Molecular Medicine

Supplemental Data

Temporal Dynamics of Clonal Evolution in Chronic Lymphocytic Leukemia with Stereotyped *IGHV4-34/IGKV2-30* Antigen Receptors: Longitudinal Immunogenetic Evidence

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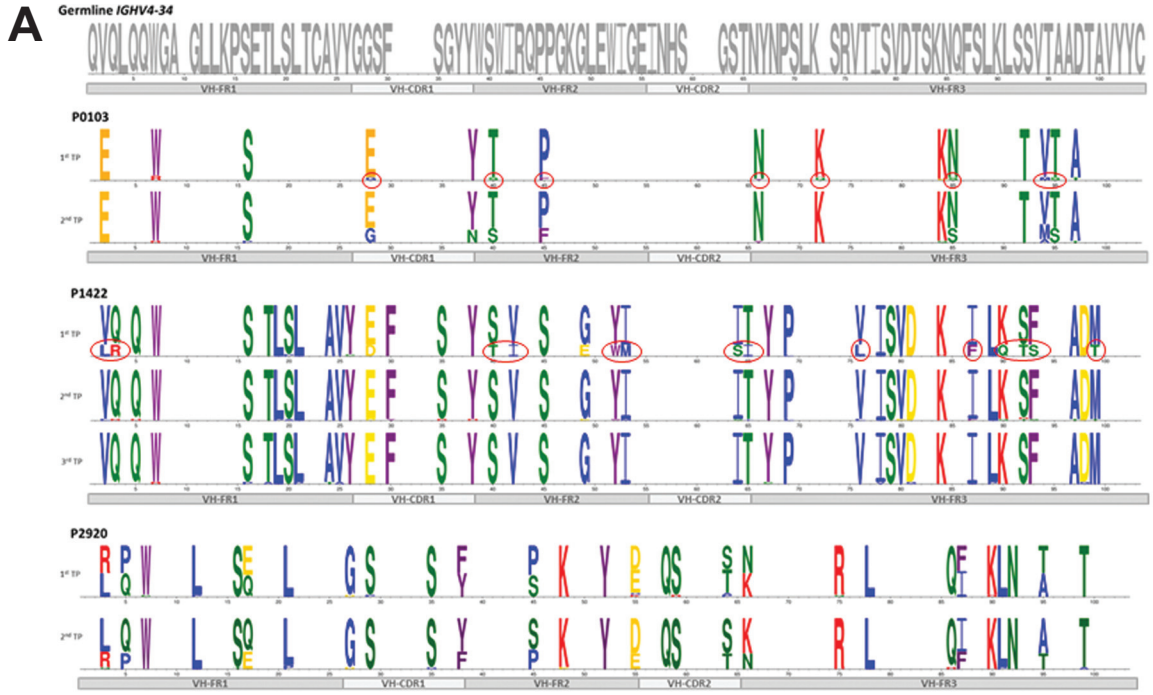

Supplementary Figure S1. Sequence logos (http://weblogo.threeplusone.com/) of alignments for both the *IGHV4-34* (A and C) and *IGKV2-30* (B and D) gene of P0103, P1422 and P2920. For the VH domain, IMGT positions 1 to 104 are represented while the VK sequences begin at position 12; each logo consists of stacks of symbols, one stack for each position of the sequence and the height of symbols within a stack indicates the relative frequency of each amino acid at that position. Blank positions indicate identity to the germline. Since unconfirmed amino acid changes or amino acids present at a low frequency occupy only a minor area within the stack, red circles are used to highlight the minor clone that persists in P0103 and also the minor clone that is undetectable at the third time-point of P1422. Logos representing the VH/VK CDR3 (IMGT positions 105-117) amino acid patterns of the aforementioned cases are also provided (C and D). Amino acids are divided in groups and color-coded as follows: GAPVLIM in blue, FYW in purple, STCNQ in green, KRH in red and DE in orange.

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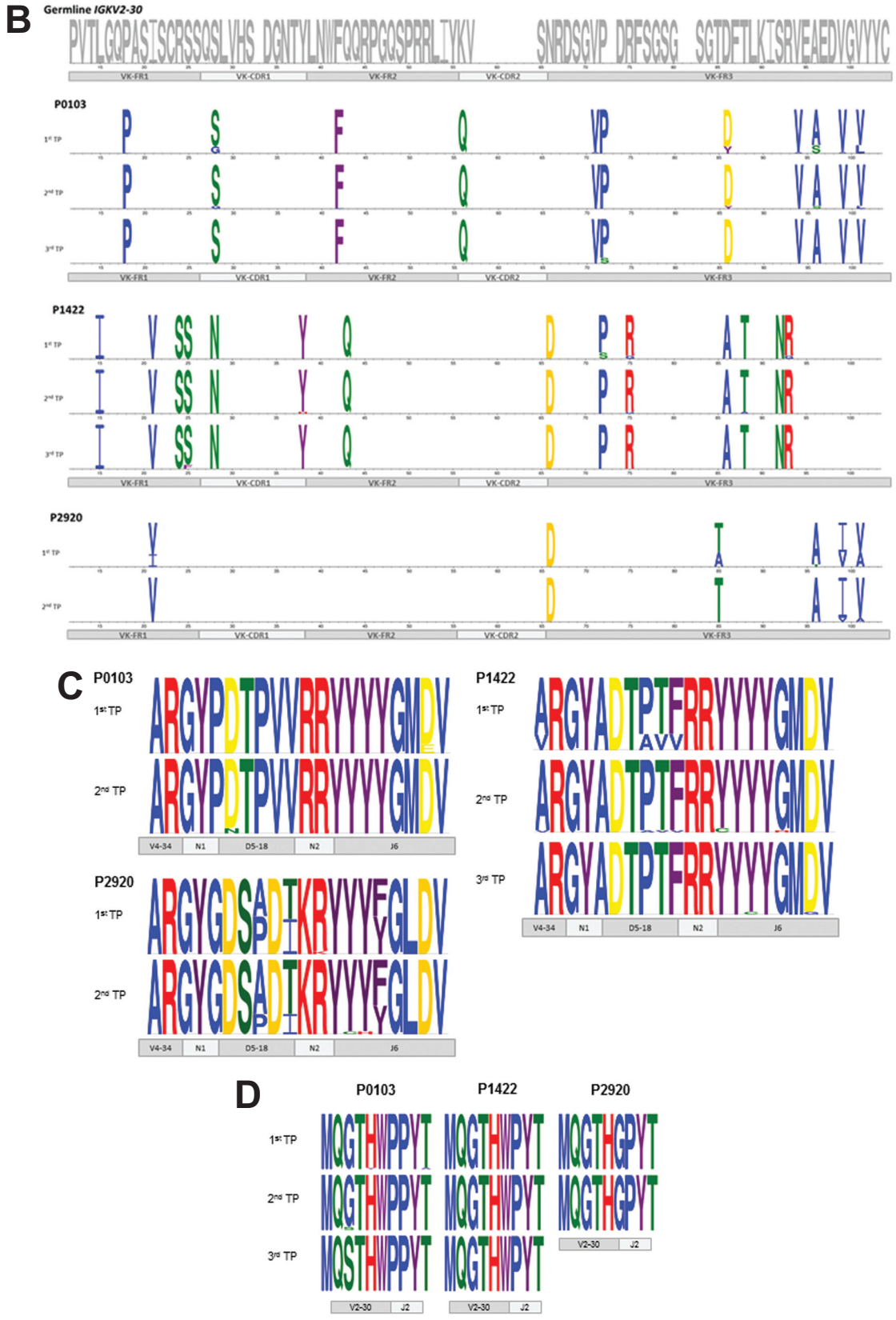
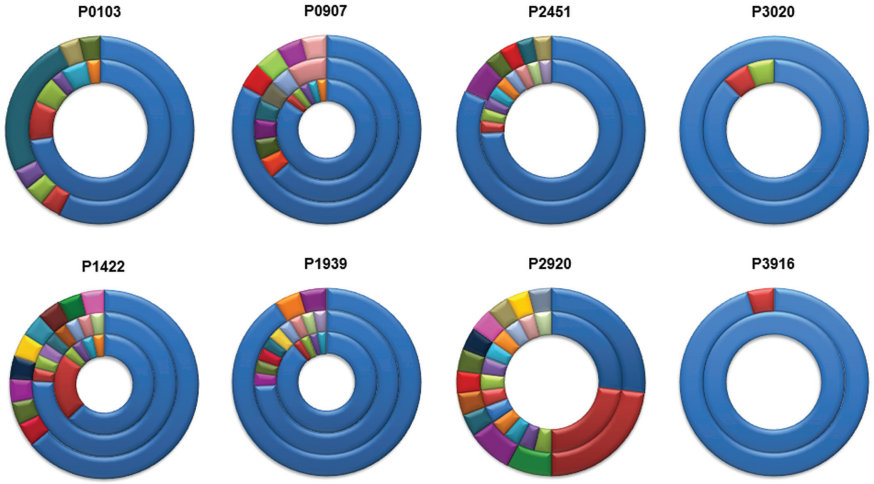
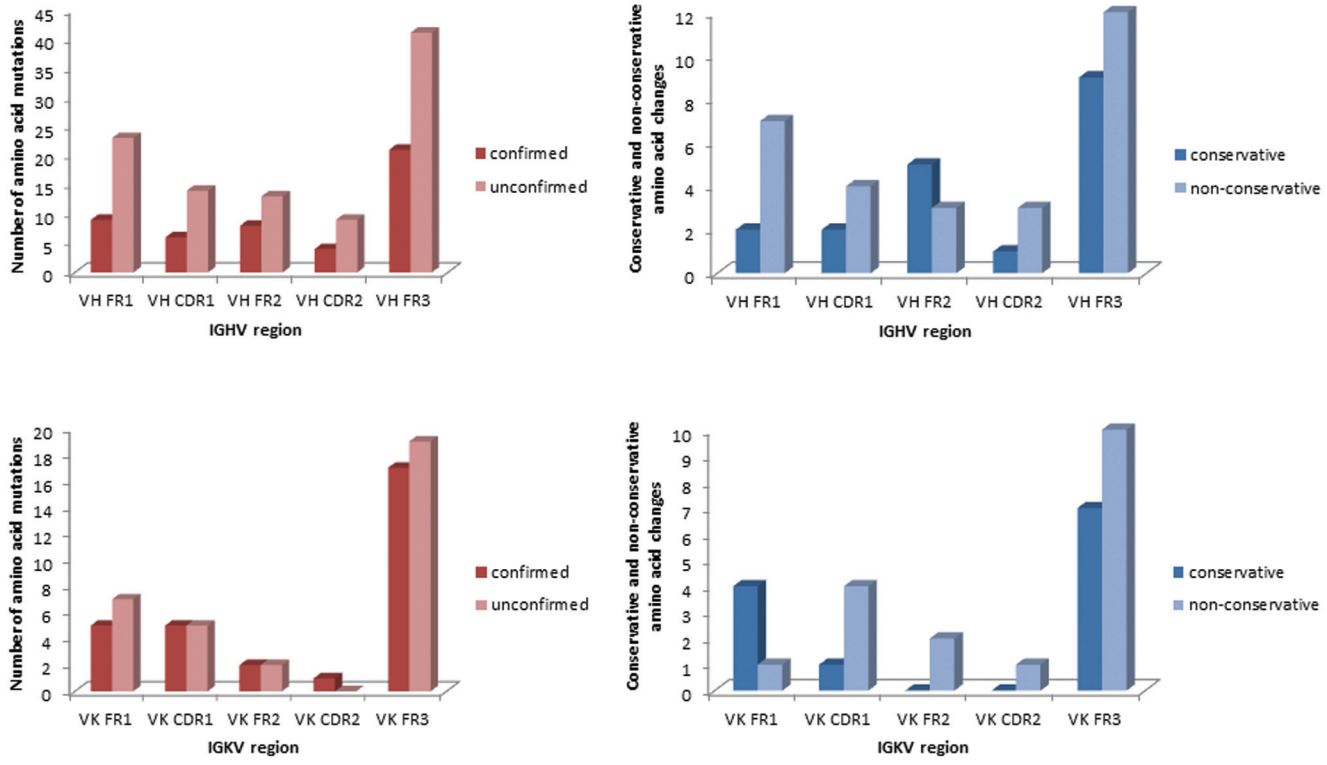


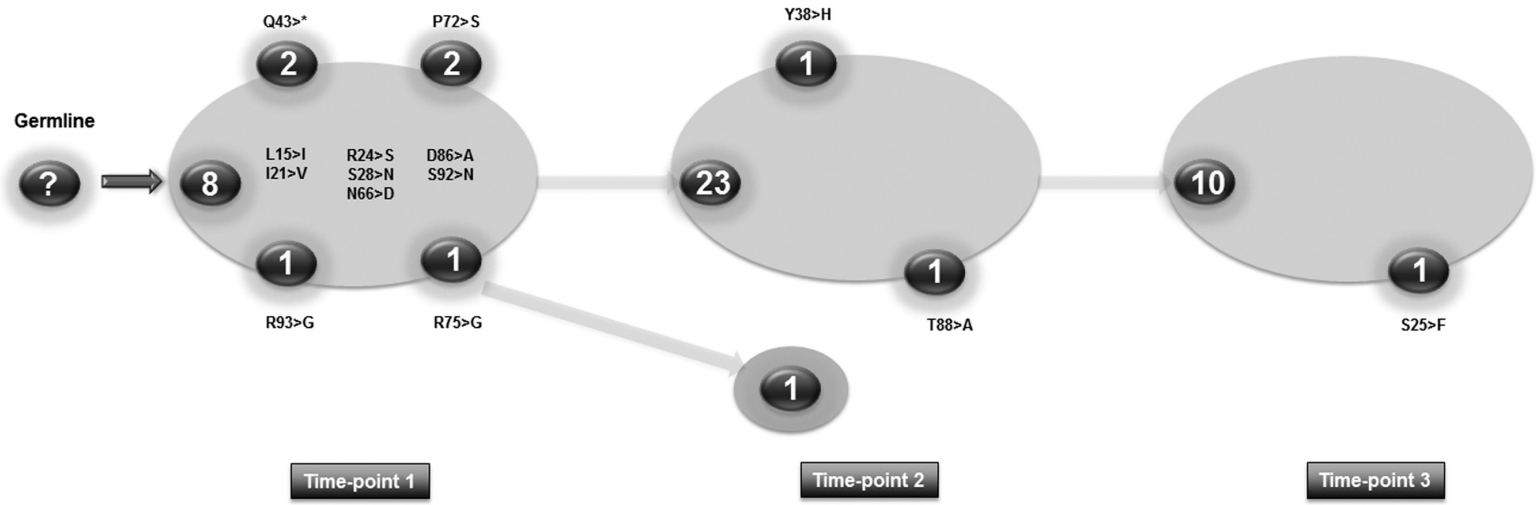
Supplementary Figure S1. *Continued.*



Supplementary Figure S2. Temporal intraclonal dynamics of CLL subset #4. The level of ID observed over time could be described as increasing, decreasing or complex, i.e. a mutation appears or disappears and then re-emerges at a subsequent time-point. The inner circle represents all the subcloned IGHV4-34 sequences analyzed for a particular patient at time-point 1. Each subsequent outer concentric circle represents additional time-points analyzed i.e. time-point 2 and time-point 3. At each time-point, clusters of identical sequences within the patient's repertoire are denoted by a different color. The same color is used at different time-points to indicate subclonal populations that have persisted. The major clone is marked in blue for all cases.



Supplementary Figure S3. Amino acid changes observed within the *IGHV4-34 and the IGKV2-30* gene of subset #4 cases analyzed.



Supplementary Figure S4. Schematic representation of temporal evolution within the *IGKV2-30* gene of CLL subset #4 (P1422). The majority of subcloned sequences at later time-points retain the mutational pattern of the initial clone while individual clones that acquire additional mutations are indicated by the black circles.

Supplementary Table S1. Demographics, clinical and molecular data for cases included in the present study.

Case identifier	Subset	Surface IGH	IGHV	Identity (%)	IGKV	Identity (%)	Sex	Date of diagnosis	Age at diagnosis	Rai	Binet	FISH data	Progression	Time to treatment (years)	Date of last follow-up	Current status
P2451	4	G	4-34*01	91.7	2-30*02	98.4	F	9/15/99	43	0	A	del 13q(26,6 %)	Yes	6.1	4/14/13	Alive
P3916	4	G	4-34*01	91.2	2-30*02	96.6	M	3/15/06	43	0	A	normal	No	not applicable	6/26/13	Alive
P3020	4	G	4-34*03	90.0	2-30*02	91.7	F	7/7/05	66	0	A	del 13q(15,2%)	No	not applicable	3/17/13	Alive
P1422	4	G	4-34*02	91.9	2-30*02	95.7	M	12/15/03	69	0	A	del 13q(11,5%)	No	not applicable	4/15/13	Alive
P1939	4	G	4-34*01	94.5	2-30*02	96.0	M	7/13/04	44	II	B	normal	Yes	1.6	6/20/13	Alive
P0103	4	G	4-34*01	95.9	2-30*02	97.3	F	9/21/95	45	0	A	normal	No	not applicable	4/8/13	Alive
P2920	4	G	4-34*01	93.5	2-30*02	97.3	M	6/10/05	51	0	A	normal	No	not applicable	6/27/13	Alive
P0907	4	G	4-34*02	93.2	2-30*02	97.0	F	2/15/03	54	0	A	del 13q(10%)	No	not applicable	6/21/13	Alive

Supplementary Table S2. IGHV-IGHD-IGHJ and IGKV-IGKJ rearrangements included in the present study.

TP: time-point; IG: immunoglobulin; VH: variable heavy; CDR3: complementarity determining region 3; D: diversity; J: joining; K: kappa; NA: not applicable; AA: amino acid.

Case	Subset	Surface IGH	IGHV	Identity (%)	IGHD	IGHJ	VH CDR3 length	VH CDR3 AA sequence	No. subcloned sequences analyzed			IGKV	Identity (%)	IGKJ	VK CDR3 length	VK CDR3 AA sequence	No. subcloned sequences analyzed		
									TP 1	TP2	TP3						TP 1	TP2	TP3
P2451	4	G	4-34*01	91.7	5-18*01	6*02	20	VRGYADTAVVRRYYYYGMDV	35	33	NA	2-30*02	98.4	2*01	10	MQGTHWPPYT	39	24	NA
P3916	4	G	4-34*01	91.2	2-15*01	6*02	20	ARGYADSDVIKRYYYYGMDV	17	22	NA	2-30*02	96.6	2*01	10	MQGTHWPPYT	15	13	NA
P3020	4	G	4-34*03	90.0	3-10*01	6*02	20	ARGYGTSDDTRRYYFYGMDV	16	21	NA	2-30*02	91.7	2*01	9	MQGSHGPYT	21	21	22
P1422	4	G	4-34*02	91.9	5-18*01	6*04	20	ARGYADTPTFRRYYYYGMDV	27	33	25	2-30*02	95.7	2*01	9	MQGTHWPYT	14	26	11
P1939	4	G	4-34*01	94.5	5-18*01	6*02	20	VRGYPDTAVVKRYYYYGMEV	35	35	21	2-30*02	96.0	2*01	10	MQGTHGPPTF	19	19	13
P0103	4	G	4-34*01	95.9	5-18*01	6*02	20	ARGYPDTPVVRRYYYYGMDV	33	28	NA	2-30*02	97.3	2*01	10	MQGTHWPPYT	38	33	8
P2920	4	G	4-34*01	93.5	4-17*01	6*02	20	ARGYGDSPDTKRYYYFGLDV	26	26	NA	2-30*02	97.3	2*01	9	MQGTHWPYT	18	11	NA
P0907	4	G	4-34*02	93.2	4-17*01	6*02	20	ARGYGTSATTKRYYYYGMDV	33	22	23	2-30*02	97.0	2*01	9	MQGTYWPYT	16	17	NA

*2 subclones from P1939 (one each from TP2 and TP3) utilize IGHJ6*01
*7 subclones from P1422 (six from TP1 and one from TP2) utilize IGHJ6*02
*2 subclones from P1422 (both from TP2) utilize IGHD3-3*01
*2 subclones from P1422 (both from TP3) utilize IGHD1-26*01
*1 subclone from P2920 (TP1) utilizes IGHD2-2*02
*1 subclone from P2920 (TP2) utilizes IGHD1-26*01
*1 subclone from P2451 (TP1) utilizes IGKJ2*02
*2 subclones from P2451 (both from TP1) have a VK CDR3 of 9 AA
*2 subclones from P1939 (both from TP1) have a VK CDR3 of 9 AA

Supplementary Table S3. Sampling period for cases included in the present study.

*TP: time-point; H: heavy; K: kappa; NA: not applicable. *sample material not available*

Case	Initial sample	TP1	Lympho-cytes ($x10^9$/l)	Sample date TP2S	Lympho-cytes ($x10^9$/l)	TP3	Lympho-cytes ($x10^9$/l)	Sampling period (months)	Case	TP1	Lympho-cytes ($x10^9$/l)	Sample date TP2	Lympho-cytes ($x10^9$/l)	TP3	Lympho-cytes ($x10^9$/l)	Sampling period (months)
P2451-H	63 months post-diagnosis	16-12-2004	69.3	03-10-2005	119.5	NA	NA	9.6	P2451-K	16-12-2004	69.3	03-10-2005	119.5	NA	NA	9.6
P3916-H	diagnosis	15-03-2006	5.2	25-06-2007	7.1	NA	NA	15.3	P3916-K	15-03-2006	5.2	25-06-2007	7.1	NA	NA	15.3
P3020-H	diagnosis	13-07-2005	9.2	15-05-2007	12.7	NA	NA	22	P3020-K	13-07-2005	9.2	15-05-2007	12.7	06-11-2008	18.9	39.8
P1422-H	diagnosis	15-12-2003	7.4	11-01-2005	6.8	27-09-2005	7.6	21.4	P1422-K	15-12-2003	7.4	11-01-2005	6.8	27-09-2005	7.6	21.4
P1939-H	diagnosis	14-07-2004	69.9	27-09-2005	50.5	14-02-2006	98.3	19.1	P1939-K	14-07-2004	69.9	27-09-2005	50.5	14-02-2006	98.3	19.1
P0103-H	81 months post-diagnosis	05-06-2002	33.1	21-12-2005	28.4	NA	NA	42.5	P0103-K	05-06-2002	33.1	21-12-2005	28.4	29-05-2008	32.8	71.8
P2920-H	diagnosis	14-06-2005	5.3	13-01-2006	5.2	NA	NA	7	P2920-K	14-06-2005	5.3	13-01-2006	5.2	NA	NA	7
P0907-H	diagnosis	15-02-2003	7.45	28-09-2004	24.5	16-05-2005	34.8	27	P0907-K	15-02-2003	7.45	NA*	24.5	16-05-2005	34.8	27

Supplementary Table S4. Incidence and topology of nucleotide mutations observed within the *IGHV4-34* gene of subset #4 cases included in the analysis.

Nucleotides are represented by a single-letter code. The number indicates the nucleotide position e.g. A8G in 28 clones indicates that 28 clones carry an adenine to guanine change at nucleotide position 8.

Total	87	confirmed	A8G in 28 clones, A8T in 29 clones, A12C in 6 clones, A14C in 22 clones, A33C in 53 clones, A33T in 49 clones, A113T in 23 clones, A124G in 53 clones, A165C in 30 clones, A165G in 3 clones, A169G in 2 clones, A189G in 2 clones, A189T in 2 clones, A214C in 2 clones, A225G in 52 clones, A234T in 39 clones, A240G in 103 clones, A254G in 10 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, A283G in 30 clones, C7G in 20 clones, C66G in 10 clones, C66T in 39 clones, C75T in 29 clones, C111T in 85 clones, C114T in 39 clones, C120T in 53 clones, C133T in 71 clones, C134T in 10 clones, C168T in 27 clones, C194T in 39 clones, C198G in 30 clones, C198T in 113 clones, C201T in 79 clones, C204T in 85 clones, C231G in 28 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 83 clones, C278T in 53 clones, C284G in 10 clones, C296T in 53 clones, C309T in 49 clones, G4T in 6 clones, G9A in 25 clones, G49C in 28 clones, G80T in 34 clones, G83A in 119 clones, G84C in 39 clones, G119C in 112 clones, G146A in 39 clones, G147A in 53 clones, G153A in 53 clones, G155A in 53 clones, G156C in 2 clones, G156T in 84 clones, G162A in 51 clones, G162T in 39 clones, G191C in 22 clones, G191T in 53 clones, G207A in 51 clones, G226C in 39 clones, G267T in 53 clones, G270A in 104 clones, G275C in 6 clones, G280A in 10 clones, G289A in 2 clones, G297T in 2 clones, G303C in 53 clones, T5A in 51 clones, T19C in 3 clones, T37C in 12 clones, T62C in 2 clones, T78C in 53 clones, T81A in 2 clones, T81G in 53 clones, T112A in 7 clones, T159G in 39 clones, T177C in 39 clones, T212C in 2 clones, T259A in 83 clones, T277A in 2 clones, T277C in 2 clones, T281C in 2 clones
Total	54	replacement	A8G in 28 clones, A8T in 29 clones, A14C in 22 clones, A113T in 23 clones, A124G in 53 clones, A165C in 30 clones, A169G in 2 clones, A214C in 2 clones, A240G in 1 clones, A254G in 10 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, A283G in 30 clones, C7G in 20 clones, C133T in 71 clones, C134T in 10 clones, C194T in 39 clones, C198G in 30 clones, C198T in 2 clones, C204T in 34 clones, C276T in 32 clones, C278T in 53 clones, C284G in 10 clones, C296T in 53 clones, G4T in 6 clones, G9A in 25 clones, G49C in 28 clones, G80T in 34 clones, G83A in 119 clones, G84C in 39 clones, G119C in 112 clones, G146A in 39 clones, G155A in 53 clones, G156C in 2 clones, G156T in 84 clones, G191C in 22 clones, G191T in 53 clones, G226C in 39 clones, G275C in 6 clones, G280A in 10 clones, G289A in 2 clones, T5A in 51 clones, T19C in 3 clones, T62C in 2 clones, T78C in 1 clones, T81A in 2 clones, T112A in 7 clones, T159G in 39 clones, T212C in 2 clones, T259A in 83 clones, T277A in 2 clones, T277C in 2 clones, T281C in 2 clones
Total	38	silent	A12C in 6 clones, A33C in 53 clones, A33T in 49 clones, A165G in 3 clones, A189G in 2 clones, A189T in 2 clones, A225G in 52 clones, A234T in 39 clones, A240G in 102 clones, C66G in 10 clones, C66T in 39 clones, C75T in 29 clones, C111T in 85 clones, C114T in 39 clones, C120T in 53 clones, C168T in 27 clones, C198T in 111 clones, C201T in 79 clones, C204T in 51 clones, C231G in 28 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 51 clones, C309T in 49 clones, G147A in 53 clones, G153A in 53 clones, G162A in 51 clones, G162T in 39 clones, G207A in 51 clones, G267T in 53 clones, G270A in 104 clones, G297T in 2 clones, G303C in 53 clones, T37C in 12 clones, T78C in 52 clones, T81G in 53 clones, T177C in 39 clones
Total	47	transition	A8G in 28 clones, A124G in 53 clones, A165G in 3 clones, A169G in 2 clones, A189G in 2 clones, A225G in 52 clones, A240G in 103 clones, A254G in 10 clones, A283G in 30 clones, C66T in 39 clones, C75T in 29 clones, C111T in 85 clones, C114T in 39 clones, C120T in 53 clones, C133T in 71 clones, C134T in 10 clones, C168T in 27 clones, C194T in 39 clones, C198T in 113 clones, C201T in 79 clones, C204T in 85 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 83 clones, C278T in 53 clones, C296T in 53 clones, C309T in 49 clones, G9A in 25 clones, G83A in 119 clones, G146A in 39 clones, G147A in 53 clones, G153A in 53 clones, G155A in 53 clones, G162A in 51 clones, G207A in 51 clones, G270A in 104 clones, G280A in 10 clones, G289A in 2 clones, T19C in 3 clones, T37C in 12 clones, T62C in 2 clones, T78C in 53 clones, T177C in 39 clones, T212C in 2 clones, T277C in 2 clones, T281C in 2 clones
Total	40	transversion	A8T in 29 clones, A12C in 6 clones, A14C in 22 clones, A33C in 53 clones, A33T in 49 clones, A113T in 23 clones, A165C in 30 clones, A189T in 2 clones, A214C in 2 clones, A234T in 39 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, C7G in 20 clones, C66G in 10 clones, C198G in 30 clones, C231G in 28 clones, C284G in 10 clones, G4T in 6 clones, G49C in 28 clones, G80T in 34 clones, G84C in 39 clones, G119C in 112 clones, G156C in 2 clones, G156T in 84 clones, G162T in 39 clones, G191C in 22 clones, G191T in 53 clones, G226C in 39 clones, G267T in 53 clones, G275C in 6 clones, G297T in 2 clones, G303C in 53 clones, T5A in 51 clones, T81A in 2 clones, T81G in 53 clones, T112A in 7 clones, T159G in 39 clones, T259A in 83 clones, T277A in 2 clones

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Supplementary Table S4. ***Continued.***

Total	137	unconfirmed	A8G in 1 clones, A12C in 1 clones, A12G in 1 clones, A14G in 1 clones, A15T in 1 clones, A27G in 3 clones, A33T in 1 clones, A40G in 1 clones, A50G in 1 clones, A52G in 1 clones, A77G in 1 clones, A103G in 2 clones, A110G in 1 clones, A138G in 1 clones, A142G in 1 clones, A143G in 1 clones, A164G in 2 clones, A165G in 3 clones, A169G in 1 clones, A169T in 1 clones, A173G in 1 clones, A175G in 1 clones, A190C in 1 clones, A190G in 1 clones, A196G in 3 clones, A196T in 2 clones, A200G in 1 clones, A232G in 1 clones, A234T in 1 clones, A242G in 1 clones, A244G in 3 clones, A250C in 1 clones, A250G in 1 clones, A251G in 1 clones, A254C in 1 clones, A254G in 1 clones, A257G in 1 clones, A268C in 1 clones, A269G in 1 clones, A274G in 1 clones, A274T in 1 clones, A293G in 1 clones, A295G in 2 clones, A308G in 1 clones, C53T in 1 clones, C66G in 1 clones, C66T in 1 clones, C69T in 1 clones, C75T in 1 clones, C111T in 1 clones, C114T in 1 clones, C126G in 1 clones, C134T in 1 clones, C194A in 1 clones, C194T in 1 clones, C198T in 1 clones, C201T in 1 clones, C204T in 1 clones, C206T in 2 clones, C210T in 1 clones, C231T in 1 clones, C236T in 1 clones, C249T in 1 clones, C264A in 1 clones, C271T in 1 clones, C276A in 1 clones, C284G in 1 clones, C288T in 1 clones, C290T in 1 clones, C309T in 2 clones, G4T in 1 clones, G9A in 1 clones, G21T in 1 clones, G32A in 1 clones, G48C in 1 clones, G57A in 1 clones, G70A in 1 clones, G80A in 3 clones, G84A in 2 clones, G84C in 1 clones, G106A in 1 clones, G119C in 1 clones, G119T in 1 clones, G139A in 1 clones, G146A in 1 clones, G162A in 2 clones, G162T in 1 clones, G163A in 1 clones, G207A in 1 clones, G224A in 1 clones, G226A in 1 clones, G226C in 1 clones, G246C in 1 clones, G270A in 1 clones, G275C in 1 clones, G280A in 1 clones, G286A in 2 clones, G289A in 2 clones, G291A in 1 clones, G297A in 2 clones, T5G in 1 clones, T19C in 2 clones, T35C in 1 clones, T46A in 1 clones, T46C in 2 clones, T56C in 1 clones, T58C in 1 clones, T58G in 1 clones, T62C in 2 clones, T72A in 2 clones, T74C in 1 clones, T76C in 1 clones, T81A in 1 clones, T85C in 1 clones, T88A in 1 clones, T89A in 2 clones, T105A in 2 clones, T109A in 1 clones, T109C in 1 clones, T112C in 1 clones, T121G in 1 clones, T125C in 2 clones, T159C in 1 clones, T159G in 2 clones, T177A in 2 clones, T177C in 1 clones, T212C in 1 clones, T227C in 1 clones, T235A in 1 clones, T239A in 1 clones, T247C in 1 clones, T259C in 2 clones, T266C in 2 clones, T272C in 1 clones, T302A in 1 clones, T306C in 1 clones, T307A in 2 clones
VH FR	70	confirmed	A8G in 28 clones, A8T in 29 clones, A12C in 6 clones, A14C in 22 clones, A33C in 53 clones, A33T in 49 clones, A124G in 53 clones, A165C in 30 clones, A165G in 3 clones, A214C in 2 clones, A225G in 52 clones, A234T in 39 clones, A240G in 103 clones, A254G in 10 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, A283G in 30 clones, C7G in 20 clones, C66G in 10 clones, C66T in 39 clones, C75T in 29 clones, C120T in 53 clones, C133T in 71 clones, C134T in 10 clones, C198G in 30 clones, C198T in 113 clones, C201T in 79 clones, C204T in 85 clones, C231G in 28 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 83 clones, C278T in 53 clones, C284G in 10 clones, C296T in 53 clones, C309T in 49 clones, G4T in 6 clones, G9A in 25 clones, G49C in 28 clones, G119C in 112 clones, G146A in 39 clones, G147A in 53 clones, G153A in 53 clones, G155A in 53 clones, G156C in 2 clones, G156T in 84 clones, G162A in 51 clones, G162T in 39 clones, G207A in 51 clones, G226C in 39 clones, G267T in 53 clones, G270A in 104 clones, G275C in 6 clones, G280A in 10 clones, G289A in 2 clones, G297T in 2 clones, G303C in 53 clones, T5A in 51 clones, T19C in 3 clones, T37C in 12 clones, T62C in 2 clones, T78C in 53 clones, T159G in 39 clones, T212C in 2 clones, T259A in 83 clones, T277A in 2 clones, T277C in 2 clones, T281C in 2 clones
VH CDR	17	confirmed	A113T in 23 clones, A169G in 2 clones, A189G in 2 clones, A189T in 2 clones, C111T in 85 clones, C114T in 39 clones, C168T in 27 clones, C194T in 39 clones, G80T in 34 clones, G83A in 119 clones, G84C in 39 clones, G191C in 22 clones, G191T in 53 clones, T81A in 2 clones, T81G in 53 clones, T112A in 7 clones, T177C in 39 clones
VH FR1	18	confirmed	A8G in 28 clones, A8T in 29 clones, A12C in 6 clones, A14C in 22 clones, A33C in 53 clones, A33T in 49 clones, C7G in 20 clones, C66G in 10 clones, C66T in 39 clones, C75T in 29 clones, G4T in 6 clones, G9A in 25 clones, G49C in 28 clones, T5A in 51 clones, T19C in 3 clones, T37C in 12 clones, T62C in 2 clones, T78C in 53 clones
VH CDR1	9	confirmed	A113T in 23 clones, C111T in 85 clones, C114T in 39 clones, G80T in 34 clones, G83A in 119 clones, G84C in 39 clones, T81A in 2 clones, T81G in 53 clones, T112A in 7 clones
VH FR2	16	confirmed	A124G in 53 clones, A165C in 30 clones, A165G in 3 clones, C120T in 53 clones, C133T in 71 clones, C134T in 10 clones, G119C in 112 clones, G146A in 39 clones, G147A in 53 clones, G153A in 53 clones, G155A in 53 clones, G156C in 2 clones, G156T in 84 clones, G162A in 51 clones, G162T in 39 clones, T159G in 39 clones
VH CDR2	8	confirmed	A169G in 2 clones, A189G in 2 clones, A189T in 2 clones, C168T in 27 clones, C194T in 39 clones, G191C in 22 clones, G191T in 53 clones, T177C in 39 clones

Continued on next page

Supplementary Table S4. ***Continued.***

VH FR3	36	confirmed	A214C in 2 clones, A225G in 52 clones, A234T in 39 clones, A240G in 103 clones, A254G in 10 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, A283G in 30 clones, C198G in 30 clones, C198T in 113 clones, C201T in 79 clones, C204T in 85 clones, C231G in 28 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 83 clones, C278T in 53 clones, C284G in 10 clones, C296T in 53 clones, C309T in 49 clones, G207A in 51 clones, G226C in 39 clones, G267T in 53 clones, G270A in 104 clones, G275C in 6 clones, G280A in 10 clones, G289A in 2 clones, G297T in 2 clones, G303C in 53 clones, T212C in 2 clones, T259A in 83 clones, T277A in 2 clones, T277C in 2 clones, T281C in 2 clones
VH FR	44	replacement	A8G in 28 clones, A8T in 29 clones, A14C in 22 clones, A124G in 53 clones, A165C in 30 clones, A214C in 2 clones, A240G in 1 clones, A254G in 10 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, A283G in 30 clones, C7G in 20 clones, C133T in 71 clones, C134T in 10 clones, C198G in 30 clones, C198T in 2 clones, C204T in 34 clones, C276T in 32 clones, C278T in 53 clones, C284G in 10 clones, C296T in 53 clones, G4T in 6 clones, G9A in 25 clones, G49C in 28 clones, G119C in 112 clones, G146A in 39 clones, G155A in 53 clones, G156C in 2 clones, G156T in 84 clones, G226C in 39 clones, G275C in 6 clones, G280A in 10 clones, G289A in 2 clones, T5A in 51 clones, T19C in 3 clones, T62C in 2 clones, T78C in 1 clones, T159G in 39 clones, T212C in 2 clones, T259A in 83 clones, T277A in 2 clones, T277C in 2 clones, T281C in 2 clones
VH CDR	10	replacement	A113T in 23 clones, A169G in 2 clones, C194T in 39 clones, G80T in 34 clones, G83A in 119 clones, G84C in 39 clones, G191C in 22 clones, G191T in 53 clones, T81A in 2 clones, T112A in 7 clones
VH FR1	11	replacement	A8G in 28 clones, A8T in 29 clones, A14C in 22 clones, C7G in 20 clones, G4T in 6 clones, G9A in 25 clones, G49C in 28 clones, T5A in 51 clones, T19C in 3 clones, T62C in 2 clones, T78C in 1 clones
VH CDR1	6	replacement	A113T in 23 clones, G80T in 34 clones, G83A in 119 clones, G84C in 39 clones, T81A in 2 clones, T112A in 7 clones
VH FR2	10	replacement	A124G in 53 clones, A165C in 30 clones, C133T in 71 clones, C134T in 10 clones, G119C in 112 clones, G146A in 39 clones, G155A in 53 clones, G156C in 2 clones, G156T in 84 clones, T159G in 39 clones
VH CDR2	4	replacement	A169G in 2 clones, C194T in 39 clones, G191C in 22 clones, G191T in 53 clones
VH FR3	23	replacement	A214C in 2 clones, A240G in 1 clones, A254G in 10 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, A283G in 30 clones, C198G in 30 clones, C198T in 2 clones, C204T in 34 clones, C276T in 32 clones, C278T in 53 clones, C284G in 10 clones, C296T in 53 clones, G226C in 39 clones, G275C in 6 clones, G280A in 10 clones, G289A in 2 clones, T212C in 2 clones, T259A in 83 clones, T277A in 2 clones, T277C in 2 clones, T281C in 2 clones
VH FR	31	silent	A12C in 6 clones, A33C in 53 clones, A33T in 49 clones, A165G in 3 clones, A225G in 52 clones, A234T in 39 clones, A240G in 102 clones, C66G in 10 clones, C66T in 39 clones, C75T in 29 clones, C120T in 53 clones, C198T in 111 clones, C201T in 79 clones, C204T in 51 clones, C231G in 28 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 51 clones, C309T in 49 clones, G147A in 53 clones, G153A in 53 clones, G162A in 51 clones, G162T in 39 clones, G207A in 51 clones, G267T in 53 clones, G270A in 104 clones, G297T in 2 clones, G303C in 53 clones, T37C in 12 clones, T78C in 52 clones
VH CDR	7	silent	A189G in 2 clones, A189T in 2 clones, C111T in 85 clones, C114T in 39 clones, C168T in 27 clones, T81G in 53 clones, T177C in 39 clones
VH FR1	8	silent	A12C in 6 clones, A33C in 53 clones, A33T in 49 clones, C66G in 10 clones, C66T in 39 clones, C75T in 29 clones, T37C in 12 clones, T78C in 52 clones
VH CDR1	3	silent	C111T in 85 clones, C114T in 39 clones, T81G in 53 clones
VH FR2	6	silent	A165G in 3 clones, C120T in 53 clones, G147A in 53 clones, G153A in 53 clones, G162A in 51 clones, G162T in 39 clones
VH CDR2	4	silent	A189G in 2 clones, A189T in 2 clones, C168T in 27 clones, T177C in 39 clones
VH FR3	17	silent	A225G in 52 clones, A234T in 39 clones, A240G in 102 clones, C198T in 111 clones, C201T in 79 clones, C204T in 51 clones, C231G in 28 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 51 clones, C309T in 49 clones, G207A in 51 clones, G267T in 53 clones, G270A in 104 clones, G297T in 2 clones, G303C in 53 clones
VH FR	39	transition	A8G in 28 clones, A124G in 53 clones, A165G in 3 clones, A225G in 52 clones, A240G in 103 clones, A254G in 10 clones, A283G in 30 clones, C66T in 39 clones, C75T in 29 clones, C120T in 53 clones, C133T in 71 clones, C134T in 10 clones, C198T in 113 clones, C201T in 79 clones, C204T in 85 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 83 clones, C278T in 53 clones, C296T in 53 clones, C309T in 49 clones, G9A in 25 clones, G146A in 39 clones, G147A in 53 clones, G153A in 53 clones, G155A in 53 clones, G162A in 51 clones, G207A in 51 clones, G270A in 104 clones, G280A in 10 clones, G289A in 2 clones, T19C in 3 clones, T37C in 12 clones, T62C in 2 clones, T78C in 53 clones, T212C in 2 clones, T277C in 2 clones, T281C in 2 clones
VH CDR	8	transition	A169G in 2 clones, A189G in 2 clones, C111T in 85 clones, C114T in 39 clones, C168T in 27 clones, C194T in 39 clones, G83A in 119 clones, T177C in 39 clones

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Supplementary Table S4. ***Continued.***

VH FR1	8	transition	A8G in 28 clones, C66T in 39 clones, C75T in 29 clones, G9A in 25 clones, T19C in 3 clones, T37C in 12 clones, T62C in 2 clones, T78C in 53 clones
VH CDR1	3	transition	C111T in 85 clones, C114T in 39 clones, G83A in 119 clones
VH FR2	10	transition	A124G in 53 clones, A165G in 3 clones, C120T in 53 clones, C133T in 71 clones, C134T in 10 clones, G146A in 39 clones, G147A in 53 clones, G153A in 53 clones, G155A in 53 clones, G162A in 51 clones
VH CDR2	5	transition	A169G in 2 clones, A189G in 2 clones, C168T in 27 clones, C194T in 39 clones, T177C in 39 clones
VH FR3	21	transition	A225G in 52 clones, A240G in 103 clones, A254G in 10 clones, A283G in 30 clones, C198T in 113 clones, C201T in 79 clones, C204T in 85 clones, C249T in 39 clones, C255T in 29 clones, C271T in 39 clones, C276T in 83 clones, C278T in 53 clones, C296T in 53 clones, C309T in 49 clones, G207A in 51 clones, G270A in 104 clones, G280A in 10 clones, G289A in 2 clones, T212C in 2 clones, T277C in 2 clones, T281C in 2 clones
VH FR	31	transversion	A8T in 29 clones, A12C in 6 clones, A14C in 22 clones, A33C in 53 clones, A33T in 49 clones, A165C in 30 clones, A214C in 2 clones, A234T in 39 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, C7G in 20 clones, C66G in 10 clones, C198G in 30 clones, C231G in 28 clones, C284G in 10 clones, G4T in 6 clones, G49C in 28 clones, G119C in 112 clones, G156C in 2 clones, G156T in 84 clones, G162T in 39 clones, G226C in 39 clones, G267T in 53 clones, G275C in 6 clones, G297T in 2 clones, G303C in 53 clones, T5A in 51 clones, T159G in 39 clones, T259A in 83 clones, T277A in 2 clones
VH CDR	9	transversion	A113T in 23 clones, A189T in 2 clones, G80T in 34 clones, G84C in 39 clones, G191C in 22 clones, G191T in 53 clones, T81A in 2 clones, T81G in 53 clones, T112A in 7 clones
VH FR1	10	transversion	A8T in 29 clones, A12C in 6 clones, A14C in 22 clones, A33C in 53 clones, A33T in 49 clones, C7G in 20 clones, C66G in 10 clones, G4T in 6 clones, G49C in 28 clones, T5A in 51 clones
VH CDR1	6	transversion	A113T in 23 clones, G80T in 34 clones, G84C in 39 clones, T81A in 2 clones, T81G in 53 clones, T112A in 7 clones
VH FR2	6	transversion	A165C in 30 clones, G119C in 112 clones, G156C in 2 clones, G156T in 84 clones, G162T in 39 clones, T159G in 39 clones
VH CDR2	3	transversion	A189T in 2 clones, G191C in 22 clones, G191T in 53 clones
VH FR3	15	transversion	A214C in 2 clones, A234T in 39 clones, A268C in 39 clones, A268T in 3 clones, A274C in 2 clones, C198G in 30 clones, C231G in 28 clones, C284G in 10 clones, G226C in 39 clones, G267T in 53 clones, G275C in 6 clones, G297T in 2 clones, G303C in 53 clones, T259A in 83 clones, T277A in 2 clones
VH FR	111	unconfirmed	A8G in 1 clones, A12C in 1 clones, A12G in 1 clones, A14G in 1 clones, A15T in 1 clones, A27G in 3 clones, A33T in 1 clones, A40G in 1 clones, A50G in 1 clones, A52G in 1 clones, A77G in 1 clones, A138G in 1 clones, A142G in 1 clones, A143G in 1 clones, A164G in 2 clones, A165G in 3 clones, A196G in 3 clones, A196T in 2 clones, A200G in 1 clones, A232G in 1 clones, A234T in 1 clones, A242G in 1 clones, A244G in 3 clones, A250C in 1 clones, A250G in 1 clones, A251G in 1 clones, A254C in 1 clones, A254G in 1 clones, A257G in 1 clones, A268C in 1 clones, A269G in 1 clones, A274G in 1 clones, A274T in 1 clones, A293G in 1 clones, A295G in 2 clones, A308G in 1 clones, C53T in 1 clones, C66G in 1 clones, C66T in 1 clones, C69T in 1 clones, C75T in 1 clones, C126G in 1 clones, C134T in 1 clones, C198T in 1 clones, C201T in 1 clones, C204T in 1 clones, C206T in 2 clones, C210T in 1 clones, C231T in 1 clones, C236T in 1 clones, C249T in 1 clones, C264A in 1 clones, C271T in 1 clones, C276A in 1 clones, C284G in 1 clones, C288T in 1 clones, C290T in 1 clones, C309T in 2 clones, G4T in 1 clones, G9A in 1 clones, G21T in 1 clones, G32A in 1 clones, G48C in 1 clones, G57A in 1 clones, G70A in 1 clones, G119C in 1 clones, G119T in 1 clones, G139A in 1 clones, G146A in 1 clones, G162A in 2 clones, G162T in 1 clones, G163A in 1 clones, G207A in 1 clones, G224A in 1 clones, G226A in 1 clones, G226C in 1 clones, G246C in 1 clones, G270A in 1 clones, G275C in 1 clones, G280A in 1 clones, G286A in 2 clones, G289A in 2 clones, G291A in 1 clones, G297A in 2 clones, T5G in 1 clones, T19C in 2 clones, T35C in 1 clones, T46A in 1 clones, T46C in 2 clones, T56C in 1 clones, T58C in 1 clones, T58G in 1 clones, T62C in 2 clones, T72A in 2 clones, T74C in 1 clones, T76C in 1 clones, T121G in 1 clones, T125C in 2 clones, T159C in 1 clones, T159G in 2 clones, T212C in 1 clones, T227C in 1 clones, T235A in 1 clones, T239A in 1 clones, T247C in 1 clones, T259C in 2 clones, T266C in 2 clones, T272C in 1 clones, T302A in 1 clones, T306C in 1 clones, T307A in 2 clones
VH CDR	26	unconfirmed	A103G in 2 clones, A110G in 1 clones, A169G in 1 clones, A169T in 1 clones, A173G in 1 clones, A175G in 1 clones, A190C in 1 clones, A190G in 1 clones, C111T in 1 clones, C114T in 1 clones, C194A in 1 clones, C194T in 1 clones, G80A in 3 clones, G84A in 2 clones, G84C in 1 clones, G106A in 1 clones, T81A in 1 clones, T85C in 1 clones, T88A in 1 clones, T89A in 2 clones, T105A in 2 clones, T109A in 1 clones, T109C in 1 clones, T112C in 1 clones, T177A in 2 clones, T177C in 1 clones

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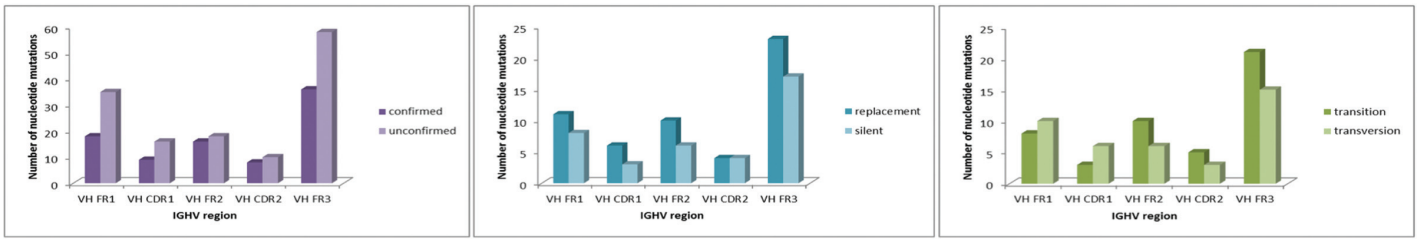
Supplementary Table S4. ***Continued.***

VH FR1	35	unconfirmed	A8G in 1 clones, A12C in 1 clones, A12G in 1 clones, A14G in 1 clones, A15T in 1 clones, A27G in 3 clones, A33T in 1 clones, A40G in 1 clones, A50G in 1 clones, A52G in 1 clones, A77G in 1 clones, C53T in 1 clones, C66G in 1 clones, C66T in 1 clones, C69T in 1 clones, C75T in 1 clones, G4T in 1 clones, G9A in 1 clones, G21T in 1 clones, G32A in 1 clones, G48C in 1 clones, G57A in 1 clones, G70A in 1 clones, T5G in 1 clones, T19C in 2 clones, T35C in 1 clones, T46A in 1 clones, T46C in 2 clones, T56C in 1 clones, T58C in 1 clones, T58G in 1 clones, T62C in 2 clones, T72A in 2 clones, T74C in 1 clones, T76C in 1 clones
VH CDR1	16	unconfirmed	A103G in 2 clones, A110G in 1 clones, C111T in 1 clones, C114T in 1 clones, G80A in 3 clones, G84A in 2 clones, G84C in 1 clones, G106A in 1 clones, T81A in 1 clones, T85C in 1 clones, T88A in 1 clones, T89A in 2 clones, T105A in 2 clones, T109A in 1 clones, T109C in 1 clones, T112C in 1 clones
VH FR2	18	unconfirmed	A138G in 1 clones, A142G in 1 clones, A143G in 1 clones, A164G in 2 clones, A165G in 3 clones, C126G in 1 clones, C134T in 1 clones, G119C in 1 clones, G119T in 1 clones, G139A in 1 clones, G146A in 1 clones, G162A in 2 clones, G162T in 1 clones, G163A in 1 clones, T121G in 1 clones, T125C in 2 clones, T159C in 1 clones, T159G in 2 clones
VH CDR2	10	unconfirmed	A169G in 1 clones, A169T in 1 clones, A173G in 1 clones, A175G in 1 clones, A190C in 1 clones, A190G in 1 clones, C194A in 1 clones, C194T in 1 clones, T177A in 2 clones, T177C in 1 clones
VH FR3	58	unconfirmed	A196G in 3 clones, A196T in 2 clones, A200G in 1 clones, A232G in 1 clones, A234T in 1 clones, A242G in 1 clones, A244G in 3 clones, A250C in 1 clones, A250G in 1 clones, A251G in 1 clones, A254C in 1 clones, A254G in 1 clones, A257G in 1 clones, A268C in 1 clones, A269G in 1 clones, A274G in 1 clones, A274T in 1 clones, A293G in 1 clones, A295G in 2 clones, A308G in 1 clones, C198T in 1 clones, C201T in 1 clones, C204T in 1 clones, C206T in 2 clones, C210T in 1 clones, C231T in 1 clones, C236T in 1 clones, C249T in 1 clones, C264A in 1 clones, C271T in 1 clones, C276A in 1 clones, C284G in 1 clones, C288T in 1 clones, C290T in 1 clones, C309T in 2 clones, G207A in 1 clones, G224A in 1 clones, G226A in 1 clones, G226C in 1 clones, G246C in 1 clones, G270A in 1 clones, G275C in 1 clones, G280A in 1 clones, G286A in 2 clones, G289A in 2 clones, G291A in 1 clones, G297A in 2 clones, T212C in 1 clones, T227C in 1 clones, T235A in 1 clones, T239A in 1 clones, T247C in 1 clones, T259C in 2 clones, T266C in 2 clones, T272C in 1 clones, T302A in 1 clones, T306C in 1 clones, T307A in 2 clones



Supplementary Table S5. Incidence and topology of nucleotide mutations observed within the *IGKV2-30* gene of subset #4 cases included in the analysis.

Nucleotides are represented by a single-letter code. The number indicates the nucleotide position e.g. A61G in 18 clones indicates that 18 clones carry an adenine to guanine change at nucleotide position 61.

Total	53	confirmed	A61G in 18 clones, A81G in 12 clones, A82G in 8 clones, A90G in 100 clones, A105G in 66 clones, A109G in 2 clones, A159G in 17 clones, A196G in 4 clones, A197C in 12 clones, A253G in 6 clones, A257C in 2 clones, A257G in 2 clones, A284G in 2 clones, C43A in 2 clones, C63T in 12 clones, C74G in 17 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, C127T in 2 clones, C130T in 7 clones, C156T in 2 clones, C194T in 2 clones, C214T in 2 clones, C276G in 12 clones, C309T in 2 clones, G72T in 2 clones, G77C in 12 clones, G83A in 2 clones, G104A in 2 clones, G117A in 2 clones, G129A in 49 clones, G129C in 2 clones, G129T in 17 clones, G256T in 8 clones, G275A in 2 clones, G282A in 12 clones, G286T in 9 clones, G291A in 8 clones, G291C in 17 clones, G295A in 22 clones, G300A in 66 clones, G300C in 17 clones, G301A in 37 clones, G301C in 9 clones, G301T in 17 clones, T89A in 17 clones, T115C in 4 clones, T120C in 13 clones, T147G in 12 clones, T297C in 17 clones, T302C in 6 clones, T303C in 62 clones
Total	33	replacement	A61G in 18 clones, A82G in 8 clones, A90G in 1 clones, A109G in 2 clones, A196G in 4 clones, A197C in 12 clones, A253G in 6 clones, A257C in 2 clones, A257G in 2 clones, A284G in 2 clones, C43A in 2 clones, C74G in 17 clones, C127T in 2 clones, C130T in 7 clones, C194T in 2 clones, C214T in 2 clones, C276G in 12 clones, G72T in 2 clones, G77C in 12 clones, G83A in 2 clones, G104A in 2 clones, G129C in 2 clones, G129T in 17 clones, G256T in 8 clones, G275A in 2 clones, G286T in 9 clones, G291C in 17 clones, G295A in 22 clones, G301A in 37 clones, G301C in 9 clones, G301T in 17 clones, T89A in 17 clones, T302C in 6 clones
Total	21	silent	A81G in 12 clones, A90G in 99 clones, A105G in 66 clones, A159G in 17 clones, C63T in 12 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, C156T in 2 clones, C309T in 2 clones, G117A in 2 clones, G129A in 49 clones, G282A in 12 clones, G291A in 8 clones, G300A in 66 clones, G300C in 17 clones, T115C in 4 clones, T120C in 13 clones, T147G in 12 clones, T297C in 17 clones, T303C in 62 clones
Total	36	transition	A61G in 18 clones, A81G in 12 clones, A82G in 8 clones, A90G in 100 clones, A105G in 66 clones, A109G in 2 clones, A159G in 17 clones, A196G in 4 clones, A253G in 6 clones, A257G in 2 clones, A284G in 2 clones, C63T in 12 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, C127T in 2 clones, C130T in 7 clones, C156T in 2 clones, C194T in 2 clones, C214T in 2 clones, C309T in 2 clones, G83A in 2 clones, G104A in 2 clones, G117A in 2 clones, G129A in 49 clones, G275A in 2 clones, G282A in 12 clones, G291A in 8 clones, G295A in 22 clones, G300A in 66 clones, G301A in 37 clones, T115C in 4 clones, T120C in 13 clones, T297C in 17 clones, T302C in 6 clones, T303C in 62 clones
Total	17	transversion	A197C in 12 clones, A257C in 2 clones, C43A in 2 clones, C74G in 17 clones, C276G in 12 clones, G72T in 2 clones, G77C in 12 clones, G129C in 2 clones, G129T in 17 clones, G256T in 8 clones, G286T in 9 clones, G291C in 17 clones, G300C in 17 clones, G301C in 9 clones, G301T in 17 clones, T89A in 17 clones, T147G in 12 clones
Total	55	unconfirmed	A90G in 1 clones, A94C in 1 clones, A105G in 1 clones, A138G in 1 clones, A150G in 1 clones, A159G in 1 clones, A216G in 1 clones, A223G in 2 clones, A229G in 1 clones, A262G in 2 clones, A277G in 1 clones, A290G in 1 clones, A308C in 1 clones, C35T in 1 clones, C49T in 1 clones, C53T in 1 clones, C59G in 1 clones, C63T in 1 clones, C74G in 1 clones, C74T in 1 clones, C85A in 1 clones, C87A in 1 clones, C111T in 1 clones, C156T in 1 clones, C206T in 1 clones, C214T in 1 clones, C252T in 1 clones, C265G in 1 clones, G88A in 1 clones, G129T in 1 clones, G153A in 1 clones, G285T in 1 clones, G286A in 1 clones, G291A in 1 clones, G291C in 1 clones, G300C in 1 clones, G301T in 1 clones, T44C in 1 clones, T73A in 1 clones, T75C in 1 clones, T89A in 1 clones, T102C in 1 clones, T112C in 1 clones, T115C in 1 clones, T124C in 1 clones, T171C in 1 clones, T212C in 2 clones, T226C in 1 clones, T281C in 1 clones, T288C in 1 clones, T296C in 1 clones, T297C in 2 clones, T302C in 1 clones, T303C in 1 clones, T307C in 1 clones
VK FR	41	confirmed	A61G in 18 clones, A159G in 17 clones, A196G in 4 clones, A197C in 12 clones, A253G in 6 clones, A257C in 2 clones, A257G in 2 clones, A284G in 2 clones, C43A in 2 clones, C63T in 12 clones, C74G in 17 clones, C127T in 2 clones, C130T in 7 clones, C156T in 2 clones, C214T in 2 clones, C276G in 12 clones, C309T in 2 clones, G72T in 2 clones, G77C in 12 clones, G117A in 2 clones, G129A in 49 clones, G129C in 2 clones, G129T in 17 clones, G256T in 8 clones, G275A in 2 clones, G282A in 12 clones, G286T in 9 clones, G291A in 8 clones, G291C in 17 clones, G295A in 22 clones, G300A in 66 clones, G300C in 17 clones, G301A in 37 clones, G301C in 9 clones, G301T in 17 clones, T115C in 4 clones, T120C in 13 clones, T147G in 12 clones, T297C in 17 clones, T302C in 6 clones, T303C in 62 clones

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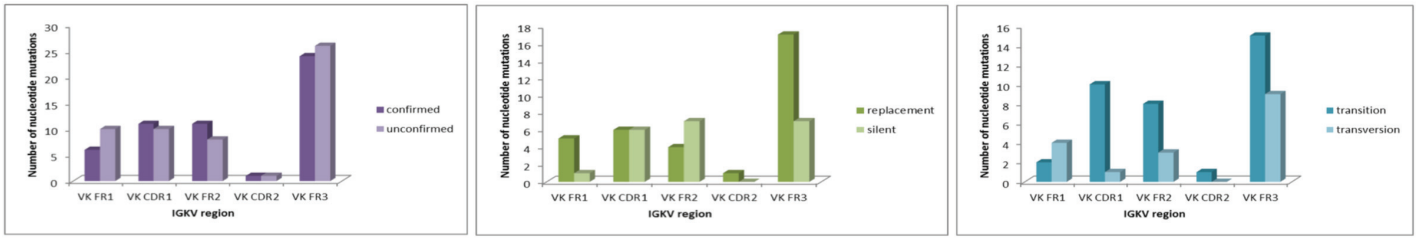
Supplementary Table S5. ***Continued.***

VK CDR	12	confirmed	A81G in 12 clones, A82G in 8 clones, A90G in 100 clones, A105G in 66 clones, A109G in 2 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, C194T in 2 clones, G83A in 2 clones, G104A in 2 clones, T89A in 17 clones
VK FR1	6	confirmed	A61G in 18 clones, C43A in 2 clones, C63T in 12 clones, C74G in 17 clones, G72T in 2 clones, G77C in 12 clones
VK CDR1	11	confirmed	A81G in 12 clones, A82G in 8 clones, A90G in 100 clones, A105G in 66 clones, A109G in 2 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, G83A in 2 clones, G104A in 2 clones, T89A in 17 clones
VK FR2	11	confirmed	A159G in 17 clones, C127T in 2 clones, C130T in 7 clones, C156T in 2 clones, G117A in 2 clones, G129A in 49 clones, G129C in 2 clones, G129T in 17 clones, T115C in 4 clones, T120C in 13 clones, T147G in 12 clones
VK CDR2	1	confirmed	C194T in 2 clones
VK FR3	24	confirmed	A196G in 4 clones, A197C in 12 clones, A253G in 6 clones, A257C in 2 clones, A257G in 2 clones, A284G in 2 clones, C214T in 2 clones, C276G in 12 clones, C309T in 2 clones, G256T in 8 clones, G275A in 2 clones, G282A in 12 clones, G286T in 9 clones, G291A in 8 clones, G291C in 17 clones, G295A in 22 clones, G300A in 66 clones, G300C in 17 clones, G301A in 37 clones, G301C in 9 clones, G301T in 17 clones, T297C in 17 clones, T302C in 6 clones, T303C in 62 clones
VK FR	26	replacement	A61G in 18 clones, A196G in 4 clones, A197C in 12 clones, A253G in 6 clones, A257C in 2 clones, A257G in 2 clones, A284G in 2 clones, C43A in 2 clones, C74G in 17 clones, C127T in 2 clones, C130T in 7 clones, C214T in 2 clones, C276G in 12 clones, G72T in 2 clones, G77C in 12 clones, G129C in 2 clones, G129T in 17 clones, G256T in 8 clones, G275A in 2 clones, G286T in 9 clones, G291C in 17 clones, G295A in 22 clones, G301A in 37 clones, G301C in 9 clones, G301T in 17 clones, T302C in 6 clones
VK CDR	7	replacement	A82G in 8 clones, A90G in 1 clones, A109G in 2 clones, C194T in 2 clones, G83A in 2 clones, G104A in 2 clones, T89A in 17 clones
VK FR1	5	replacement	A61G in 18 clones, C43A in 2 clones, C74G in 17 clones, G72T in 2 clones, G77C in 12 clones
VK CDR1	6	replacement	A82G in 8 clones, A90G in 1 clones, A109G in 2 clones, G83A in 2 clones, G104A in 2 clones, T89A in 17 clones
VK FR2	4	replacement	C127T in 2 clones, C130T in 7 clones, G129C in 2 clones, G129T in 17 clones
VK CDR2	1	replacement	C194T in 2 clones
VK FR3	17	replacement	A196G in 4 clones, A197C in 12 clones, A253G in 6 clones, A257C in 2 clones, A257G in 2 clones, A284G in 2 clones, C214T in 2 clones, C276G in 12 clones, G256T in 8 clones, G275A in 2 clones, G286T in 9 clones, G291C in 17 clones, G295A in 22 clones, G301A in 37 clones, G301C in 9 clones, G301T in 17 clones, T302C in 6 clones
VK FR	15	silent	A159G in 17 clones, C63T in 12 clones, C156T in 2 clones, C309T in 2 clones, G117A in 2 clones, G129A in 49 clones, G282A in 12 clones, G291A in 8 clones, G300A in 66 clones, G300C in 17 clones, T115C in 4 clones, T120C in 13 clones, T147G in 12 clones, T297C in 17 clones, T303C in 62 clones
VK CDR	6	silent	A81G in 12 clones, A90G in 99 clones, A105G in 66 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones
VK FR1	1	silent	C63T in 12 clones
VK CDR1	6	silent	A81G in 12 clones, A90G in 99 clones, A105G in 66 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones
VK FR2	7	silent	A159G in 17 clones, C156T in 2 clones, G117A in 2 clones, G129A in 49 clones, T115C in 4 clones, T120C in 13 clones, T147G in 12 clones
VK FR3	7	silent	C309T in 2 clones, G282A in 12 clones, G291A in 8 clones, G300A in 66 clones, G300C in 17 clones, T297C in 17 clones, T303C in 62 clones
VK FR	25	transition	A61G in 18 clones, A159G in 17 clones, A196G in 4 clones, A253G in 6 clones, A257G in 2 clones, A284G in 2 clones, C63T in 12 clones, C127T in 2 clones, C130T in 7 clones, C156T in 2 clones, C214T in 2 clones, C309T in 2 clones, G117A in 2 clones, G129A in 49 clones, G275A in 2 clones, G282A in 12 clones, G291A in 8 clones, G295A in 22 clones, G300A in 66 clones, G301A in 37 clones, T115C in 4 clones, T120C in 13 clones, T297C in 17 clones, T302C in 6 clones, T303C in 62 clones
VK CDR	11	transition	A81G in 12 clones, A82G in 8 clones, A90G in 100 clones, A105G in 66 clones, A109G in 2 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, C194T in 2 clones, G83A in 2 clones, G104A in 2 clones
VK FR1	2	transition	A61G in 18 clones, C63T in 12 clones
VK CDR1	10	transition	A81G in 12 clones, A82G in 8 clones, A90G in 100 clones, A105G in 66 clones, A109G in 2 clones, C93T in 37 clones, C108T in 2 clones, C114T in 4 clones, G83A in 2 clones, G104A in 2 clones
VK FR2	8	transition	A159G in 17 clones, C127T in 2 clones, C130T in 7 clones, C156T in 2 clones, G117A in 2 clones, G129A in 49 clones, T115C in 4 clones, T120C in 13 clones

Continued on next page

Supplementary Table S5. ***Continued.***

VK CDR2	1	transition	C194T in 2 clones
VK FR3	15	transition	A196G in 4 clones, A253G in 6 clones, A257G in 2 clones, A284G in 2 clones, C214T in 2 clones, C309T in 2 clones, G275A in 2 clones, G282A in 12 clones, G291A in 8 clones, G295A in 22 clones, G300A in 66 clones, G301A in 37 clones, T297C in 17 clones, T302C in 6 clones, T303C in 62 clones
VK FR	16	transversion	A197C in 12 clones, A257C in 2 clones, C43A in 2 clones, C74G in 17 clones, C276G in 12 clones, G72T in 2 clones, G77C in 12 clones, G129C in 2 clones, G129T in 17 clones, G256T in 8 clones, G286T in 9 clones, G291C in 17 clones, G300C in 17 clones, G301C in 9 clones, G301T in 17 clones, T147G in 12 clones
VK CDR	1	transversion	T89A in 17 clones
VK FR1	4	transversion	C43A in 2 clones, C74G in 17 clones, G72T in 2 clones, G77C in 12 clones
VK CDR1	1	transversion	T89A in 17 clones
VK FR2	3	transversion	G129C in 2 clones, G129T in 17 clones, T147G in 12 clones
VK FR3	9	transversion	A197C in 12 clones, A257C in 2 clones, C276G in 12 clones, G256T in 8 clones, G286T in 9 clones, G291C in 17 clones, G300C in 17 clones, G301C in 9 clones, G301T in 17 clones
VK FR	44	unconfirmed	A138G in 1 clones, A150G in 1 clones, A159G in 1 clones, A216G in 1 clones, A223G in 2 clones, A229G in 1 clones, A262G in 2 clones, A277G in 1 clones, A290G in 1 clones, A308C in 1 clones, C35T in 1 clones, C49T in 1 clones, C53T in 1 clones, C59G in 1 clones, C63T in 1 clones, C74G in 1 clones, C74T in 1 clones, C156T in 1 clones, C206T in 1 clones, C214T in 1 clones, C252T in 1 clones, C265G in 1 clones, G129T in 1 clones, G153A in 1 clones, G285T in 1 clones, G286A in 1 clones, G291A in 1 clones, G291C in 1 clones, G300C in 1 clones, G301T in 1 clones, T44C in 1 clones, T73A in 1 clones, T75C in 1 clones, T115C in 1 clones, T124C in 1 clones, T212C in 2 clones, T226C in 1 clones, T281C in 1 clones, T288C in 1 clones, T296C in 1 clones, T297C in 2 clones, T302C in 1 clones, T303C in 1 clones, T307C in 1 clones
VK CDR	11	unconfirmed	A90G in 1 clones, A94C in 1 clones, A105G in 1 clones, C85A in 1 clones, C87A in 1 clones, C111T in 1 clones, G88A in 1 clones, T89A in 1 clones, T102C in 1 clones, T112C in 1 clones, T171C in 1 clones
VK FR1	10	unconfirmed	C35T in 1 clones, C49T in 1 clones, C53T in 1 clones, C59G in 1 clones, C63T in 1 clones, C74G in 1 clones, C74T in 1 clones, T44C in 1 clones, T73A in 1 clones, T75C in 1 clones
VK CDR1	10	unconfirmed	A90G in 1 clones, A94C in 1 clones, A105G in 1 clones, C85A in 1 clones, C87A in 1 clones, C111T in 1 clones, G88A in 1 clones, T89A in 1 clones, T102C in 1 clones, T112C in 1 clones
VK FR2	8	unconfirmed	A138G in 1 clones, A150G in 1 clones, A159G in 1 clones, C156T in 1 clones, G129T in 1 clones, G153A in 1 clones, T115C in 1 clones, T124C in 1 clones
VK CDR2	1	unconfirmed	T171C in 1 clones
VK FR3	26	unconfirmed	A216G in 1 clones, A223G in 2 clones, A229G in 1 clones, A262G in 2 clones, A277G in 1 clones, A290G in 1 clones, A308C in 1 clones, C206T in 1 clones, C214T in 1 clones, C252T in 1 clones, C265G in 1 clones, G285T in 1 clones, G286A in 1 clones, G291A in 1 clones, G291C in 1 clones, G300C in 1 clones, G301T in 1 clones, T212C in 2 clones, T226C in 1 clones, T281C in 1 clones, T288C in 1 clones, T296C in 1 clones, T297C in 2 clones, T302C in 1 clones, T303C in 1 clones, T307C in 1 clones



Supplementary Table S6. Incidence and topology of amino acid changes observed within subset #4 cases included in the analysis.

Amino acids are represented by a single-letter code. The number indicates the codon position e.g. E55D in 30 clones indicates that 30 clones have a glutamic acid to aspartic acid change at codon 55.

Amino acid changes observed within the *IGHV4-34* gene of subset #4 cases included in the analysis.

Total	48	confirmed	A97T in 2 clones, E17Q in 28 clones, E55D in 30 clones, F87I in 83 clones, G27I in 34 clones, G28D in 39 clones, G28E in 138 clones, G36D in 22 clones, G49E in 39 clones, I42V in 53 clones, I53M in 39 clones, K72Q in 2 clones, K90N in 32 clones, K90Q in 39 clones, K90Y in 3 clones, L21P in 2 clones, L71P in 2 clones, N57D in 2 clones, N66K in 30 clones, N85S in 10 clones, P45F in 10 clones, P45S in 60 clones, Q3E in 20 clones, Q3L in 29 clones, Q3R in 28 clones, Q5P in 22 clones, S40T in 112 clones, S64I in 53 clones, S64T in 20 clones, S92H in 2 clones, S92N in 33 clones, S92T in 49 clones, S93F in 53 clones, S93P in 2 clones, S93T in 2 clones, T65I in 39 clones, T95A in 30 clones, T95S in 10 clones, T99M in 53 clones, V2E in 51 clones, V2L in 6 clones, V76L in 38 clones, V94A in 2 clones, V94M in 10 clones, W7R in 3 clones, W52Y in 53 clones, Y38F in 23 clones, Y38N in 7 clones
Total	19	conservative	E55D in 30 clones, G27I in 34 clones, I42V in 53 clones, I53M in 39 clones, L21P in 2 clones, L71P in 2 clones, N85S in 10 clones, S40T in 112 clones, S64T in 20 clones, S92N in 33 clones, S92T in 49 clones, S93T in 2 clones, T95S in 10 clones, V2L in 6 clones, V76L in 38 clones, V94A in 2 clones, V94M in 10 clones, W52Y in 53 clones, Y38F in 23 clones
Total	29	non-conservative	A97T in 2 clones, E17Q in 28 clones, F87I in 83 clones, G28D in 39 clones, G28E in 138 clones, G36D in 22 clones, G49E in 39 clones, K72Q in 2 clones, K90N in 32 clones, K90Q in 39 clones, K90Y in 3 clones, N57D in 2 clones, N66K in 30 clones, P45F in 10 clones, P45S in 60 clones, Q3E in 20 clones, Q3L in 29 clones, Q3R in 28 clones, Q5P in 22 clones, S64I in 53 clones, S92H in 2 clones, S93F in 53 clones, S93P in 2 clones, T65I in 39 clones, T95A in 30 clones, T99M in 53 clones, V2E in 51 clones, W7R in 3 clones, Y38N in 7 clones,
Total	100	unconfirmed	A24T in 1 clones, A96T in 2 clones, A97T in 2 clones, A97V in 1 clones, D81G in 1 clones, D98G in 1 clones, E17G in 1 clones, E55G in 2 clones, E55K in 1 clones, F30I in 1 clones, F30Y in 2 clones, F87L in 2 clones, G11E in 1 clones, G27D in 2 clones, G27N in 1 clones, G28D in 1 clones, G28E in 1 clones, G36N in 1 clones, G47R in 1 clones, G49E in 1 clones, H58R in 1 clones, I42M in 1 clones, I42T in 2 clones, I53M in 2 clones, I78V in 1 clones, K14E in 1 clones, K48E in 1 clones, K48R in 1 clones, K84E in 1 clones, K84Q in 1 clones, K84R in 1 clones, K90Q in 1 clones, K90R in 1 clones, L12P in 1 clones, L19P in 1 clones, L21P in 2 clones, L71P in 1 clones, L89P in 1 clones, L89S in 1 clones, L91P in 1 clones, N57D in 1 clones, N57Y in 1 clones, N66D in 3 clones, N66Y in 2 clones, N85S in 1 clones, N85T in 1 clones, P45F in 1 clones, P69L in 2 clones, Q3R in 1 clones, Q5H in 1 clones, Q5R in 1 clones, Q86R in 1 clones, R75Q in 1 clones, S16P in 2 clones, S16T in 1 clones, S20A in 1 clones, S20P in 1 clones, S29P in 1 clones, S35G in 2 clones, S35R in 1 clones, S40I in 1 clones, S40T in 1 clones, S59G in 1 clones, S59R in 2 clones, S64A in 1 clones, S64P in 1 clones, S79F in 1 clones, S79T in 1 clones, S83P in 1 clones, S92A in 1 clones, S92R in 1 clones, S92T in 1 clones, T18A in 1 clones, T18I in 1 clones, T65I in 1 clones, T65N in 1 clones, T82A in 3 clones, T95S in 1 clones, T99A in 2 clones, V2G in 1 clones, V2L in 1 clones, V25A in 1 clones, V76I in 1 clones, V76L in 1 clones, V76P in 1 clones, V80E in 1 clones, V94M in 1 clones, V101E in 1 clones, W7C in 1 clones, W7R in 2 clones, W41G in 1 clones, Y26C in 1 clones, Y26H in 1 clones, Y37C in 1 clones, Y37H in 1 clones, Y37N in 1 clones, Y38H in 1 clones, Y67C in 1 clones, Y103N in 1 clones, Y103S in 1 clones

Amino acid changes observed within the *IGKV2-30* gene of subset #4 cases included in the analysis.

Total	30	confirmed	A96S in 9 clones, D86A in 2 clones, D86G in 2 clones, D86Y in 8 clones, E95G in 2 clones, E97D in 17 clones, G35E in 2 clones, I21V in 18 clones, L15I in 2 clones, N66D in 4 clones, N66T in 12 clones, P72S in 2 clones, Q43* in 2 clones, Q44* in 7 clones, R24S in 2 clones, S25C in 35 clones, S26T in 12 clones, S28G in 8 clones, S28N in 2 clones, S65F in 2 clones, S92N in 2 clones, S92R in 12 clones, T37A in 2 clones, T85A in 6 clones, V30E in 17 clones, V99I in 22 clones, V101A in 6 clones, V101F in 17 clones, V101I in 37 clones, V101L in 9 clones
Total	12	conservative	E97D in 17 clones, I21V in 18 clones, L15I in 2 clones, N66T in 12 clones, S25C in 35 clones, S26T in 12 clones, S28N in 2 clones, S92N in 2 clones, V99I in 22 clones, V101A in 6 clones, V101I in 37 clones, V101L in 9 clones
Total	18	non-conservative	A96S in 9 clones, D86A in 2 clones, D86G in 2 clones, D86Y in 8 clones, E95G in 2 clones, G35E in 2 clones, N66D in 4 clones, P72S in 2 clones, Q43* in 2 clones, Q44* in 7 clones, R24S in 2 clones, S28G in 8 clones, S65F in 2 clones, S92R in 12 clones, T37A in 2 clones, T85A in 6 clones, V30E in 17 clones, V101F in 17 clones
Total	33	unconfirmed	A96T in 1 clones, E95D in 1 clones, E97D in 1 clones, E97G in 1 clones, F42L in 1 clones, F76L in 1 clones, L15P in 1 clones, L29I in 1 clones, L89V in 1 clones, P12L in 1 clones, P18L in 1 clones, P72S in 1 clones, Q17* in 1 clones, Q43H in 1 clones, R75G in 2 clones, R93G in 1 clones, S20C in 1 clones, S25C in 1 clones, S25F in 1 clones, S32R in 1 clones, S69F in 1 clones, S77G in 1 clones, T88A in 2 clones, V30E in 1 clones, V30M in 1 clones, V71A in 2 clones, V94A in 1 clones, V99A in 1 clones, V101A in 1 clones, V101F in 1 clones, Y38H in 1 clones, Y103H in 1 clones, Y103S in 1 clones

Supplementary Table S7. Topology of mutations observed within the *IGHV4-34* gene of subset #4 cases included in the analysis; only positions targeted by ID are shown.

Amino acids are represented by a single-letter code. In the header, the AA indicated is the germline AA and the number refers to the codon position according to the IMGT unique numbering for V-DOMAIN (V-QUEST Version 2.1.2). n: number of subclones sequences analyzed; CM: confirmed mutation; UCM: unconfirmed mutation; s: shared mutation; ID: intraclonal diversification; AA: amino acid
Within the table, a single letter indicates that all subcloned sequences at that timepoint carry that specific AA i.e. a shared mutation. A number before an AA change refers to the number of subcloned sequences containing that AA change.

	n	2:V	3:Q	5:Q	7:W	11:G	12:L	14:K	16:S	17:E	18:T	19:L	20:S	21:L	24:A	25:V	26:Y	27:G
P0103-H1	33	E	-	-	3:W7R	-	-	-	-	-	-	-	-	-	-	-	-	-
P0103-H2	28	E	-	-	1:W7R	-	-	-	1:S16P	-	-	-	-	-	-	-	-	-
P0907-H1	33	31:V2E 1:V2G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	L
P0907-H2	22	E	-	-	-	-	-	-		1:E17G	-	-	-	-	-	-	1:Y26H	L
P0907-H3	23	E	-	-	-	-	-	1:K14E	-	-	-	-	-	-	-	-	-	L
P1422-H1	27	6:V2L	6:Q3R	-	-	-	-	-	-	-	-	-	1:S20P	-	-	-	1:Y26C	-
P1422-H2	33	1:V2L	1:Q3R	1:Q5H	-	-	-	-	-	-	-	1:L19P	1:S20A	-	-	-	-	-
P1422-H3	25	2:V2Y	2:Q3S	-	1:W7R	-	-	-	1:S16P	-	1:T18A	-	-	1:L21P	1:A24T	1:V25A	-	-
P1939-H1	35	E	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I
P1939-H2	35	E	E	-	-	1:G11E	-	-	-	-	-	-	-	-	-	-	-	34:G27I 1:G27N
P1939-H3	21	20:V2E	20:Q3E	1:Q5R	-	-	-	-	-	-	-	-	-	-	-	-	-	I
P2451-H1	35	E	-	-	-	-	-	-	-	-	-	-	-	1:L21P	-	-	-	-
P2451-H2	33	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P2920-H1	26	-	12:Q3L 14: Q3R	14:Q5P	1:W7C	-	1:L12P	-	-	11:E17Q	-	-	-	-	-	-	-	1:G27D
P2920-H2	26	-	17:Q3L 8:Q3R	8:Q5P	-	-	-	-	1:S16T	17:E17Q	-	-	-	2:L21P	-	-	-	1:G27D
P3020-H1	16	M	H	K	-	-	-	-	-	-	1:T18I	-	-	-	-	-	-	-
P3020-H2	21	M	H	K	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P3916-H1	17	I	-	K	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P3916-H2	22	I	-	K	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	N = 511																	

	n	28:G	29:S	30:F	35:S	36:G	37:Y	38:Y	40: S	41:W	42:I	45:P	47:G	48:K	49:G
P0103-H1	33	31:G28E	-	-	-	-	-	-	31:S40T	-	-	2:P45F	-	-	-
P0103-H2	28	20: G28E	-	-	-	-	-	7:Y38N	20:S40T	-	-	8:P45F	-	-	-
P0907-H1	33	D	-	-	T	D	-	-	T	-	1:I42T	-	-	-	-
P0907-H2	22	D	-	1:F30Y	T	D	-	-	21:S40T 1:S40I	-	-	-	-	-	-
P0907-H3	23	D	-	-	T	22:G36D 1:G36N	-	-	T	-	-	-	-	-	-
P1422-H1	27	21:G28E 6:G28D	-	-	-	-	-	-	6:S40T	-	21:I42V	S	-	-	6:G49E
P1422-H2	33	32:G28E 1:G28D	-	1:F30Y	1:S35R	-	-	1:Y38H	1:S40T	-	32:I42V	S	-	-	1:G49E
P1422-H3	25	E	-	-	-	-	-	-	-	-	V	S	-	-	-
P1939-H1	35	34:G28E	-	-	-	-	1:Y37C	-	T	-	-	A	-	-	-
P1939-H2	35	E	-	1:F30I	1:S35G	-	1:Y37N	-	T	-	-	A	-	-	-
P1939-H3	21	E	-	-	-	-	-	-	T	-	-	A	-	-	-
P2451-H1	35	1:G28E 33:G28D	-	-	-	-	-	-	34:S40T	1:W41G	1:I42M	1:P45F 33:P45S	1:G47R	-	33:G49E
P2451-H2	33	D	-	-	-	-	1:Y37H	-	T	-	1:I42T	S	-	1:K48R	E
P2920-H1	26	-	1:S29P	-	-	-	-	14:Y38F	-	-	-	11:P45S	-	-	-
P2920-H2	26	-	-	-	1:S35G	-	-	9:Y38F	-	-	-	16:P45S	-	1:K48E	-
P3020-H1	16	-	-	-	-	D	T	-	-	-	-	S	-	M	-
P3020-H2	21	-	-	-	-	D	T	-	-	-	-	S	-	M	-
P3916-H1	17	D	-	-	-	-	-	F	-	-	-	S	A	-	-
P3916-H2	22	D	-	-	-	-	-	F	-	-	-	S	A	-	-
	N = 511														

Continued on next page

Supplementary Table S7. ***Continued.***

	n	52:W	53:I	55:E	57:N	58:H	59:S	64:S	65:T	66:N	67:Y	69:P	71:L	72:K	75:R
P0103-H1	33	-	-	-	-		-	-	-	1:N66Y	-	-	-	2:K72Q	-
P0103-H2	28	-	-	-	-	-	-	-	-	1:N66Y	-	-	-	-	-
P0907-H1	33	C	-	1:E55G	D	-	1:S59R	-	-	-	-	-	-	-	-
P0907-H2	22	C	-	-	D	-	-	-	-	1:N66D	-	-	2:L71P	-	-
P0907-H3	23	C	-	-	D	-	-	-	-	-	-	-	-	-	-
P1422-H1	27	21:W52Y	6:I53M	-	-	-	-	21:S64I	6:T65I	-	-	1:P69L	-	-	-
P1422-H2	33	32:W52Y	1:I53M	-	-	-	-	32:S64I	1:T65I	-	1:Y67C	1:P69L	-	-	-
P1422-H3	25	Y	-	-	-	-	-	I	-	-	-	-	-	-	-
P1939-H1	35	-	-	-	-	-	-	I	1:T65N	1:N66D	-	-	-	-	-
P1939-H2	35	-	-	-	2:N57D	-	1:S59G	I	-	1:N66D	-	-	-	-	-
P1939-H3	21	-	1:I53M	-	-	-	-	I	-	-	-	-	-	-	-
P2451-H1	35	-	33:I53M	-	1:N57D	1:H58R	-	-	33:T65I	-	-	-	-	-	-
P2451-H2	33	-	M	-	-	-	-	-	I	-	-	-	-	-	-
P2920-H1	26	Y	-	1:E55G 12:E55D 1:E55K	-	Q	1:S59R	1:S64A 1:S64P 12:S64T	-	12:N66K	-	-	-	-	1:R75Q
P2920-H2	26	Y	-	18:E55D	-	Q	-	8:S64T	-	18:N66K	-	-	-	-	-
P3020-H1	16	L	-	Q	-	-	F	-	A	-	-	-	1:L71P	-	-
P3020-H2	21	L	-	Q	-	-	F	-	A	-	-	-	-	-	-
P3916-H1	17	-	-	-	-	S	-	-	-	-	-	-	-	-	-
P3916-H2	22	-	-	-	1:N57Y	S	-	-	-	-	-	-	-	-	-
	N = 511														

	n	76:V	78:V	79:S	80:V	81:D	82:T	83:S	84:K	85:N	86:Q	87:F	89:L	90:K	91:L	92:S	93:S	94:V	95:T
P0103-H1	33	-	-	-	-	-	-	-	1K84E	2:N85S	-	-	-	-	-	T	-	2:V94M	2:T95S
P0103-H2	28	-	-	-	-	-	-	-	1K84Q	8:N85S	-	-	-	-	-	T	-	8:V94M	2:V94A 8:T95S
P0907-H1	33	-	-	-	-	-	-	-	-	-	-	-	1:L89S	-	-	T	-	-	-
P0907-H2	22	1:V76I	-	1:S79F	-	-	-	-	-	-	-	-	-	-	-	21:S92T	-	-	-
P0907-H3	23	-	-	-	-	-	-	1:S83P	-	-	-	1:F87L	-	-	-	22:S92T 1:S92A	-	-	-
P1422-H1	27	6:V76L	-	1:S79T	-	-	-	-	1:K84R	-	-	21:F87I	-	6:K90Q	-	6:S92T	21:S93F	-	-
P1422-H2	33	1:V76L	-	-	1:V80E	-	-	-	-	-	-	32:F87I	-	1:K90Q	-	1:S92T 1:S92R	32:S93F	-	-
P1422-H3	25	-	1:I78V	-	-	1:D81G	-	-	-	-	-	I	1:L89P	-	-	-	F	-	-
P1939-H1	35	-	-	-	-	-	1:T82A	-	-	-	-	-	-	N	-	N	-	-	-
P1939-H2	35	-	-	-	-	-	-	-	-	1:N85T	-	-	-	32:K90N 3:K90Y	-	33:S92N 2:S92H	-	-	-
P1939-H3	21	-	-	-	-	-	1:T82A	-	-	-	-	-	-	N	-	N	-	-	-
P2451-H1	35	32:V76L 1:V76P	-	-	-	-	1:T82A	-	-	1:N85S	-	1:F87L	-	33:K90Q	-	T	2:S93P	1:V94M	1:T95S
P2451-H2	33	L	-	-	-	-	-	-	-	-	-	-	-	Q	-	T	2:S93T	-	-
P2920-H1	26	-	L	-	-	-	-	-	-	-	-	13:F87I	-	1:K90R	-	N	-	-	12:T95A
P2920-H2	26	-	L	-	-	-	-	-	-	-	1:Q86R	17:F87I	-	-	1:L91P	N	-	-	18:T95A
P3020-H1	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	T	-	L	-
P3020-H2	21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	T	-	L	-
P3916-H1	17	-	-	-	I	-	A	-	-	-	-	-	-	-	-	-	-	-	-
P3916-H2	22	-	-	-	I	-	A	-	-	-	-	-	-	-	-	-	-	-	-
	N = 511																		

	n	96:A	97:A	98:D	99:T	101:V	103:Y	CM	UCM	S	
P0103-H1	33	-	2:A97T	-	-	-	-	9	2	2	
P0103-H2	28	-	1:A97T	-	-	-	-	8	5	2	
P0907-H1	33	-	-	-	-	1:V101E	-	1	6	8	
P0907-H2	22	-	1:A97V	-	-	-	-	3	8	7	
P0907-H3	23	-	-	-	-	-	-	2	5	7	
P1422-H1	27	-	-	-	21:T99M	-	-	17	5	1	
P1422-H2	33	-	1:A97T	-	32:T99M	-	-	7	20	1	
P1422-H3	25	-	-	1:D98G	M	-	-	2	11	8	
P1939-H1	35	-	-	-	-	-	-	1	4	8	& shared positions at codons 68 and 88 which are not affected by ID
P1939-H2	35	1:A96T	-	-	-	-	1:Y103S	6	10	6	& shared positions at codons 68 and 88 which are not affected by ID
P1939-H3	21	-	-	-	-	-	1:Y103N	2	4	7	& shared positions at codons 68 and 88 which are not affected by ID
P2451-H1	35	1:A96T	-	-	-	-	-	9	15	2	
P2451-H2	33	-	-	-	1:T99A	-	-	1	4	10	
P2920-H1	26	-	-	-	-	-	-	11	11	4	
P2920-H2	26	-	-	-	1:T99A	-	-	12	7	4	
P3020-H1	16	-	-	-	-	-	-	0	2	13	& shared positions at codons 22, 56 and 74 which are not affected by ID
P3020-H2	21	-	-	-	-	-	-	0	0	13	& shared positions at codons 22, 56 and 74 which are not affected by ID
P3916-H1	17	-	-	-	S	-	-	0	0	10	
P3916-H2	22	-	-	-	S	-	-	0	1	10	
	N = 511							91[a]	120[a]	123[a]	

[a]Column totals.

Supplementary Table S8. Topology of mutations observed within the *IGKV2-30* gene of subset #4 cases included in the analysis; only positions targeted by ID are shown.

Amino acids are represented by a single-letter code. In the header, the AA indicated is the germline AA and the number refers to the codon position according to the IMGT unique numbering for V-DOMAIN (V-QUEST Version 2.1.2). n: number of subclones sequences analyzed; CM: confirmed mutation; UCM: unconfirmed mutation; s: shared mutation; ID: intraclonal diversification; AA: amino acid

Within the table, a single letter indicates that all subcloned sequences at that timepoint carry that specific AA i.e. a shared mutation. A number before an AA change refers to the number of subcloned sequences containing that AA change.

	n	12:P	15:L	17:Q	18:P	20:S	21:I	24:R	25:S	26:S	28:S	29:L	30:V
P0103-K1	38	-	-	-	1:P18L	-	-	-	-	-	6:S28G	-	-
P0103-K2	33	-	-	-	-	-	-	-	-	-	2:S28G	-	-
P0103-K3	8	-	-	-	-	-	-	-	-	-	-	-	-
P0907-K1	16	-	-	-	-	-	V	-	-	-	-	-	-
P0907-K2	17	-	-	-	-	-	V	-	-	-	-	-	-
P1422-K1	14	-	I	-	-	-	V	S	-	-	N	-	-
P1422-K2	26	-	I	-	-	-	V	S	-	-	N	-	-
P1422-K3	11	-	I	-	-	-	V	S	1:S25F	-	N	-	-
P1939-K1	19	-	-	-	-	-	2:I21V	-	17:S25C	-	-	-	17:V30E
P1939-K2	19	1:P12L	-	-	-	-	-	-	18:S25C	-	-	-	E
P1939-K3	13	-	-	-	-	-	-	-	C	-	-	-	E
P2451-K1	39	-	2:L15I	-	-	-	3:I21V	2:R24S	-	-	2:S28N	-	1:V30M
P2451-K2	24	-	1:L15P	1:Q17*	-	-	-	-	-	-	-	-	-
P2920-K1	18	-	-	-	-	-	13:I21V	-	-	-	-	-	-
P2920-K2	11	-	-	-	-	-	V	-	-	-	-	-	-
P3020-K1	21	-	-	-	A	-	-	T	-	-	-	-	-
P3020-K2	21	-	-	-	A	1:S20C	-	T	-	-	-	1:L29I	-
P3020-K3	22	-	-	-	A	-	-	T	-	-	-	-	-
P3916-K1	15	-	-	-	-	-	-		-	T	-	-	-
P3916-K2	13	-	-	-	-	-	-	-	1:S25C	12:S26T	-	-	1:V30E
	N = 398												

	n	32:S	35:G	37:T	38:Y	42:F	43:Q	44:Q	65:S	66:N	69:S	71:V	72:P
P0103-K1	38	-	-	-	-	-	-	-	-	-	-	1:V71A	-
P0103-K2	33	-	-	-	-	1:F42L	-	-	-	-	-	-	-
P0103-K3	8	-	-	-	-	-	-	-	-	-	-	-	1:P72S
P0907-K1	16	-	-	-	-	-	H	-	2:S65F	D	-	-	-
P0907-K2	17	-	-	-	-	-	H	-	-	D	-	-	-
P1422-K1	14	-	-	-	-	-	2:Q43*	-	-	D	-	-	2:P72S
P1422-K2	26	-	-	-	1:Y38H	-	-	-	-	D	-	-	-
P1422-K3	11	-	-	-	-	-	-	-	-	D	-	-	-
P1939-K1	19	-	-	-	-	-	H	-	-	2:N66D	-	-	-
P1939-K2	19	-	-	2:T37A	-	-	H	-	-	-	1:S69F	-	-
P1939-K3	13	-	-	-	-	-	H	-	-	-	-	-	-
P2451-K1	39	-	-	-	-	-	-	-	-	2:N66D	-	-	-
P2451-K2	24	-	-	-	-	-	-	-	-	-	-	1:V71A	-
P2920-K1	18	-	-	-	-	-	-	-	-	D	-	-	-
P2920-K2	11	-	-	-	-	-	-	-	-	D	-	-	-
P3020-K1	21	-	-	-	-	-	H	-	-	D	-	-	-
P3020-K2	21	1:S32R	-	-	-	-	H	-	-	D	-	-	-
P3020-K3	22	-	-	-	-	-	H	7:Q44*	-	D	-	-	-
P3916-K1	15	-	2:G35E	-	-	-	-	-	-	T	-	-	-
P3916-K2	13	-	-	-	-	-	1:Q43H	-	-	12:N66T	-	-	-
	N = 398												

Continued on next page

Supplementary Table S8. ***Continued.***

	n	75:R	76:F	77:G	85:T	86:D	88:T	89:L	92:S	93:R	94:V	95:E
P0103-K1	38	-	-	-	-	6:D86Y	-	-	-	-	1:V94A	-
P0103-K2	33	-	-	-	-	2:D86Y	-	-	-	-	-	-
P0103-K3	8	-	-	-	-	-	-	-	-	-	-	-
P0907-K1	16	-	-	-	-	-	-	-	-	-	-	2:E95G
P0907-K2	17	-	-	-	-	-	-	-	-	-	-	-
P1422-K1	14	1:R75G	-	-	-	A	-	-	N	1:R93G	-	-
P1422-K2	26	1:R75G	-	-	-	A	1:T88A	-	N	-	-	-
P1422-K3	11	-	-	-	-	A	-	-	N	-	-	-
P1939-K1	19	-	-	-	-	2:D86G	-	-	-	-	-	-
P1939-K2	19	-	-	-	-	-	-	1:L89V	-	-	-	-
P1939-K3	13	-	-	-	-	-	-	-	-	-	-	-
P2451-K1	39	-	1:F76L	-	-	2:D86A	1:T88A	-	2:S92N	-	-	-
P2451-K2	24	-	-	-	-	-	-	-	-	-	-	1:E95D
P2920-K1	18	-	-	-	6:T85A	-	-	-	-	-	-	-
P2920-K2	11	-	-	-	-	-	-	-	-	-	-	-
P3020-K1	21	-	-	-	-	T	-	-	T	-	-	-
P3020-K2	21	-	-	1:S77G	-	T	-	-	T	-	-	-
P3020-K3	22	-	-	-	-	T	-	-	T	-	-	-
P3916-K1	15	-	-	-	-	-	-	-	R	-	-	-
P3916-K2	13	-	-	-	-	-	-	-	12:S92R	-	-	-
	N = 398											

	n	96:A	97:E	99:V	101:V	103:Y	CM	UCM	S	
P0103-K1	38	7:A96S	-	1:V99A	7:V101L	-	9	6	0	& sharedmutation at codons 56 which is not affected by ID
P0103-K2	33	2:A96S	-	-	2:V101L	-	6	1	0	& sharedmutation at codons 56 which is not affected by ID
P0103-K3	8	-	-	-	-	-	0	1	0	& sharedmutation at codons 56 which is not affected by ID
P0907-K1	16	-	-	-	-	1:Y103H	2	2	3	
P0907-K2	17	-	-	-	-	-	0	0	3	
P1422-K1	14	-	-	-	-	-	5	2	7	
P1422-K2	26	-	-	-	-	-	1	5	7	
P1422-K3	11	-	-	-	-	-	0	1	7	
P1939-K1	19	-	17:E97D	-	17:V101F	-	9	1	1	
P1939-K2	19	-	D	-	F	1:Y103S	5	5	4	
P1939-K3	13	-	D	-	F	-	0	0	5	
P2451-K1	39	-	-	-	37:V101I	-	11	4	0	
P2451-K2	24	-	-	-	I	-	1	6	1	
P2920-K1	18	1:A96T	-	12:V99I	6:V101A	-	6	1	1	
P2920-K2	11	-	-	10:V99I	1:V101A	-	1	3	2	
P3020-K1	21	-	-	I	-	-	0	0	7	& shared mutations at codons 13,22,36,39,49 & 90 which are not affected by ID
P3020-K2	21	-	1:E97G	I	-	-	0	5	7	& shared mutations at codons 13,22,36,39,49 & 90 which are not affected by ID
P3020-K3	22	-	-	I	-	-	1	0	7	& shared mutations at codons 13,22,36,39,49 & 90 which are not affected by ID
P3916-K1	15	-	-	-	-	-	1	3	3	
P3916-K2	13	-	1:E97D	-	1:V101F	-	3	5	0	
	N = 398									