3	14	46,XY			normal
P280	M	60	O	A	NO	8/31/09	ALIVE	MD	lambda	2.5	15	46,XY,t(9;12)(p11;q11)			
P2528	F	52	I	A	NO	9/28/09	ALIVE	MD	kappa	1.8	15				
P8699	F							MD	kappa	0.5	24.3				
P3020	F	66	O	A	NO	10/15/09	ALIVE	G	kappa	0.5		46,XX			Del13q
P6610	F	47	O	A	NO	6/19/09	ALIVE	MD	kappa	0.5	5.4	46,XX			normal
P4557	F	58	O	A	NO	11/17/09	ALIVE	MD	kappa	0.2	20	45,X,-X,inv(9)(p11q13)			normal
P103	F	45	O	A	NO	1/20/10	ALIVE	G	kappa	1.7		46,XX			normal
P1082	F	67	O	A	NO	10/11/09	ALIVE	G	kappa	0.9		46,XX			normal
P3916	M	43	O	A	NO	1/18/10	ALIVE	G	kappa	2.5	14	46,XY			
P3021	M	44	I	A	NO	12/7/09	ALIVE	G	kappa	0.3	19	46,XY			
P2740	M	47	O	A	NO	10/12/09	ALIVE	MD	kappa	0.7					
P3551	F	58	O	A	NO	11/25/09	ALIVE	G	kappa	0.8		46,XX			normal
P1563	M	69	II	B	YES	8/27/08	ALIVE	MD	kappa	0.5	18.6	46,XY			Del13q
P6520	M	44	O	A	YES	12/16/09	ALIVE	G	kappa	0.9	3.1	46,XY (17)			Del13q
P9297	M	69	O	A	NO	11/16/09	ALIVE	G	kappa	0.5	11.9				
P711	M	65	II	B	YES	12/11/09	ALIVE	MD	kappa	4.7	8	47,XY,+12/46,XY,del(13)(q12q14)/46,XY,del(14)(q24)			
P1626	M	37	O	A	YES	10/24/09	ALIVE	G	kappa	2	9	46,XY			Del13q
P775	F	42	II	B	YES	5/14/09	ALIVE	MD	lambda	1.1		46,XX			normal
P781	F	55	II	A	NO	11/12/09	ALIVE	G	kappa	1.4		46,XX			Del13q
P4994	M	68	O	A	YES	5/27/09	ALIVE	M	lambda	0.1	0.4	46,XY			Del13q+Del13q
P1615	F	61	O	A	YES	11/16/08	ALIVE	G	kappa	18	33	47,XX,+12			Trisomy 12
P1050	F	64	II	B	YES	2/11/09	DEAD	G	kappa	91.3		Not determined			Del13q+Del13q
P2446	M	72	O	A	NO	1/25/10	ALIVE	G	kappa	54		47,XY,+12			Trisomy 12
P104	M	69	O	A	YES	12/2/09	ALIVE	MD	lambda	51.3		46,XY			Trisomy 12
P1522	M	63	O	A	YES	5/20/10	DEAD	MD	lambda	2.1		46,XY			Del13q+Del13q
P6264	M	54	O	A	NO	1/18/10	ALIVE	MD	lambda	0.6	5.2	46,XY (20)			Del13q
P9391	M							MD	kappa	85.6	47.7				
P1173	F	62	O	A	YES	12/17/09	ALIVE	MD	kappa	22.5	30	46,XX			Trisomy 12
P5092	M	77	IV	C	YES	11/12/09	ALIVE	MD	kappa	0.7	7.3	46,XY,del(11)(q14)			Del13q+Del11q

**Supplementary Table S2.** BCR molecular characteristics and subset assignment of CLL cases included in the study.

Subset nomenclature according to Stamatopoulos et al, 2007; Murray et al, 2008.

Lab Identifier	IGHV	IGHD	IGHJ	%	Subset
P4699	IGHV1-18*01	IGHD6-19*01	IGHJ4*02	99.70	1
P3506	IGHV1-2*02	IGHD6-19*01	IGHJ4*02	99.70	1
P3870	IGHV1-2*02	IGHD6-19*01	IGHJ4*02	100.00	1
P2355	IGHV1-2*02	IGHD6-19*01	IGHJ4*02	100.00	1
P3073	IGHV1-3*01	IGHD6-19*01	IGHJ4*02	100.00	1
P1173	IGHV5- $\alpha$ *01	IGHD6-19*01	IGHJ4*02	99.60	1
P5092	IGHV5- $\alpha$ *03	IGHD6-19*01	IGHJ4*02	100.00	1
P3020	IGHV4-34*01	IGHD3-10*01	IGHJ6*02	90.00	4
P103	IGHV4-34*01	IGHD3-10*01	IGHJ6*02	95.90	4
P3916	IGHV4-34*01	IGHD3-10*01	IGHJ6*02	91.20	4
P3551	IGHV4-34*01	IGHD5-12*01	IGHJ6*02	93.30	4
P6520	IGHV4-34*02	IGHD3-10*01	IGHJ6*02	94.40	4
P1626	IGHV4-34*02	IGHD4-17*01	IGHJ6*02	94.80	4
P1615	IGHV4-39*01	IGHD6-13*01	IGHJ5*02	100.00	8
P1050	IGHV4-39*01	IGHD6-13*01	IGHJ5*02	100.00	8
P2446	IGHV4-39*06	IGHD6-13*01	IGHJ5*02	99.70	8
P1082	IGHV4-34*01	IGHD2-15*01	IGHJ6*02	96.30	16
P781	IGHV4-34*04	IGHD1-26*01	IGHJ6*02	95.00	16
P9297	IGHV4-34*02	IGHD2-2*01	IGHJ6*02	95.09	16
P4295	IGHV1-2*02	IGHD2-8*02	IGHJ4*02	93.80	
P2685	IGHV1-3*01	IGHD1-26*01	IGHJ5*02	87.80	
P8805	IGHV1-69*01	IGHD2-15*01	IGHJ5*02	100.00	
P9320	IGHV1-69*01	IGHD3-16*02	IGHJ3*02	100.00	
P1697	IGHV1-69*01	IGHD3-22*01	IGHJ4*03	93.90	
P571	IGHV1-69*01	IGHD3-10*01	IGHJ6*02	99.40	
P8762	IGHV1-69*06	IGHD5-24*01	IGHJ4*02	100.00	
P1618	IGHV1-8*01	IGHD2-15*01	IGHJ5*02	91.90	
P1156	IGHV3-13*01	IGHD3-3*01	IGHJ3*02	88.70	
P5283	IGHV3-20*01	IGHD6-19*01	IGHJ1*01	97.20	
P511	IGHV3-20*01	IGHD3-3*01	IGHJ5*02	100.00	
P2329	IGHV3-21*01	IGHD4-4*01	IGHJ4*02	96.30	
P7155	IGHV3-23*01	IGHD2-15*01	IGHJ3*02	100.00	
P2618	IGHV3-23*01	IGHD6-6*01	IGHJ4*02	95.90	
P8192	IGHV3-23*01	IGHD3-9*01	IGHJ4*02	91.90	
P7794	IGHV3-23*04	IGHD2-15*01	IGHJ4*02	87.85	
P6124	IGHV3-30*01	IGHD3-10*01	IGHJ5*02	100.00	
P9940	IGHV3-30*03	IGHD3-3*01	IGHJ6*03	94.44	
P4383	IGHV3-30*03	IGHD3-10*01	IGHJ4*02	95.10	
P6460	IGHV3-30*03	IGHD3-10*01	IGHJ6*02	94.10	
P1894	IGHV3-30*18	IGHD1-26*01	IGHJ3*02	92.90	
P427	IGHV3-30*18	IGHD5-24*01	IGHJ2*01	91.20	
P2577	IGHV3-33*01	IGHD6-6*01	IGHJ3*02	91.90	
P2548	IGHV3-33*01	IGHD2-15*01	IGHJ5*02	100.00	
P5231	IGHV3-43*01	IGHD5-5*01	IGHJ4*02	100.00	
P5728	IGHV3-48*01	IGHD3-16*01	IGHJ4*02	97.60	
P5949	IGHV3-49*03	IGHD1-1*01	IGHJ6*02	95.20	
P4875	IGHV3-53*02	IGHD2-15*01	IGHJ3*02	92.60	
P7961	IGHV3-64*05	IGHD3-3*01	IGHJ4*02	99.30	
P5017	IGHV3-7*01	IGHD2-2*01	IGHJ6*02	100.00	
P6068	IGHV3-7*01	IGHD3-22*01	IGHJ4*02	94.80	

*Continued*

Supplementary Table S2. *Continued.*

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P1055	IGHV3-74*02	IGHD4-17*01	IGHJ4*03	92.20
P1188	IGHV3-9*01	ND	IGHJ6*02	96.30
P280	IGHV4-31*01	IGHD4-4*01	IGHJ6*02	94.30
P2528	IGHV4-34*01	IGHD1-14*01	IGHJ4*02	95.60
P8699	IGHV4-34*01	IGHD3-3*01	IGHJ4*02	91.93
P5610	IGHV4-34*01	IGHD4-23*01	IGHJ6*02	94.70
P4557	IGHV4-34*01	IGHD2-2*01	IGHJ4*02	97.20
P3021	IGHV4-34*01	IGHD3-10*01	IGHJ3*02	93.50
P2740	IGHV4-34*01	IGHD4-4*01	IGHJ4*02	95.90
P1563	IGHV4-34*01	IGHD1-26*01	IGHJ6*03	93.20
P711	IGHV4-34*02	IGHD6-19*01	IGHJ4*03	97.40
P775	IGHV4-34*04	IGHD2-8*01	IGHJ3*01	94.10
P4994	IGHV4-34*12	IGHD6-6*01	IGHJ4*02	94.00
P104	IGHV4-39*06	IGHD2-2*01	IGHJ6*02	99.60
P1522	IGHV4-61*02	IGHD6-6*01	IGHJ3*02	98.30
P6264	IGHV5-51*01	IGHD2-2*01	IGHJ6*03	92.70
P9391	IGHV5-51*01	IGHD1-26*01	IGHJ4*02	93.40

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**Supplementary Table S3.** CD25 and CD86 expression after stimulation of TLRs and NOD2 with appropriate, specific ligands. The percentages are normalized to the unstimulated control.

M: mutated *IGHV*; U: Unmutated *IGHV*; M/4: mutated, subset #4; M/4-34: mutated, *IGHV*4-34 case, non subset #4/16; M/16: mutated, subset #16; UM/1: unmutated, subset #1; UM/8: unmutated, subset #8

CpG: ODN 2006; PAM: Pam3CSK4; M: MALP-2; I: imiquimod; L: loxoribine; O: ORN09

\*n: number of responsive cases.

Cohort	n*	median	range
CpG/CD25	67/67	55.9	10.7-94.9
CpG/CD86	44/67	24.9	0.8-82.6
PAM/CD25	57/67	37.5	1.7-89.4
PAM/CD86	49/67	28.4	2.6-74.6
M/CD25	55/67	29.8	2.1-80.1
M/CD86	44/67	15.5	-8.5-70.9
MDP/CD25	55/67	23.8	-1.4-72.1
MDP/CD86	35/67	10.3	-2-56.3
I/CD25	39/67	14.4	-9-93.7
I/CD86	21/67	4	-9.5-45.3
L/CD25	none	1.6	-6.7-9.6
L/CD86	4/67	0.25	-7.7-47.6
O/CD25	none	0.4	-6-9.8
O/CD86	none	0.1	-4.8-9.5
LPS/CD25	none	2.05	-8.2-9.7
LPS/CD86	none	0.8	-5.2-9.7

## MEDIAN VALUES

	M	UM	subset #4	subset #1	subset #16	subset #8	non #4/16
CpG/CD25	51.30	64.90	61.85	54.10	37.4	83	32.8
CpG/CD86	40.35	8.20	56.75	4.30	24.9	26.8	41.8
PAM/CD25	33.00	52.40	57.85	30.70	36.5	82.8	7.9
PAM/CD86	29.25	24.30	50.95	11.00	55.5	36.5	9.8
M/CD25	22.10	33.70	35.05	30.10	47	38.2	10.6
M/CD86	21.25	11.80	41.35	6.30	41.1	16.4	15.3
MDP/CD25	21.75	30.70	27.80	30.70	28.8	21	14.65
MDP/CD86	15.15	5.60	31.45	2.80	27.5	8.1	16.2
I/CD25	8.40	50.10	11.00	46.80	7.2	75.6	2.35
I/CD86	3.55	4.20	7.50	0.50	14.9	18.3	2
L/CD25	-4.95	2.35	-8.40	3.95	-11.7	-0.6	-5.2
L/CD86	-1.05	0.95	-2.80	0.20	-2.4	1.1	-1.2
O/CD25	0.40	0.55	-0.10	2.20	0.7	0.55	0.05
O/CD86	0.00	-0.15	-0.65	-0.20	0	1.25	-0.55
LPS/CD25	2.20	2.00	1.30	2.50	7	2.3	1.95
LPS/CD86	1.70	0.00	2.75	0.00	4.7	2.1	1.5

## P VALUES

	M vs. UM	#4 vs. #1	#4 vs. #16	#1 vs. #8	#4 vs. non #4/16	#16 vs. non #4/16	M vs. #4	M vs. #16	UM vs. #1	UM vs. #8
CpG/CD25	0.088	0.773	0.082	0.090	<b>0.022</b>	0.932	0.488	0.270	0.243	0.059
CpG/CD86	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.031</b>	<b>0.048</b>	0.118	0.428	0.055	0.451	0.174	0.274
PAM/CD25	0.071	0.427	0.373	<b>0.050</b>	<b>0.007</b>	0.193	0.252	0.984	0.145	<b>0.050</b>
PAM/CD86	0.361	<b>0.034</b>	0.869	0.162	<b>0.003</b>	<b>0.038</b>	0.093	0.265	0.275	0.194
M/CD25	0.002	0.692	0.254	0.588	<b>0.033</b>	<b>0.004</b>	0.276	<b>0.021</b>	0.582	0.515
M/CD86	0.181	<b>0.049</b>	0.298	0.699	<b>0.022</b>	<b>0.002</b>	0.080	<b>0.004</b>	0.492	0.853
MDP/CD25	0.073	0.979	0.429	0.942	<b>0.019</b>	0.262	0.320	0.907	0.697	0.930
MDP/CD86	<b>0.002</b>	<b>0.001</b>	0.270	0.795	<b>0.019</b>	0.395	<b>0.021</b>	0.508	0.540	0.969
I/CD25	<b>&lt;0.001</b>	<b>0.026</b>	0.910	0.073	0.009	0.035	0.638	0.686	0.433	<b>0.028</b>
I/CD86	0.134	0.057	0.983	0.074	0.214	0.285	0.405	0.530	0.200	<b>0.034</b>
L/CD25	0.000	0.003	0.337	0.338	0.503	0.195	0.284	0.073	0.338	0.288
L/CD86	0.451	0.452	0.897	0.181	0.181	0.310	0.169	0.270	0.252	0.073
O/CD25	0.389	0.095	0.411	0.438	0.540	0.291	0.436	0.471	0.037	0.786
O/CD86	0.629	0.525	0.463	0.373	0.776	0.516	0.834	0.596	0.367	0.349
LPS/CD25	0.640	0.737	0.041	0.781	0.997	0.015	0.473	0.000	0.516	0.001
LPS/CD86	0.637	0.372	0.077	0.488	0.663	0.077	0.751	0.005	0.460	0.001



**Supplementary Table S4.** Percentage of live cells after TLR and NOD2 stimulation. In cases where the percentage of live cells in the control was less than 10%, only the protective effect was evaluated.

CTL: control; C: CpG ODN 2006;  
P: Pam3CSK4; MA: MALP-2; M: MDP;  
I: imiquimod; L: loxoribine; O: ORN09;  
LP:LPS

Lab Identifier	median	range
CTL Day3	68.7	38-94.8
CTL Day6	50.35	0.8-91.5
CTL Day9	26	0.3-83.4
C Day3	63.9	6.4-96.7
C Day6	44.75	1.7-93.6
C Day9	22.7	0.3-83.2
P Day3	71.6	40.2-95.3
P Day6	60.45	3.8-92.9
P Day9	52.3	0.1-82.1
MA Day3	66	14.8-93.9
MA Day6	54.35	2.1-91.9
MA Day9	51.1	0.2-82.8
M Day3	78	0.9-97
M Day6	65.6	1.1-92.7
M Day9	62.4	0.2-88.9
I Day3	67.7	14.4-93.5
I Day6	31.35	0.5-86.3
I Day 9	8.6	0.3-56.1
L Day3	69.35	9.2-95.3
L Day6	35.8	3.6-93.3
L Day9	4.7	0.5-84.6
O Day3	72.55	37.3-94.5
O Day6	51.3	0.8-92.6
O Day9	28.95	0.5-86.7
LP Day3	70.2	14-94
LP Day6	51.9	0.9-93
LP Day9	26.4	0.4-82.2

**Supplementary Table S5.** Median and p values of live cells, after TLR and NOD2 stimulation, for all compared groups in the study.

Before analysis values were normalized to the unstimulated controls  
M:mutated *IGHV*; UM: Unmutated *IGHV*; non #4/16: mutated, *IGHV*4-34 case, non subset #4/16

C: CpG ODN 2006; P: Pam3CSK4; MA: MALP-2; M: MDP; I: imiquimod; L: loxoribine.

	Median Values				
	M	UM	subset #4	subset #1	non #4/16
C Day3	-7.5	7.7	-7.5	23.7	-35.5
P Day3	2.9	-1	5.85	5.7	-1.6
MA Day3	-3.3	-4.8	0.35	-2.95	-4.9
M Day3	2.95	5.5	9.75	18.3	-11
I Day3	-21.45	1.2	-1.9	8.7	-32.8
L Day3	-3.65	-3.2	3.8	0.2	-21.4
C Day6	-16.65	1.65	-14.1	4.55	-28.5
P Day6	1.65	-2.15	9.8	-0.9	-1.85
MA Day6	2.7	-4.2	6.6	-4.2	-5.8
M Day6	0.65	9.65	7	12.85	-0.75
I Day6	-27.3	-7.3	-18	3.2	-43.15
L Day6	-22.4	1.1	-14.3	0.25	-15.85
C Day9	0	-26.6	11.1	-6.85	-6.6
P Day9	16.9	-3.6	44.3	-1.65	15.3
MA Day9	17.1	-8.1	42.2	-8.1	6.8
M Day9	21.6	10.15	36.6	16.6	12.9
I Day 9	-24.5	-28.95	-24.9	-19.45	-40
L Day9	-11.3	-5	-17.25	-20.1	-14.2
	P VALUES				
	M vs. UM	#4 vs. #1	#4 vs. non #4/16	M vs. #4	UM vs. #1
C Day3	0.007	0.031	0.674	0.625	0.050
P Day3	0.341	0.456	0.058	0.495	0.068
MA Day3	0.629	0.736	0.934	0.687	0.171
M Day3	0.174	0.202	0.863	0.744	0.009
I Day3	0.007	0.198	0.188	0.290	0.145
L Day3	0.832	0.875	0.115	0.656	0.649
C Day6	0.006	0.198	0.543	0.621	0.660
P Day6	0.911	0.298	0.171	0.012	0.787
MA Day6	0.184	0.108	0.142	0.049	0.947
M Day6	0.102	0.498	0.491	0.308	0.735
I Day6	0.007	0.371	0.050	0.076	0.485
L Day6	0.422	0.849	0.543	0.450	0.633
C Day9	0.735	0.992	0.684	0.980	0.724
P Day9	0.006	0.003	0.080	0.029	0.726
MA Day9	0.001	0.001	0.050	0.026	0.952
M Day9	0.062	0.016	0.100	0.074	0.178
I Day 9	0.661	0.938	0.216	0.918	0.506
L Day9	0.473	0.777	0.984	0.568	0.695