AlloSeq™ Assign®

AlloSeq Assign Motifs

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CareDx Technical Support

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TEC747-S_AlloSeq Assign 1.0_Motifs version 1.0 Effective 14 Jun 22

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Overview

Reporting of sequence motifs from AlloSeq Assign enables efficient means of identifying potentially problematic donor/patient mismatches. The sequence motifs reported by AlloSeq Assign have been included as they are of clinical significance in patient outcomes. Review of the motifs may aid in selecting a donor that will reduce the risk of rejection or GVHD in the patient.

Motif	Clinical Significance
HLA-B rs1050458C>T	This SNP located in exon 1 of HLA-B has been implicated in significantly higher risk of severe GVHD when it is mismatched. For donor patient pairs that are HLA-B genotype mismatched, selecting a donor that is matched at this marker reduces this risk.
HLA-G rs1610696C>G	**Reports suggest elevated HLA-G expression is associated with reduced allograft rejection**. Patient G + Donor C = reduced risk of rejection. Patient C + Donor C = best outcome.
HLA-DPB1 rs9277534A>G	This SNP is associated with level of DPB1 expression. The rs9277534-A allele is associated with low DPB1 expression, whereas the rs9277534-G allele is associated with high DPB1 expression. **Among recipients of HLA-DPB1-mismatched transplants from donors with the low-expression allele, recipients with the high-expression allele had a high risk of GVHD.** For donor patient pairs that are DPB1 mismatched, this marker can be used to select a DPB1-mismatched donors who generate a permissive DPB1 mismatch against low-expression patient DPB1 alleles.
MICA rs1051792G>A	**This marker has been implicated in a higher risk of GVHD when it is mismatched.** Donor + patient mismatched at rs1051792 = increased risk. Donor + patient matched at rs1051792 = reduced risk.
MICB98 Met/Ile	**This marker has been implicated in a higher risk of GVHD when it is mismatched.** Donor + Patient matched at HLA&MICA but mismatched at MICB98 = increased risk of GVHD, and higher rate of relapse. Donor + Patient matched at HLA&MICA AND matched at MICB98 = decreased risk of GVHD.

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HLA Class I Motifs

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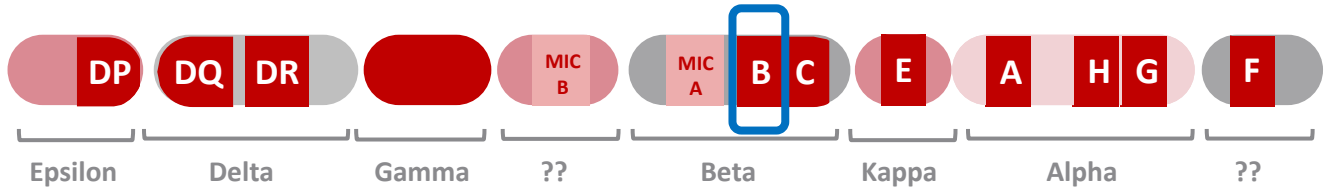

HLA-B rs1050458C>T

Motif ID:	**rs1050458C>T**	Locus:	**HLA-B**	Implemented (Ref. Version #):	3.41
Supporting Publication:	Petersdorf EW, Carrington M, O'hUigin C, Bengtsson M, De Santis D, Dubois V, Gooley T, Horowitz M, Hsu K, Madrigal JA, Maiers MJ, Malkki M, McKallor C, Morishima Y, Oudshoorn M, Spellman SR, Villard J, Stevenson P; International Histocompatibility Working Group in Hematopoietic Cell Transplantation. **Role of HLA-B exon 1 in graft-versus-host disease after unrelated haemopoietic cell transplantation: a retrospective cohort study**. *Lancet Haematol*. 2020 Jan;7(1):e50-e60.				
Impact of polymorphism:	The mature HLA Class I molecule that is expressed on the cell surface is encoded by exons 2–7. Exon 1 of Class I genes encodes a separate leader peptide, which is not a structural moiety of the mature Class I molecule, but can be bound and presented by Class I, notably HLA-E. HLA-A and HLA-C leader sequences are largely invariant and encode methionine at the –21 position. A sequence dimorphism (rs1050458) in exon 1 of HLA-B gives rise to leader peptides containing methionine (Met; M) or threonine (Thr; T), which differentially influence natural killer and T-cell alloresponses. ***Severe GVHD was significantly higher with HLA-B leader mismatching compared to leader matching, and when the shared HLA-B allotype had an M leader compared with a T leader.*** The preferred HLA-B-mismatched donor is leader-matched and shares a T leader allotype. This mutation is common among HLA-B*07, 08, 14, 38, 39, 42, 48, 67, 73 and 81 allele groups.				

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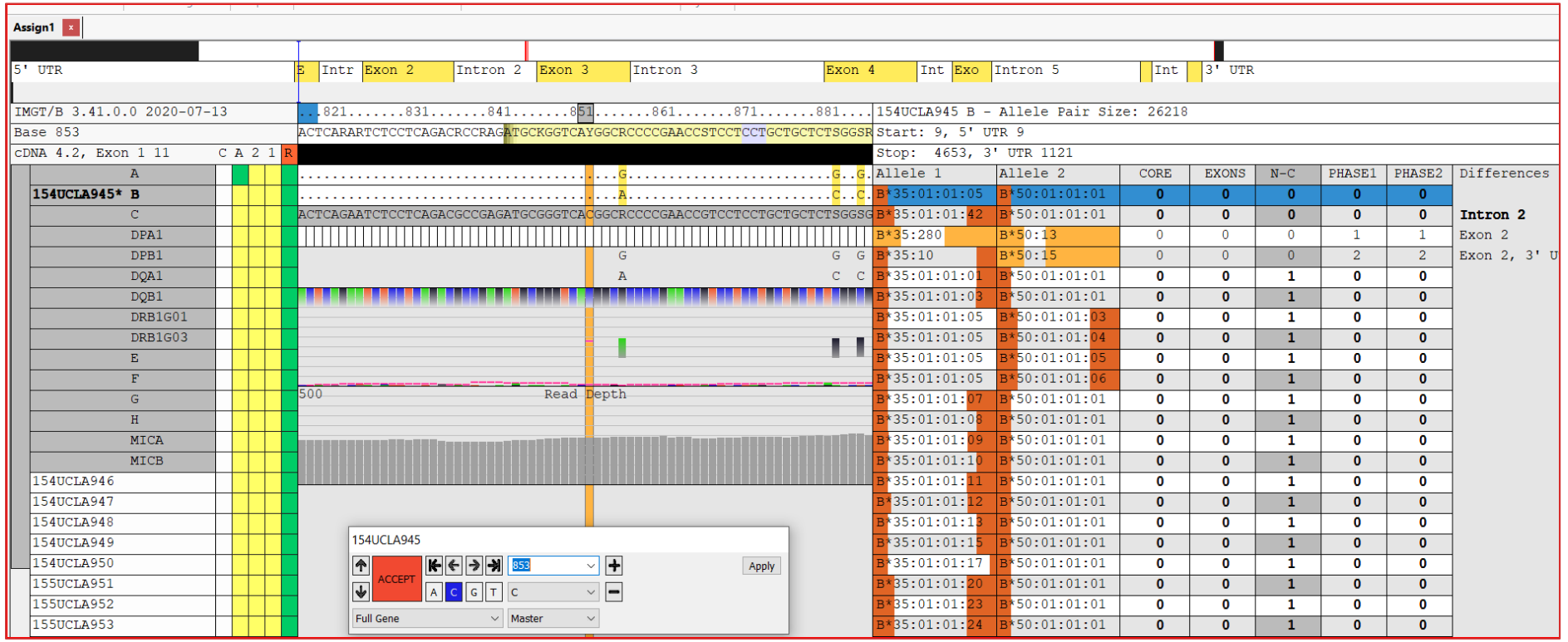
Motif ID:	rs1050458C>T	Locus:	HLA-B	Implemented (Ref. Version #):	3.41

Example Display:

Homozygous C



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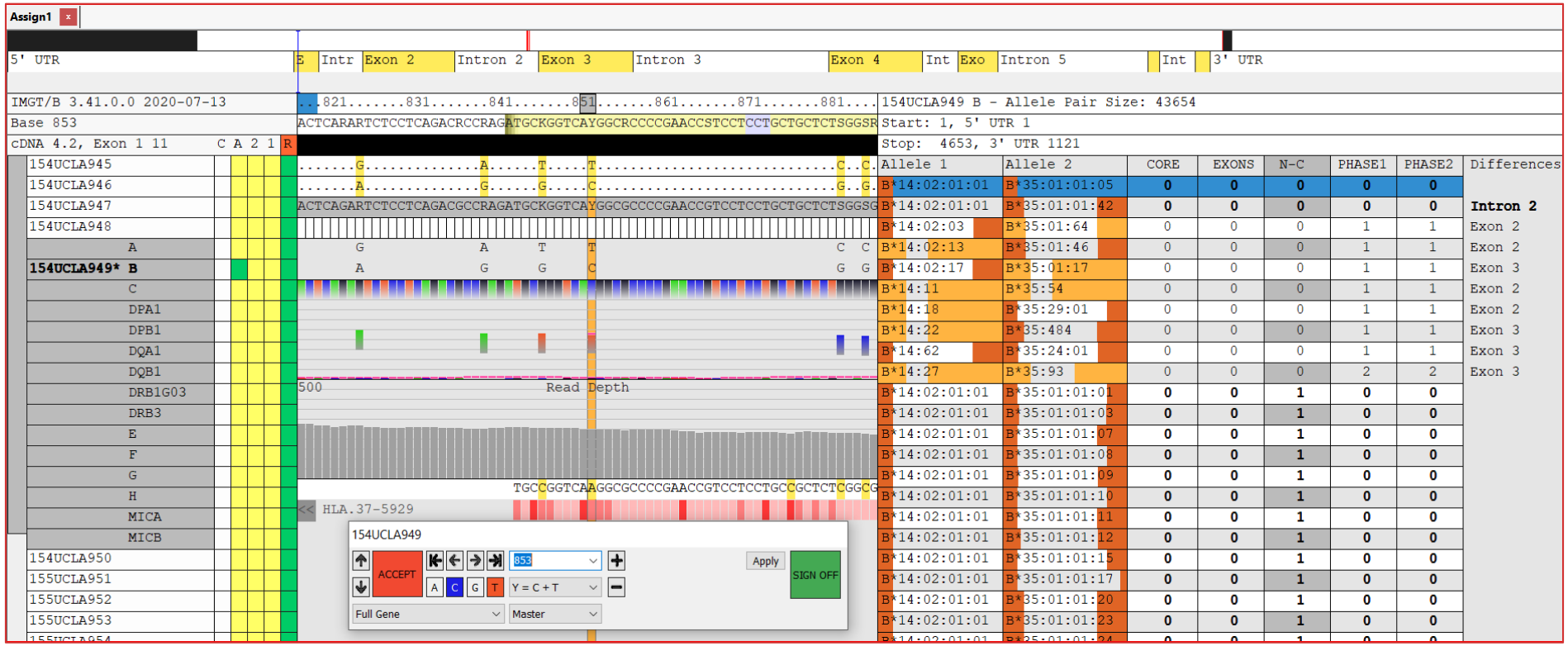
Motif ID:	rs1050458C>T	Locus:	HLA-B	Implemented (Ref. Version #):	3.41

Example Display:

Heterozygous C/T



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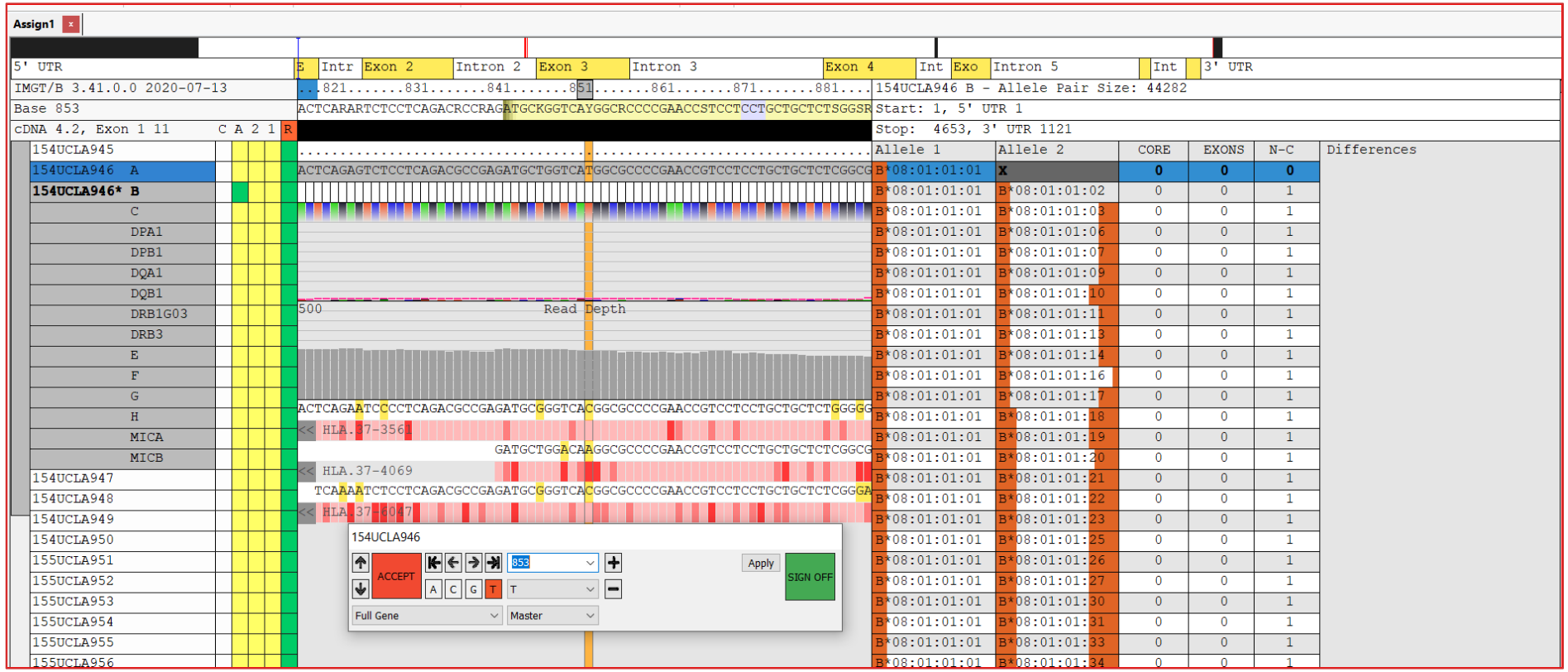
Motif ID:	**rs1050458C>T**	Locus:	**HLA-B**	Implemented (Ref. Version #):	3.41

Example Display:

Homozygous T



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Motif ID:	**rs1050458C>T**	Locus:	**HLA-B**	Implemented (Ref. Version #):	3.41

Example Display:

Summary Table Report:

Motifs.

	IMGT/F	IMGT/G	IMGT/H	IMGT/A	IMGT/E	IMGT/C	IMGT/B	IMGT/MICA	IMGT/MICB
154UCLA945		rs1610696:					Bw6, rs1050458:CC	129Met, 129\	98Ile
154UCLA946		rs1610696:**				Bw6	Bw6, rs1050458:TT	129Val	98Met
154UCLA947		rs1610696:GC				Bw6	Bw6, rs1050458:TT	129Val	98Met, 98Ile
154UCLA948		rs1610696:**		Bw4		Bw6	Bw4, Bw6, rs1050458:CC	129Val	98Ile
154UCLA949		rs1610696:		Bw4		Bw6	Bw6, rs1050458:TC	129Met	98Ile

Genotyping Report:

Reference: **IMGT/B 3.41.0.0 2020-07-13**

Summary

The allele pairs listed below are compatible with the consensus sequence.

B*14:02:01:01	B*35:01:01:05	
B*14:02:01:01	B*35:01:01:42	Intron 2

Motifs: Bw6, rs1050458:TC Heterozygous

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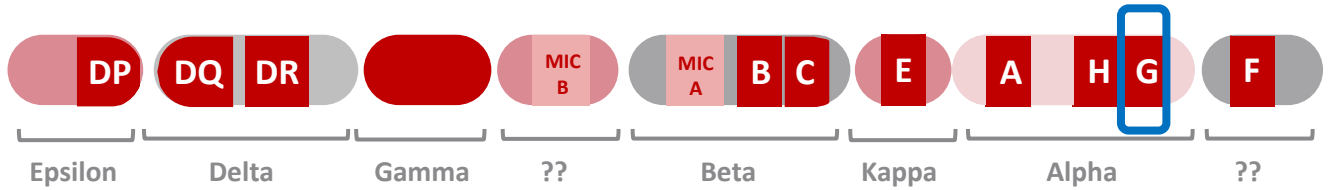

HLA-G rs1610696C>G

Motif ID:	**rs1610696C>G**	Locus:	**HLA-G**	Implemented (Ref. Version #):	3.41
Supporting Publication:	Adamson MB, Di Giovanni B, Ribeiro RVP, Yu F, Lazarte J, Rao V, Delgado DH. **HLA-G +3196 polymorphism as a risk factor for cell mediated rejection following heart transplant.** *Hum Immunol*. 2020 Apr;81(4):134-140.				
Impact of polymorphism:	Human leukocyte antigen-G (HLA-G) is an immune checkpoint which dampens the immune response. Reports suggest elevated HLA-G expression is associated with reduced allograft rejection. The +3196C/G polymorphism is located within the 3'UTR of the HLA-G gene, 3196 base pairs downstream of the initiation sequence. The 3'UTR, specifically exon 8, is a vital component for HLA-G transcriptional regulation. The current study identified the +3196 G allele as a risk factor for cell mediated rejection (CMR). Compared to the minor GG genotype, CG had a 47.2% reduction in CMR risk while CC had a 66.9% reduction. Note: Equivalent to c.*287C>G (using standard HGVS nomenclature, which means 287 bp downstream of the T in the TGA stop codon). Currently this position is not included in IMGT /Unknown.				

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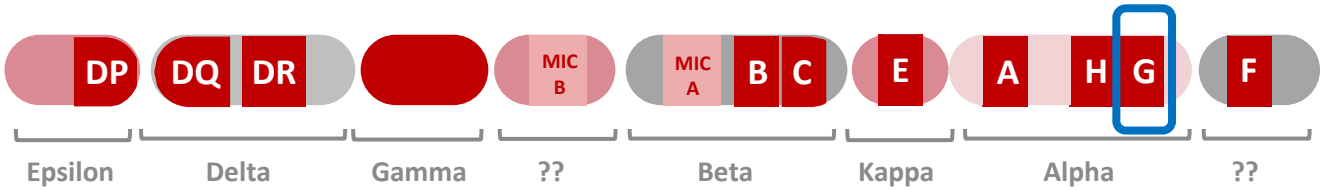
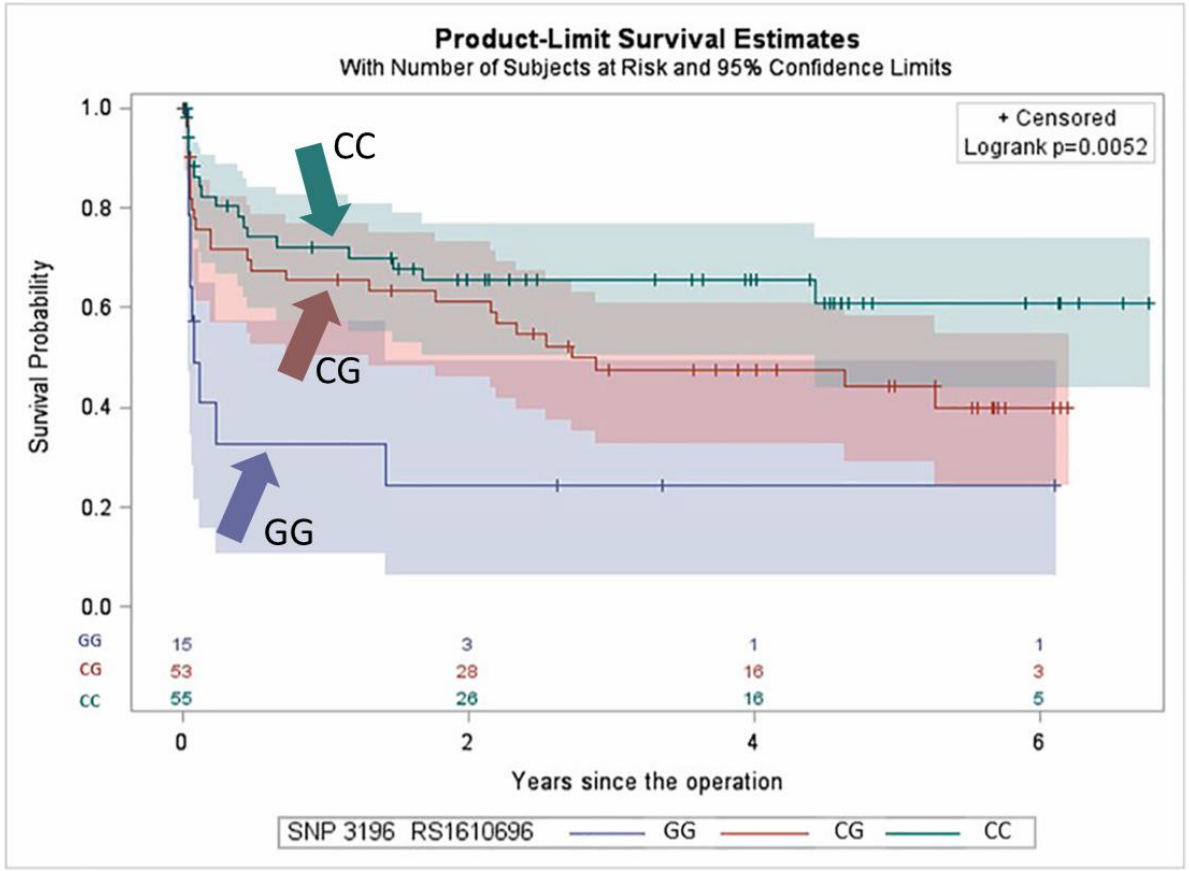


HLA-G rs1610696C>G

The freedom from cell mediated rejection (CMR) stratified by each +3196C/G genotype. Highest risk was observed in the group homozygous for the G risk allele, whereas the lowest risk was observed with the presence of the C allele. Risk of CMR increased proportionally with an increase in the number of risk allele G (p = 0.0052).



Adamson. et al. *Hum Immunol*. 2020 Apr;81(4):134-140

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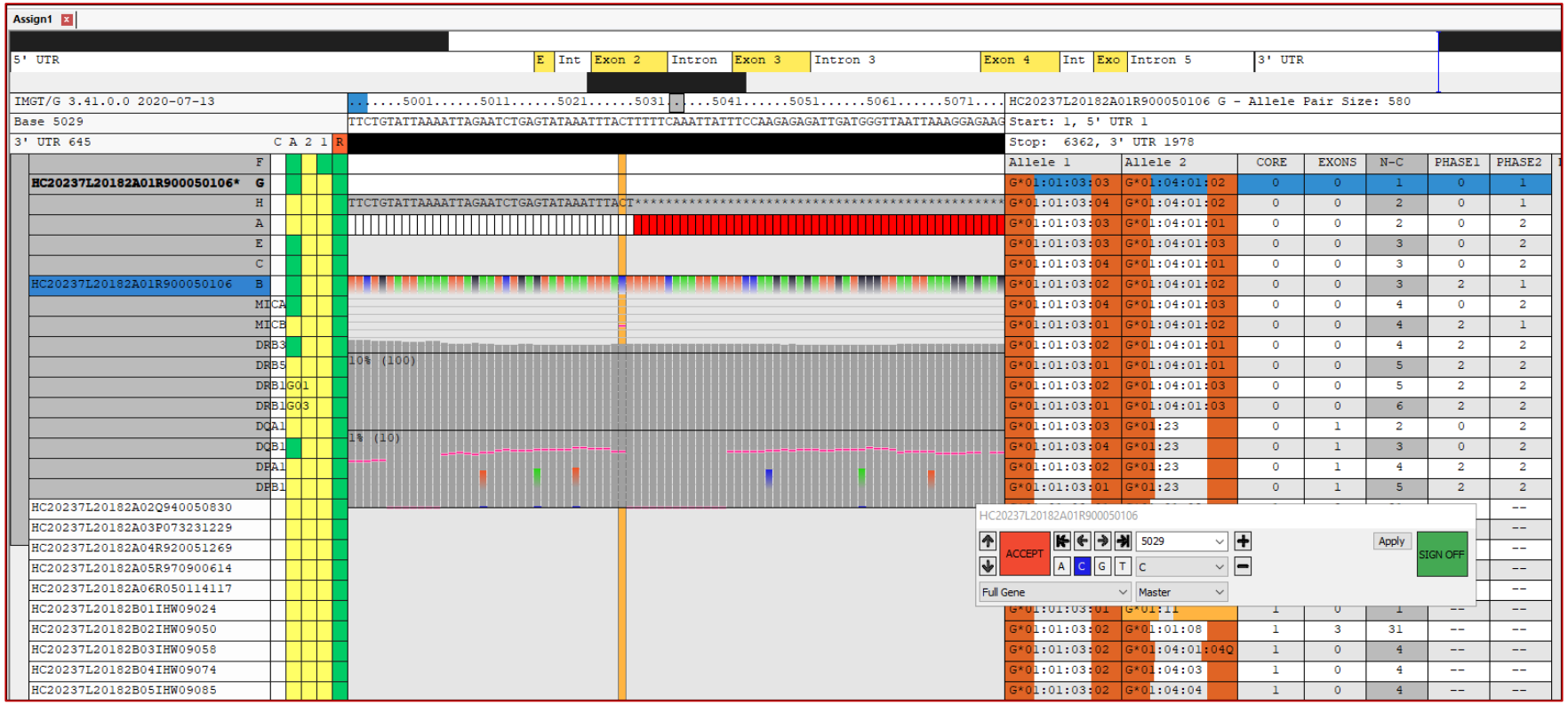
Motif ID:	rs1610696C>G	Locus:	HLA-G	Implemented (Ref. Version #):	3.41

Example Display:

Homozygous C



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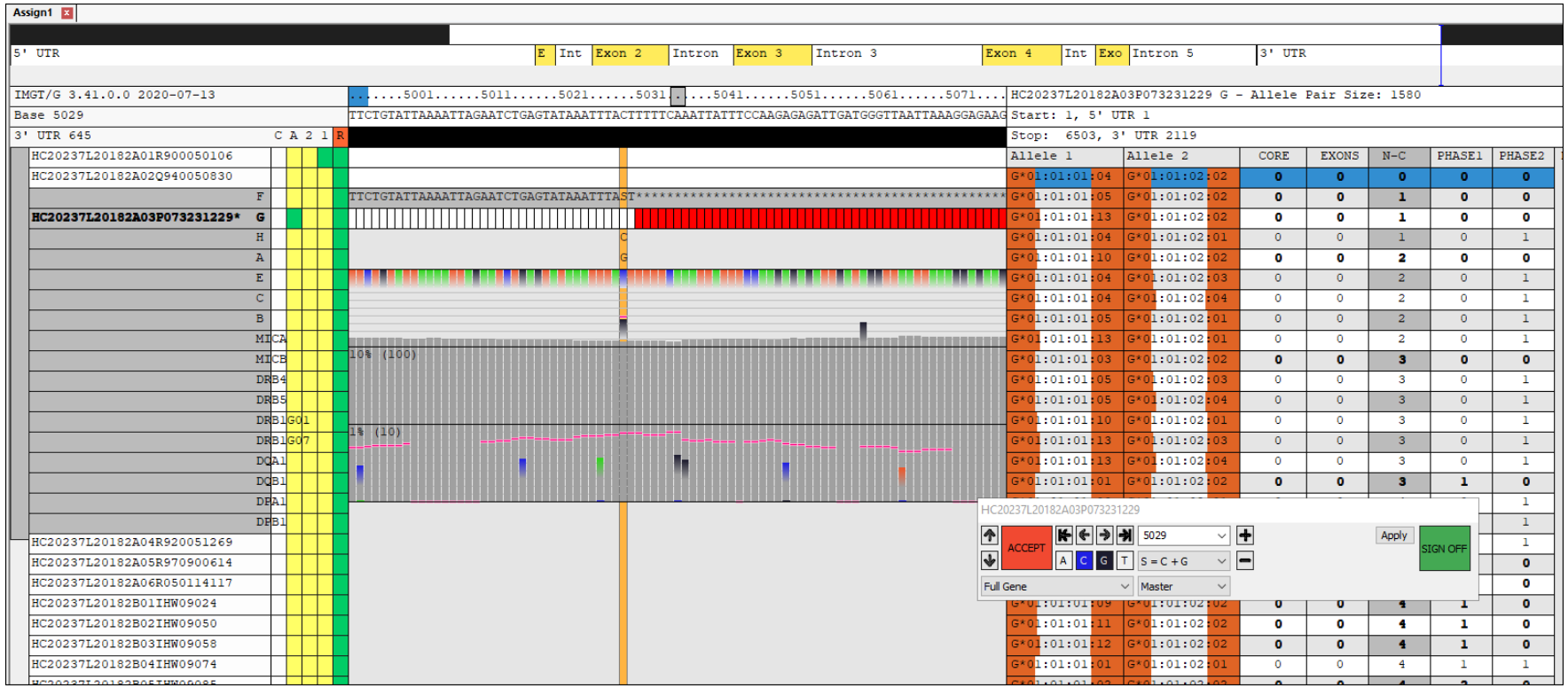
Motif ID:	**rs1610696C>G**	Locus:	**HLA-G**	Implemented (Ref. Version #):	3.41

Example Display:

Heterozygous C/G



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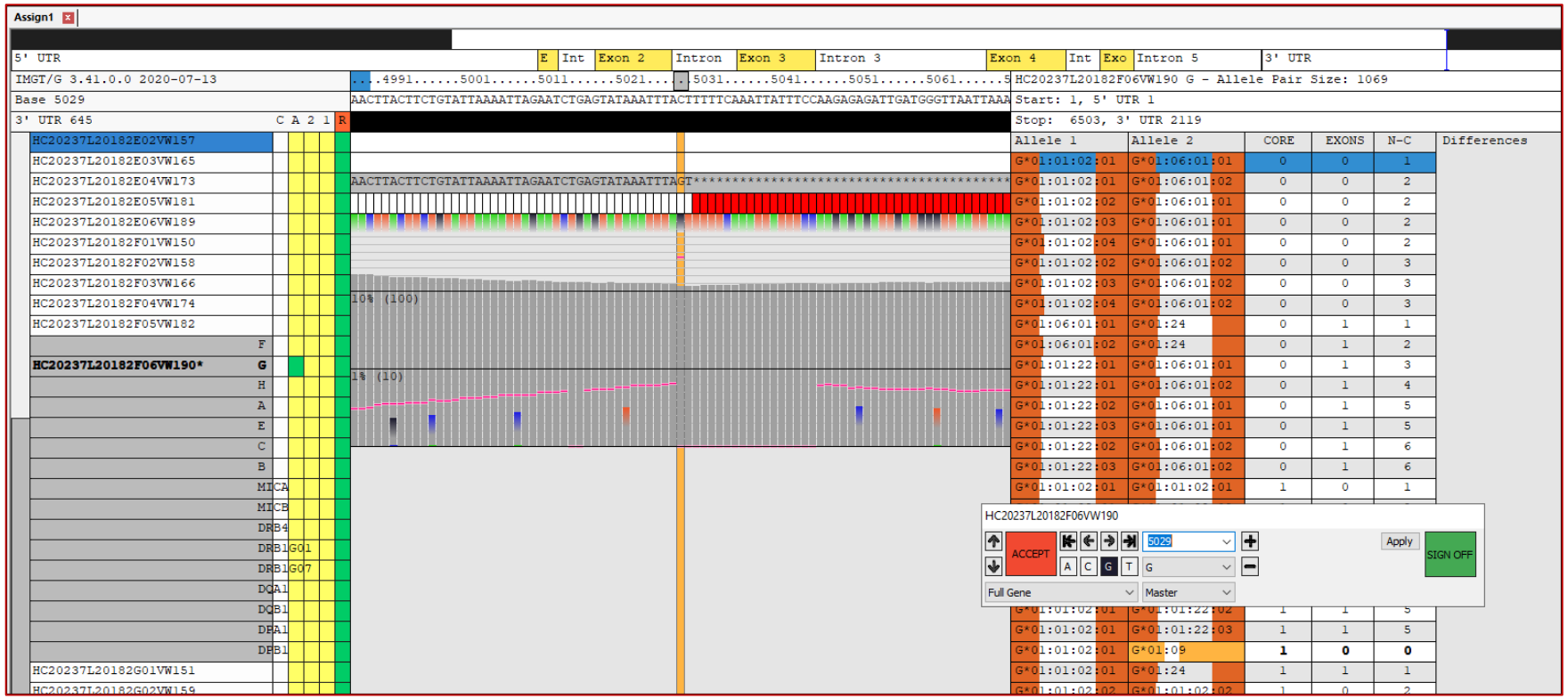
Motif ID:	**rs1610696C>G**	Locus:	**HLA-G**	Implemented (Ref. Version #):	3.41
Example Display:	**Homozygous G** 				

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Motif ID:	**rs1610696C>G**	Locus:	**HLA-G**	Implemented (Ref. Version #):	3.41

Example Display:

Summary Table Report:

Motifs.

	IMGT/F	IMGT/G	IMGT/H	IMGT/A	IMGT/E	IMGT/C	IMGT/B	IMGT/MICA	IMGT/MICB	IMGT/DRB3	IMGT/DRB4	IMGT/DRB5	IMGT/DRB1	IMGT/DQA1	IMGT/DQB1	IMGT/DPA1	IMGT/DPB1
HC20237L20182A01R900050106		rs1610696:CC		Bw4		Bw6	Bw6, rs1050	129Val	98Ile								rs9277534:GG
HC20237L20182A02Q940050830		rs1610696:CC				Bw6	Bw4, rs1050	129Met, 129	98Ile								rs9277534:GA
HC20237L20182A03P073231229		rs1610696:CG	Heterozygous			Bw6	Bw4, Bw6, rs	129Val	98Ile								rs9277534:GA
HC20237L20182A04R920051269		rs1610696:GG	Homozygous G			Bw6	Bw6, rs1050	129Val	98Met, 98Ile								rs9277534:AA
HC20237L20182A05R970900614		rs1610696:CG				Bw6	Bw4, Bw6, rs	129Val	98Met, 98Ile								rs9277534:GG
HC20237L20182A06R050114117		rs1610696:CG				Bw6	Bw4, Bw6, rs	129Val	98Ile								rs9277534:GA
HC20237L20182B01IHW09024		rs1610696:CC	Homozygous C			Bw6	Bw6, rs1050	129Met, 129	98Ile								rs9277534:GG
HC20237L20182B02IHW09050		rs1610696:CC				Bw6	Bw4, rs1050	129Val	98Ile								rs9277534:AA
HC20237L20182B03IHW09058		rs1610696:CC				Bw6	Bw6, rs1050	129Met	98Ile								rs9277534:GG

Genotyping Report:

Reference: IMGT/G 3.41.0.0 2020-07-13

Summary

The allele pairs listed below are compatible with the consensus sequence.

G*01:01:01:05	G*01:01:03:03

Motifs: rs1610696:CC Homozygous C

Reference: IMGT/G 3.41.0.0 2020-07-13

Summary

The allele pairs listed below are compatible with the consensus sequence.

G*01:01:01:04	G*01:01:02:02

Motifs: rs1610696:CG Heterozygous C/G

Reference: IMGT/G 3.41.0.0 2020-07-13

Summary

The allele pairs listed below are compatible with the consensus sequence.

G*01:01:02:01	G*01:01:22:01

Motifs: rs1610696:GG Homozygous G

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HLA Class II Motifs

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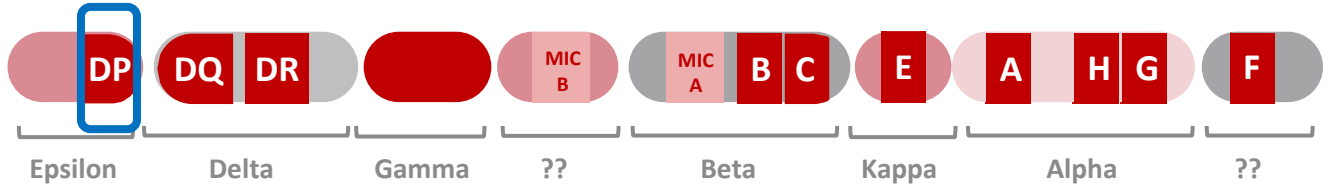

HLA-DPB1 rs9277534A>G

Motif ID:	**rs9277534A>G**	Locus:	**HLA-DPB1**	Implemented (Ref. Version #):	3.37.0
Supporting Publication:	• Petersdorf EW, Malkki M, O'hUigin C, Carrington M, Gooley T, Haagenson MD, Horowitz MM, Spellman SR, Wang T, Stevenson P. **High HLA-DP Expression and Graft-versus-Host Disease**. *N Engl J Med*. 2015 Aug 13;373(7):599-609 • Schöne B, Bergmann S, Lang K, Wagner I, Schmidt AH, Petersdorf EW, Lange V. **Predicting an HLA-DPB1 expression marker based on standard DPB1 genotyping: Linkage analysis of over 32,000 samples.** *Hum Immunol*. 2018 Jan;79(1):20-27.				
Impact of polymorphism:	HLA-DPB1 expression is associated with the rs9277534 A/G polymorphism located in the 3'UTR of the HLA-DPB1 gene. The rs9277534-A allele is associated with low DPB1 expression, whereas the rs9277534-G allele is associated with high DPB1 expression. Among recipients of HLA-DPB1-mismatched transplants from donors with the low-expression allele, recipients with the high-expression allele had a high risk of GVHD. When DPB1-matched donors are not available, this expression marker can be used to prospectively identify DPB1-mismatched donors who generate a permissive DPB1 mismatch against low-expression patient DPB1 alleles.				

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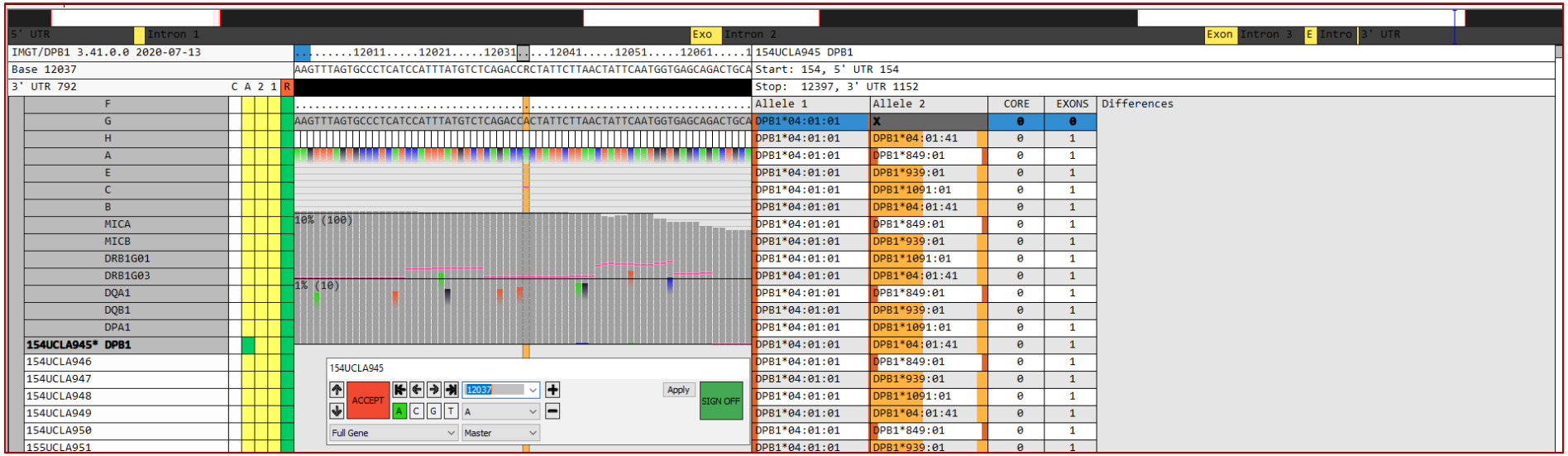
Motif ID:	**rs9277534A>G**	Locus:	**HLA-DPB1**	Implemented (Ref. Version #):	3.37.0

Example Display:

Homozygous A



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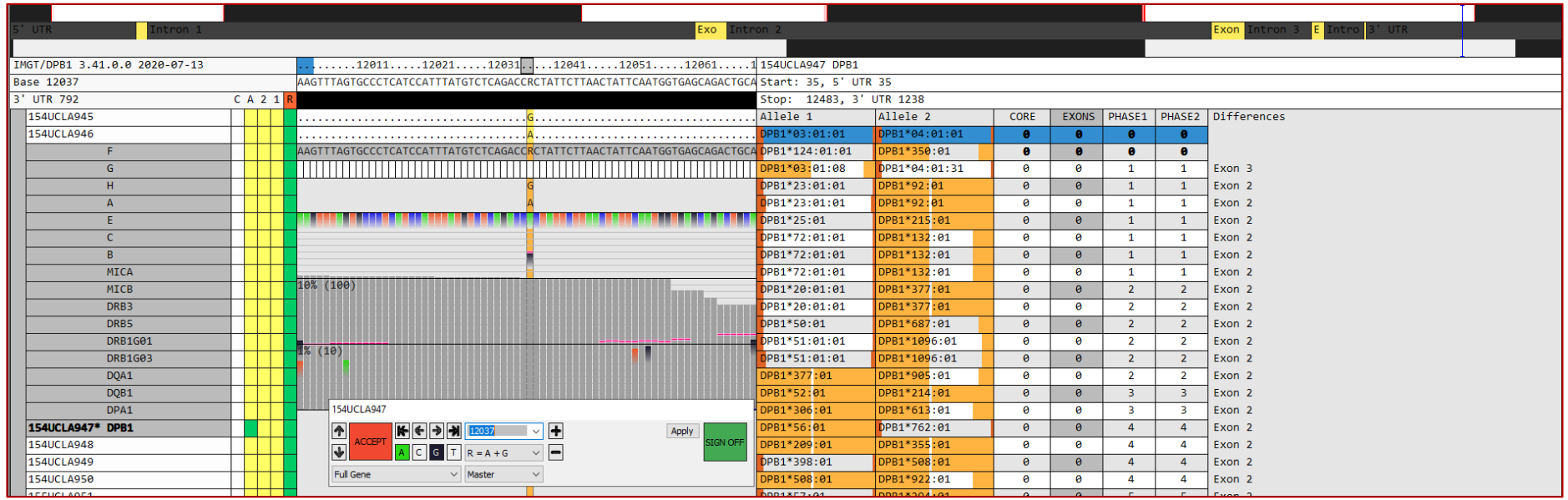
Motif ID:	rs9277534A>G	Locus:	HLA-DPB1	Implemented (Ref. Version #):	3.37.0

Example Display:

Heterozygous A/G



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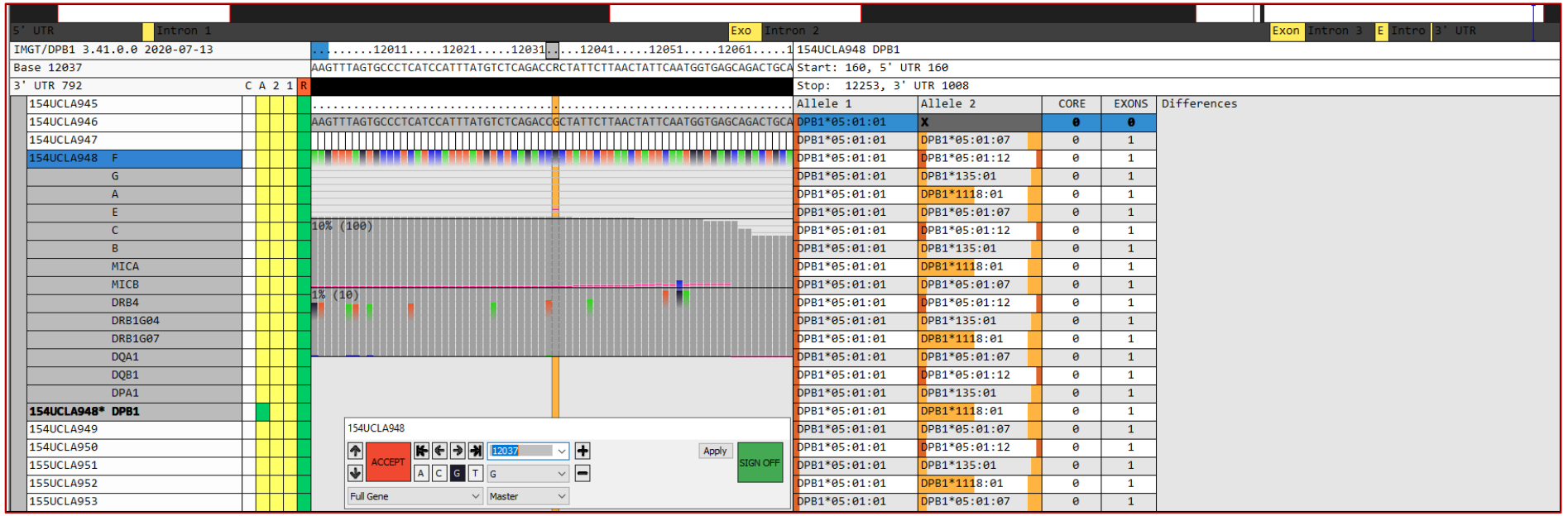
Motif ID:	rs9277534A>G	Locus:	HLA-DPB1	Implemented (Ref. Version #):	3.37.0

Example Display:

Homozygous G



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Motif ID:	**rs9277534A>G**	Locus:	**HLA-DPB1**	Implemented (Ref. Version #):	3.37.0

Example Display:

Summary Table Report:

Motifs.

	IMGT/DPB1	
154UCLA945	rs9277534:AA	Homozygous A
154UCLA946	rs9277534:GG	Homozygous G
154UCLA947	rs9277534:GA	Heterozygous A/G

Genotyping Report:

Sample: 154UCLA945
Reference: IMGT/DPB1 3.41.0.0 2020-07-13

Summary

The allele pairs listed below are compatible with the consensus sequence.

DPB1*04:01:01	X

Motifs: rs9277534:AA Homozygous A

Sample: 154UCLA947
Summary

The allele pairs listed below are compatible with the consensus sequence.

DPB1*03:01:01	DPB1*04:01:01
DPB1*124:01:01	DPB1*350:01

Motifs: rs9277534:GA Heterozygous A/G

Sample: 154UCLA948
Summary

The allele pairs listed below are compatible with the consensus sequence.

DPB1*05:01:01	X

Motifs: rs9277534:GG Homozygous G

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Additional MHC Motifs

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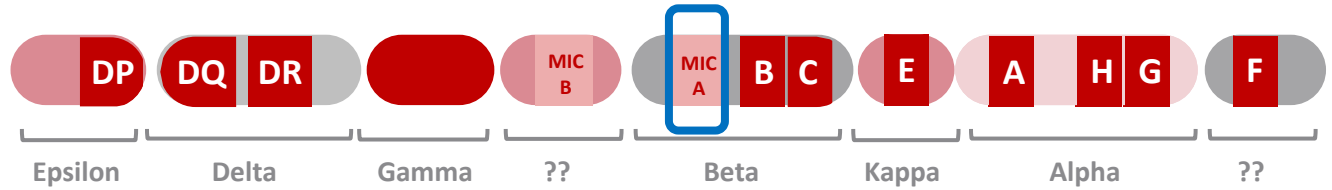

MICA rs1051792G>A; MICA-129Val/Met

Motif ID:	**rs1051792G>A; MICA-129Val/Met**	Locus:	**MICA**	Implemented (Ref. Version #):	3.37.0.1
Supporting Publication:	• Isernhagen A, Malzahn D, Bickeböller H, Dressel R. **Impact of the MICA-129Met/Val Dimorphism on NKG2D-Mediated Biological Functions and Disease Risks**. *Front Immunol*. 2016 Dec 12;7:588 • Fuerst D, Neuchel C, Niederwieser D, Bunjes D, Gramatzki M, Wagner E, Wulf G, Glass B, Pfreundschuh M, Einsele H, Arnold R, Stuhler G, Schaefer-Eckart K, Freitag S, Casper J, Kaufmann M, Wattad M, Hertenstein B, Klein S, Ringhoffer M, Mytilineos D, Tsamadou C, Mueller C, Schrezenmeier H, Mytilineos J. **Matching for the MICA-129 polymorphism is beneficial in unrelated hematopoietic stem cell transplantation**. *Blood.* 2016 Dec 29;128(26):3169-3176.				
Impact of polymorphism:	The MICA-129Val/Met dimorphism, caused by SNP rs1051792 at nucleotide position 454 (G>A) of the MICA gene causes a valine (Val) to methionine (Met) exchange at position 129 of the MICA protein, separating MICA into isoforms that bind NKG2D with high (Met) and low affinities (Val). Adverse overall survival and worse outcome for disease-free survival was observed in the 10/10 match group if MICA-129 was mismatched (10/10, hazard ratio, 1.77). Higher rates of acute GVHD were seen in MICA-129 mismatched cases. Exon 3, Position 8403 in AlloSeq Assign				

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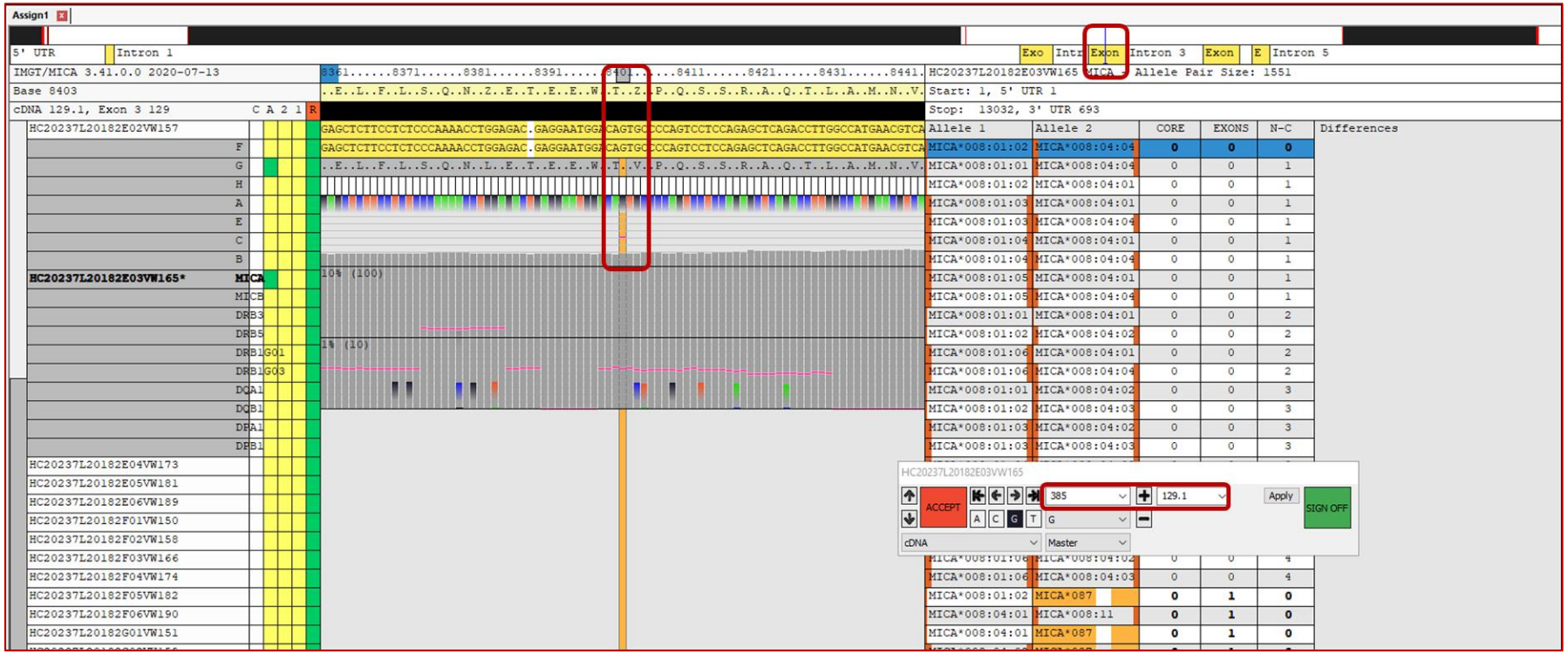
Motif ID:	**rs1051792G>A; MICA-129Val/Met**	Locus:	**MICA**	Implemented (Ref. Version #):	3.37.0.1
Example Display:	**Homozygous G - 129Val/Val** 				

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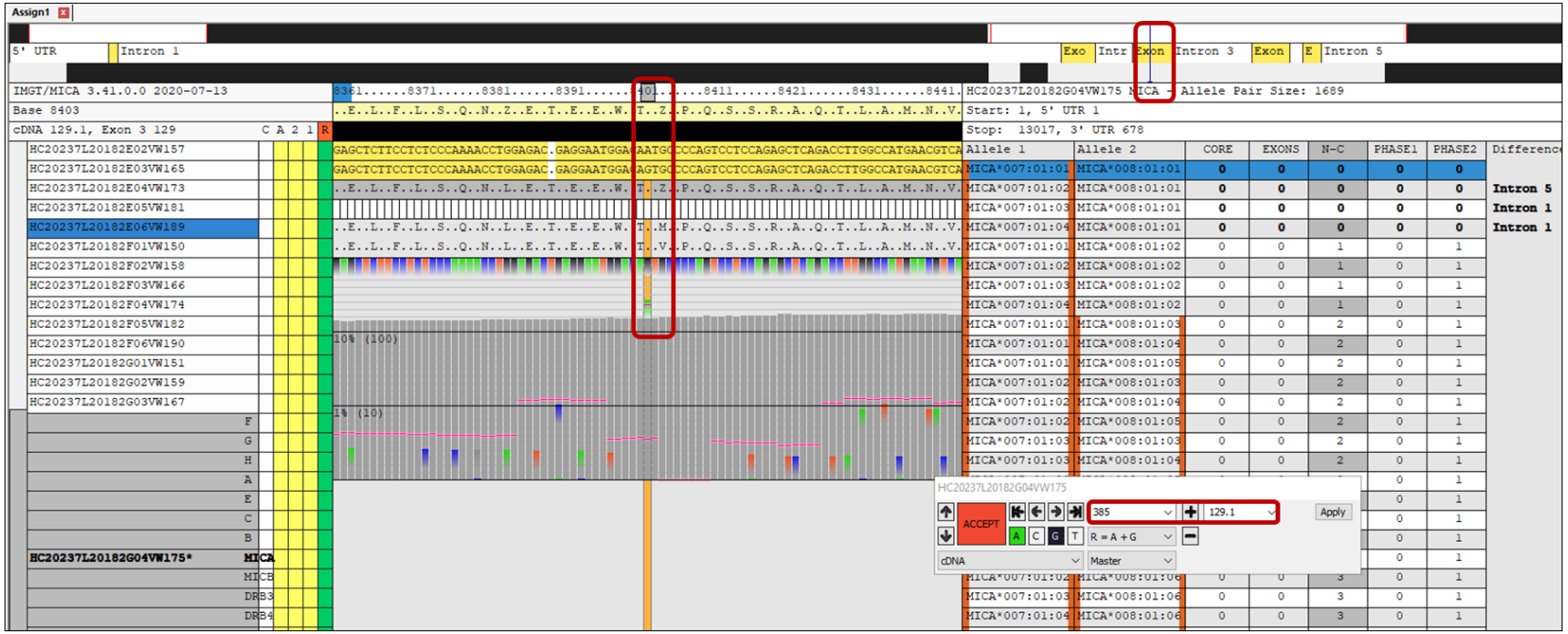
Motif ID:	rs1051792G>A; MICA-129Val/Met	Locus:	MICA	Implemented (Ref. Version #):	3.37.0.1
Example Display:	**Heterozygous G/A- 129Met/Val** 				

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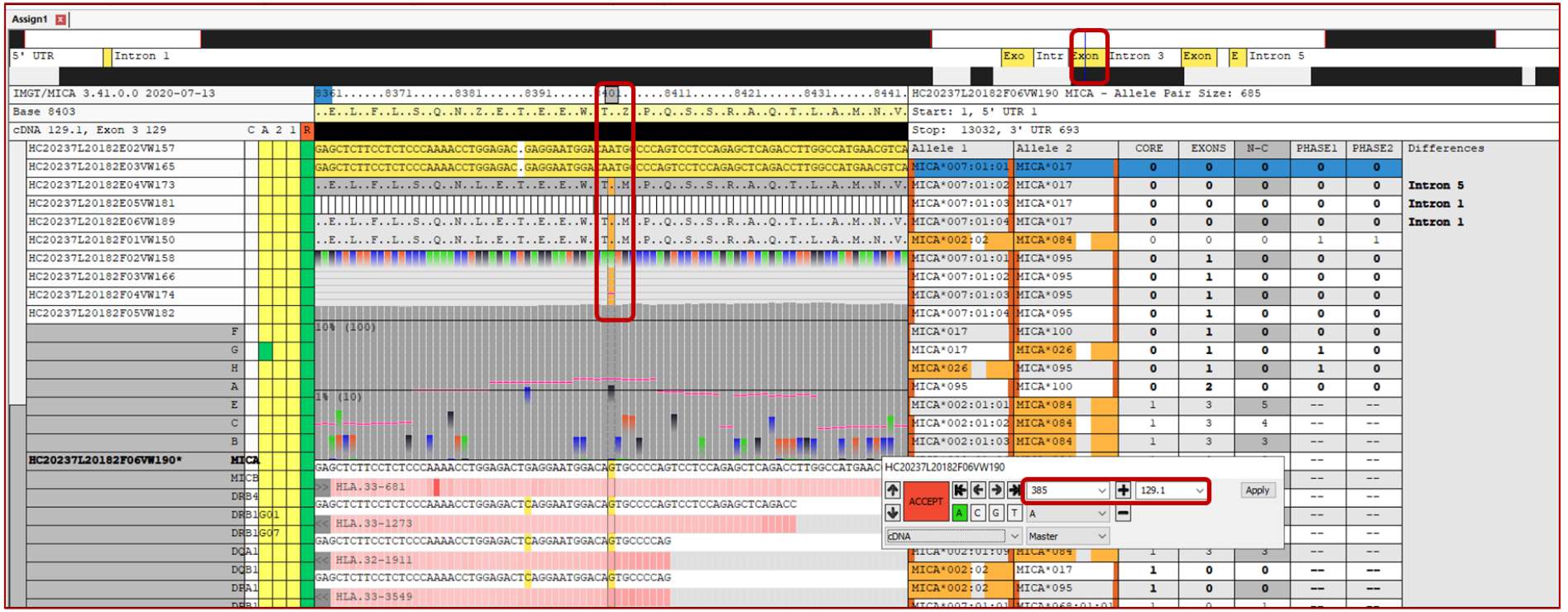
Motif ID:	rs1051792G>A; MICA-129Val/Met	Locus:	MICA	Implemented (Ref. Version #):	3.37.0.1
Example Display:	**Homozygous A – 129Met/Met**				



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Motif ID:	**rs1051792G>A; MICA-129Val/Met**	Locus:	**MICA**	Implemented (Ref. Version #):	3.37.0.1

Example Display:

Summary Table Report:

Motifs.

	IMGT/F	IMGT/G	IMGT/H	IMGT/A	IMGT/E	IMGT/C	IMGT/B	IMGT/MICA
HC20237L20182A01R900050106		rs1610696:CC		Bw4		Bw6	Bw6, rs1050	129Val
HC20237L20182A02Q940050830		rs1610696:CC				Bw6	Bw4, rs1050	129Met, 129Val
HC20237L20182A03P073231229		rs1610696:CG				Bw6	Bw4, Bw6, rs	129Val
HC20237L20182A04R920051269		rs1610696:GG				Bw6	Bw6, rs1050	129Val
HC20237L20182A05R970900614		rs1610696:CG				Bw6	Bw4, Bw6, rs	129Val
HC20237L20182A06R050114117		rs1610696:CG				Bw6	Bw4, Bw6, rs	129Val
HC20237L20182B01IHW09024		rs1610696:CC				Bw6	Bw6, rs1050	129Met, 129Val
HC20237L20182B02IHW09050		rs1610696:CC				Bw6	Bw4, rs1050	129Val
HC20237L20182B03IHW09058		rs1610696:CC				Bw6	Bw6, rs1050	129Met

Homozygous G

Heterozygous G/A

Homozygous A

Genotyping Report:

Sample: HC20237L20182B04IHW09074
Summary

The allele pairs listed below are compatible with the consensus sequence.

MICA*008:04:02	MICA*027:01:01	
MICA*008:04:02	MICA*027:01:02	Intron 1

Motifs: 129Val Homozygous G

Sample: HC20237L20182C04S4RI295119a
Summary

The allele pairs listed below are compatible with the consensus sequence.

MICA*002:01:03	MICA*008:04:02	
MICA*002:01:04	MICA*008:04:02	Intron 1
MICA*002:01:07	MICA*008:04:02	Intron 1
MICA*002:01:08	MICA*008:04:02	Intron 1

Motifs: 129Met, 129Val Heterozygous G/A

Sample: HC20237L20182C06S6UI976259a
Summary

The allele pairs listed below are compatible with the consensus sequence.

MICA*011:01:01	MICA*018:01:01	
MICA*011:01:01	MICA*018:01:03	Intron 1
MICA*011:01:06	MICA*018:01:01	Intron 1
MICA*011:01:06	MICA*018:01:03	Intron 1

Motifs: 129Met Homozygous A

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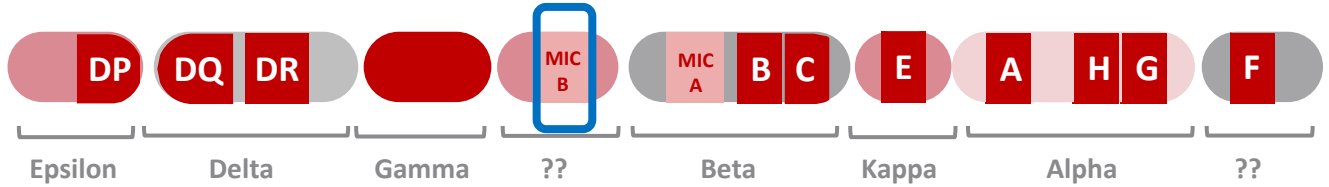

MICB98 Met/Ile

Motif ID:	**MICB98 Met/Ile**	Locus:	**MICB**	Implemented (Ref. Version #):	3.37.0.1
Supporting Publication:	Carapito R, Aouadi I, Pichot A, Spinnhirny P, Morlon A, Kotova I, Macquin C, Rolli V, Cesbron A, Gagne K, Oudshoorn M, van der Holt B, Labalette M, Spierings E, Picard C, Loiseau P, Tamouza R, Toubert A, Parissiadis A, Dubois V, Paillard C, Maumy-Bertrand M, Bertrand F, von dem Borne PA, Kuball JHE, Michallet M, Lioure B, Peffault de Latour R, Blaise D, Cornelissen JJ, Yakoub-Agha I, Claas F, Moreau P, Charron D, Mohty M, Morishima Y, Socié G, Bahram S. **Compatibility at amino acid position 98 of MICB reduces the incidence of graft-versus-host disease in conjunction with the CMV status**. *Bone Marrow Transplant*. 2020 Jul;55(7):1367-1378.				
Impact of polymorphism:	The isoleucine (Ile) to methionine (Met) substitution in MICB amino acid position 98 is a key polymorphic residue involved in UL16 binding. A MICB98 mismatched but otherwise fully HLA and MICA matched donor increases risk of both acute and chronic GvHD development. MICB98 mismatches showed a GvHD-independent association with a higher incidence of CMV infection/reactivation. In addition, MICB98 mismatches were associated with a higher rate of relapse. The variation Ile > Met is exclusively present in MICB*008. Mismatch occurs in approximately 6% of transplantations.				

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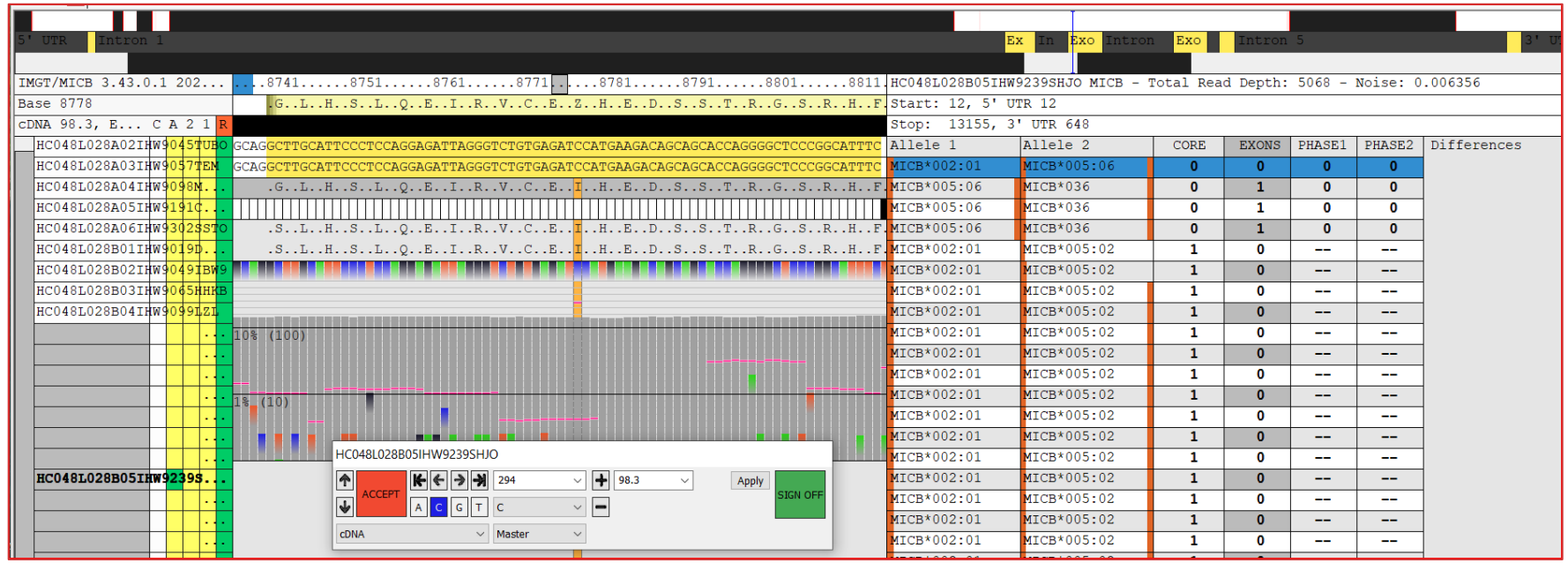
Motif ID:	**MICB98 Met/Ile**	Locus:	**MICB**	Implemented (Ref. Version #):	3.37.0.1

Example Display:

Homozygous C Ile/Ile



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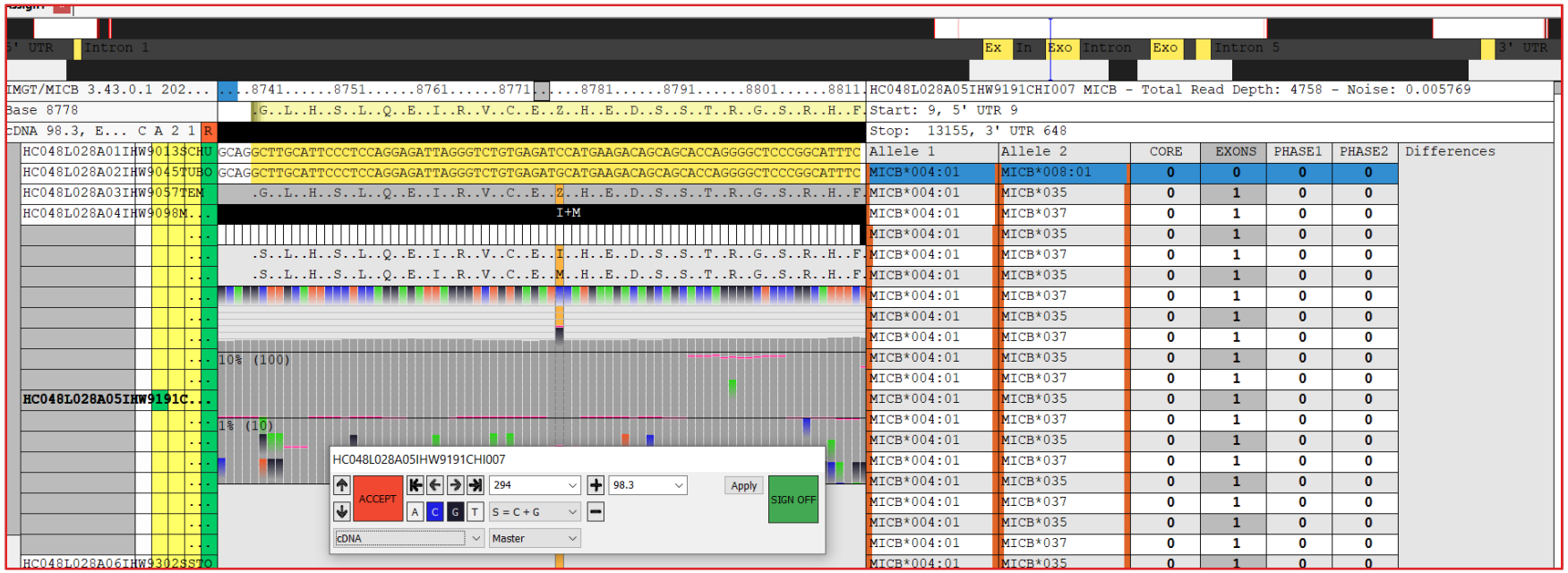
Motif ID:	**MICB98 Met/Ile**	Locus:	**MICB**	Implemented (Ref. Version #):	3.37.0.1

Example Display:

Heterozygous C/G Ile/Met



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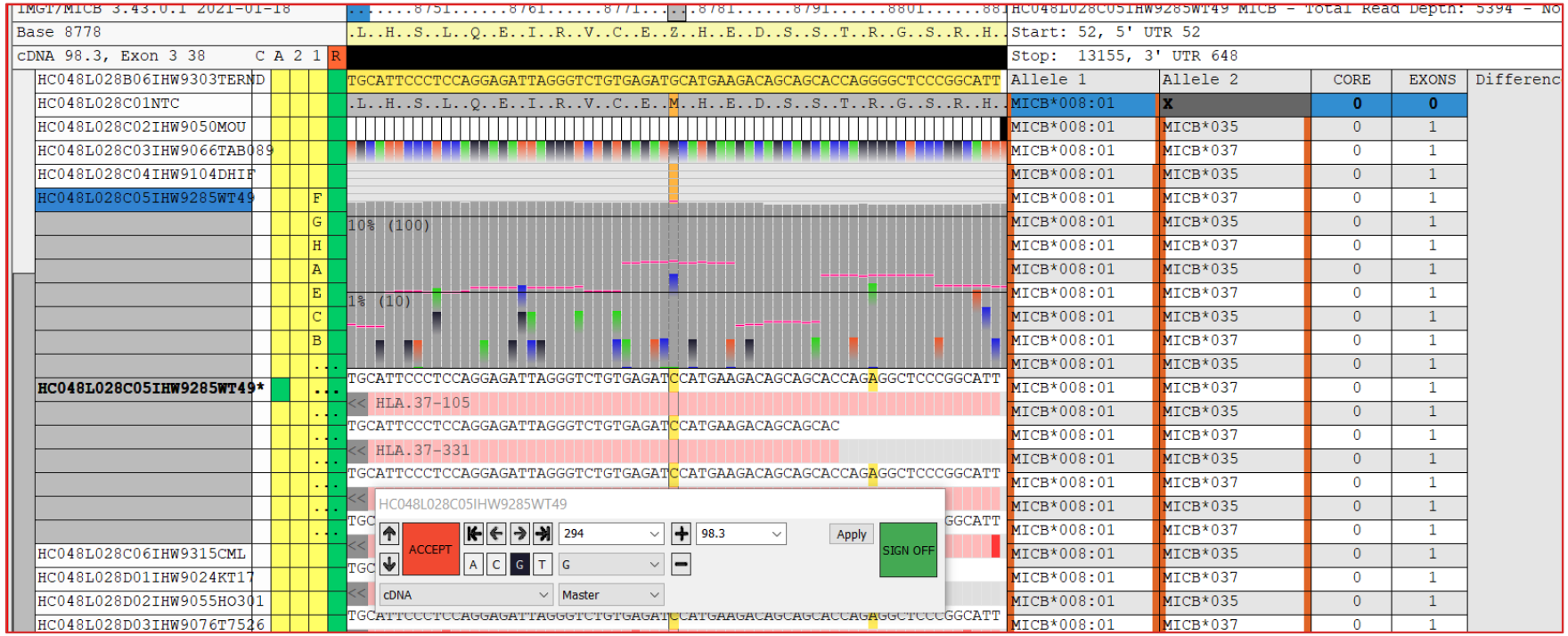
Motif ID:	**MICB98 Met/Ile**	Locus:	**MICB**	Implemented (Ref. Version #):	3.37.0.1

Example Display:

Homozygous G Met/Met



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Motif ID:	**MICB98 Met/Ile**	Locus:	**MICB**	Implemented (Ref. Version #):	3.37.0.1

Example Display:

Summary Table Report:

Motifs.

	IMGT/MICB	
HC048L028C05IHW9285WT49	98Met	Homozygous G
HC048L028C06IHW9315CML	98Met, 98Ile	Heterozygous C/G
HC048L028D01IHW9024KT17	98Ile	
HC048L028D02IHW9055HO301	98Ile	
HC048L028D03IHW9076T7526	98Ile	
HC048L028D04IHW9134WHONP199	98Ile	Homozygous C
HC048L028D05IHW9297HAG	98Ile	
HC048L028D06IHW9320BEL5GB	98Ile	

Genotyping Report:

Sample: HC048L028A02IHW9045TUBO
Summary

The allele pairs listed below are compatible with the consensus sequence.

MICB*002:01	MICB*005:02

Motifs: 98Ile Homozygous C

Sample: HC048L028A05IHW9191CHI007
Summary

The allele pairs listed below are compatible with the consensus sequence.

MICB*004:01	MICB*008:01

Motifs: 98Met, 98Ile Heterozygous C/G

Sample: HC048L028C05IHW9285WT49
Summary

The allele pairs listed below are compatible with the consensus sequence.

MICB*008:01	X

Motifs: 98Met Homozygous G

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