

Appendix 1

Table S1: Acid-base classification of *HLA-DRB1* alleles

<i>HLA-DRB1</i> alleles	AA sequence at positions 13,70–74	Tezenas' classification	Mattey's classification	De Vries' classification	Reviron	Acid-base classification
*01:03, *04:02, *11:02; *13:01, *13:02, *13:04	x** ⁻ -D-E-RAA	S1	D70+	P	XP4n	A
*11:03,	x** ⁻ -D-E-RAA	S1	D70+	N	XP4n	A
*13:23; *15	R-Q-A-RAA	S1	D70-	P	XP4p	BN
*13:03	S-D-K-RAA	S2	D70+	P	XP4n	NN
*04:01; *04:13	H-Q-K-RAA	S2	SE	SE	SE	BB
*12:01, *13:06, *13:25, *14:22,	G-D-R-RAA	S3D	D70+	P	XP4n	NN
*11:01, *11:04, *13:05; *16	S-D-R-RAA	S3D	D70+	N	XP4p	NN
*01:01, *01:02	F-Q-R-RAA	S3P	SE	SE	SE	BN
*04:04, *04:05, *04:08	H-Q-R-RAA	S3P	SE	SE	SE	BB
*14:02	S-Q-R-RAA	S3P	SE	SE	SE	BN
*10:01	F-R-R-RAA	S3P	SE	SE	SE	BN
*03	x** ⁻ -Q-K-RGR	X	D70-	N	XP4p	X
*04:03, *04:06; *04:07, *04:11; *04:59	x** ⁻ -Q-R-RAE	X	D70-	N	XP4p	X

*07:01	x**-D-R-RGQ	X	D70+	P	XP4n	X
*08	x**-D-R-RAL	X	D70+	N	XP4n	X
*09:01	x**-R-R-RAE	X	D70-	N	XP4p	X
*14:01; *14:04	x**-R-R-RAE	X	D70-	N	XP4p	X

RA : rheumatoid arthritis; AA: amino acid; D for aspartic acid, Q for glutamine, R for arginine, A for alanine, E for glutamic acid, K for lysine, G for glycine, L for leucine, I for isoleucine; F for phenylalanine; ACPA: anti-citrullinated peptide antibodies; BB: allele group containing basic AA at position 13, 70 and 71, BN: allele group containing either a basic amino acid at position 13 and a neutral or acid and basic amino acid at position 70 and 71 or a neutral amino acid at position 13 and a basic amino acid at position 70 and 71, A: allele group containing acid amino acids at position 70 and 71; NN: allele group with a neutral amino acid at position 13 and either a basic and an acidic amino acid at positions 70 and 71 or 2 neutral amino acids at position 70 and 71; X: allele group not containing RAA sequence at position 72-74;; N: allele group not containing an isoleucine at position 67; P: allele group containing an isoleucine at position 67; SE: Shared Epitope; D70-: allele group not containing an aspartic acid at position 70; D70+: allele group containing an aspartic acid at position 70. XP4p: fourth pocket positively charged according to Revirion's classification; XP4n: fourth pocket not charged or negatively charged;** : the amino acid at position 13 could be a Serine, Histidine, Glycine, Tryptophane or a Phenylalanine

Table S2: Number of patients with ACPA presence depending on *HLA-DRB1* allele carriage according to acid-base classification in ESPOIR and EAC

Cohort	ESPOIR		EAC	
	ACPA-presence	ACPA-absence	ACPA-presence	ACPA-absence
BB carriers	162 (71.4)	65 (28.6)	177 (70.8)	73 (29.2)
BB non carriers	135 (35.1)	250 (64.9)	137 (40.1)	205 (59.9)
BN carriers	135 (50.4)	133 (49.6)	143 (55.0)	117 (45.0)
BN non carriers	162 (47.1)	182 (52.9)	171 (51.5)	161 (48.5)
A carriers	45 (30.6)	102 (69.4)	39 (33.6)	77 (66.4)
A non carriers	252 (54.2)	213 (45.8)	275 (57.8)	201 (42.2)
NN and X carriers	167 (40.8)	242 (59.2)	183 (47.0)	206 (53.0)
NN and X non carriers	130 (64.0)	73 (36.0)	131 (64.5)	72 (35.5)

BB: allele group containing basic AA at position 13, 70 and 71, BN: allele group containing either a basic amino acid at position 13 and a neutral or acid and basic amino acid at position 70 and 71 or a neutral amino acid at position 13 and a basic amino acid at position 70 and 71, A: allele group containing acid amino acids at position 70 and 71; NN: allele group with a neutral amino acid at position 13 and either a basic and an acidic amino acid at positions 70 and 71 or 2 neutral amino acids at position 70 and 71; X: allele group not containing RAA sequence at position 72-74;

Table S3 : Number of patients with ACPA presence depending on *HLA-DRB1* genotypes according to acid-base classification in ESPOIR and EAC

Number of patients with ACPA presence (%)	ESPOIR	EAC
NN/NN, X/NN or XX referent	30 (32.6)	31 (34.0)
SA/SA, SA/NN or SA/X	20 (22.2)	13 (20.3)
BN/BN, BN/NN or BN/X	77 (45.0)	83 (51.9)
SA/BB	17 (68.0)	16 (64.0)
BN/BB	50 (76.9)	50 (68.5)
BB/BB	33 (86.8)	29 (93.5)

BB: allele group containing basic AA at position 13, 70 and 71, BN: allele group containing either a basic amino acid at position 13 and a neutral or acid and basic amino acid at position 70 and 71 or a neutral amino acid at position 13 and a basic amino acid at position 70 and 71, A: allele group containing acid amino acids at position 70 and 71; NN: allele group with a neutral amino acid at position 13 and either a basic and an acidic amino acid at positions 70 and 71 or 2 neutral amino acids at position 70 and 71; X: allele group not containing RAA sequence at position 72-74;

Table S4: Number of patients with progression depending on *HLA-DRB1* allele carriage according to acid-base classification in ESPOIR and EAC

	ESPOIR		EAC	
	Patients with progression, number (%)	Patients without progression, number (%)	Patients with progression, number (%)	Patients without progression, number (%)
BB carriers	85 (44.3)	107 (55.7)	85 (47.2)	95 (52.8)
BB non carriers	67 (20.7)	257 (79.3)	79 (33.5)	157 (66.5)
BN carriers	65 (28.8)	161 (71.2)	74 (40.7)	108 (59.3)
BN non carriers	87 (30.0)	203 (70.0)	90 (38.5)	144 (61.5)
A carriers	20 (15.4)	110 (84.6)	16 (20.0)	64 (80.0)
A non carriers	132 (34.2)	254 (65.8)	148 (44.1)	188 (56.0)
NN and X carriers	90 (26.3)	252 (73.7)	101 (37.4)	169 (62.6)
NN and X non carriers	62 (35.6)	112 (64.4)	63 (43.2)	83 (56.9)

BB: allele group containing basic AA at position 13, 70 and 71, BN: allele group containing either a basic amino acid at position 13 and a neutral or acid and basic amino acid at position 70 and 71 or a neutral amino acid at position 13 and a basic amino acid at position 70 and 71, A: allele group containing acid amino acids at position 70 and 71; NN: allele group with a neutral amino acid at position 13 and either a basic and an acidic amino acid at positions 70 and 71 or 2 neutral amino acids at position 70 and 71; X: allele group not containing RAA sequence at position 72-74;

Table S5. ACPA presence in patients with or without progression according to each allele of acid-base classification

Allele carriage	ESPOIR			EAC		
	ACPA presence in patients with progression N (%)	ACPA presence in patients without progression N (%)	p value	ACPA presence in patients with progression N (%)	ACPA presence in patients without progression N (%)	p value
A	13 (65)	28 (25)	<0.001	10 (67)	17 (27)	0.003
BB	72 (85)	71 (66)	0.004	76 (89)	55 (59)	<0.001
BN	46 (71)	69 (43)	<0.001	62 (86)	41 (38)	<0.001
X and NN	66 (73)	82 (33)	<0.001	69 (70)	65 (39)	<0.001

BB: allele group containing basic AA at position 13, 70 and 71, BN: allele group containing either a basic amino acid at position 13 and a neutral or acid and basic amino acid at position 70 and 71 or a neutral amino acid at position 13 and a basic amino acid at position 70 and 71, A: allele group containing acid amino acids at position 70 and 71; NN: allele group with a neutral amino acid at position 13 and either a basic and an acidic amino acid at positions 70 and 71 or 2 neutral amino acids at position 70 and 71; X: allele group not containing RAA sequence at position 72-74;

Table S6: Number of patients with progression depending on *HLA-DRB1* genotypes according to acid-base classification in ESPOIR and EAC

Number of patients with progression (%)	ESPOIR	EAC
NN/NN, X/NN or XX referent	18 (24.3)	25 (37.3)
SA/SA, SA/NN or SA/X	7 (8.9)	9 (20.9)
BN/BN, BN/NN or BN/X	37 (26.1)	42 (39.3)
SA/BB	8 (36.4)	4 (22.2)
BN/BB	23 (41.8)	29 (51.8)
BB/BB	18 (52.9)	15 (65.2)

BB: allele group containing basic AA at position 13, 70 and 71, BN: allele group containing either a basic amino acid at position 13 and a neutral or acid and basic amino acid at position 70 and 71 or a neutral amino acid at position 13 and a basic amino acid at position 70 and 71, A: allele group containing acid amino acids at position 70 and 71; NN: allele group with a neutral amino acid at position 13 and either a basic and an acidic amino acid at positions 70 and 71 or 2 neutral amino acids at position 70 and 71; X: allele group not containing RAA sequence at position 72-74;