Minutes of IARC meeting 123, June 2nd, 2023

In attendance: Ayelet Peres, Gur Yaari, Andrew Collins, Corey Watson, Mats Ohlin, James Heather

1. **Approval of minutes of meeting 122**
   Approved

2. **Next meeting**
   To be determined

3. **Prioritize test submissions to TRIG**

   Test cases are to be submitted to the IUIS Nomenclature subcommittee: TRBV7-7*i01, IGHV3-13*i01, IGHV3-30*i02

4. **Germline reference set manuscript**
   The manuscript has undergone extensive editing and not yet been submitted to the GLDG working group for approval. Following an update of OGRDB, it is expected that the manuscript will be submitted to the WG for discussion. Discussion on the matter of naming of duplicated sequences.

5. **Assessment of inference TRBV12-5*01_C28G_T140A in P4_I21_S1 (S00036)**

   TRBV12-5*01_C28G_T140A (substitutions: H10D, M47K) has been inferred in three genotypes in the VDJbase P4 data set, including in VDJbase P4_I21_S1, a haplotypable data set (based on heterozygocity in TRBJ1-6). The genotype is also implied to carry TRBV12-5*01. No other gene in the IMGT database is highly similar to these alleles of TRBV12-5. The novel allele is the lesser expressed allele in the repertoire (33% allelic frequency; 0.19% of the total error-free population). It is represented by 58 error-free sequences and 56 unique CDR3s in the error-free set. Haplotyping based on allelic diversity in TRBJ1-6 demonstrates association of TRBV12-5*01 with only one of the haplotypes (TRBV12-5*01_C28G_T140A was not associated with any allele of TRBJ1-6).
   The allele has also been inferred in a separate study and is reported in GenBank with accession number MZ339646 (Corcoran et al. (2023) Immunity 56, 635-652.E6 (DOI: 10.1016/j.immuni.2023.01.026)).

>MZ339646.1 Homo sapiens T-cell receptor TRB locus
TRBV12-5*01_S2866 mRNA, partial cds
GATGCTAGAGTCACCCAGACACCAAGGGACAAGGTGACAGAGATGGGACAAGAA
GTAACAATGAGATGTCAGCCAATTTTAGGCCACAATACTGTTTTCTGGTACAGA
CAGACCATGAAGCAAGGACTGGAGTTGCTGGCTTACTTCCGCAACCGGGCTCCT
CTAGATGATTCGGGGATGCCGAAGGATCGATTCTCAGCAGAGATGCCTGATGCA
ACTTTAGCCACTCTGAAGATCCAGCCCTCAGAACCCAGGGACTCAGCTGTGTAT
TTTTGTGCTAGTGGTTTGGT

The allele has also been identified by genomic sequencing of sample HG01175 (Rodriguez et al. (2022) Cell Genom 2, 100228. doi: 10.1016/j.xgen.2022.100228)) in which it is reported in Supplementary Table S4 as sequence N_240.

>N_240
GATGCTAGAGTCACCCAGACACCAAGGGACAAGGTGACAGAGATGGGACAAGAA
GTAACAATGAGATGTCAGCCAATTTTAGGCCACAATACTGTTTTCTGGTACAGA
CAGACCATGAAGCAAGGACTGGAGTTGCTGGCTTACTTCCGCAACCGGGCTCCT
CTAGATGATTCGGGGATGCCGAAGGATCGATTCTCAGCAGAGATGCCTGATGCA
ACTTTAGCCACTCTGAAGATCCAGCCCTCAGAACCCAGGGACTCAGCTGTGTAT
TTTTGTGCTAGTGGTTTGGT

The low expression level of the allele and the lack of its association with the haplotypable TRBJ1-6 gene limits the validity of the transcriptomic data supporting the inference. As IARC focuses on high quality inference data as the primary source of information, it is considered that this particular inference does leave some room for doubt. Consequently, IARC affirms the sequence at Level 0. The inference of the complete sequence based solely on transcriptomic data is challenging also in this case. With the genomic data (from a different subject) as support it is acknowledged that the allele likely has a 3’-end identical to other alleles of TRBV12-5.

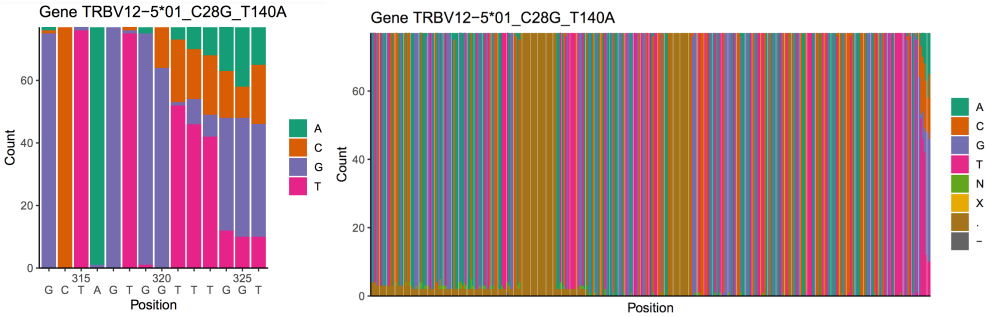
>TRBV12-5*01_C28G_T140A
GATGCTAGAGTCACCCAGACACCAAGGGACAAGGTGACAGAGATGGGACAAGAA
GTAACAATGAGATGTCAGCCAATTTTAGGCCACAATACTGTTTTCTGGTACAGA
CAGACCATGAAGCAAGGACTGGAGTTGCTGGCTTACTTCCGCAACCGGGCTCCT
CTAGATGATTCGGGGATGCCGAAGGATCGATTCTCAGCAGAGATGCCTGATGCA
ACTTTAGCCACTCTGAAGATCCAGCCCTCAGAACCCAGGGACTCAGCTGTGTAT
TTTTGTGCTAGTGGTTTGGT

Result summary: TRBV12-5*01_C28G_T140A	No rearrangement found		
V-GENE and allele	Homsap TRBV12-5*01 F	score = 1362	identity = 99.28% (274/276 nt)
FR-IMGT lengths, CDR-IMGT lengths	[5.6.X]		

1. Alignment for V-GENE and allele identification

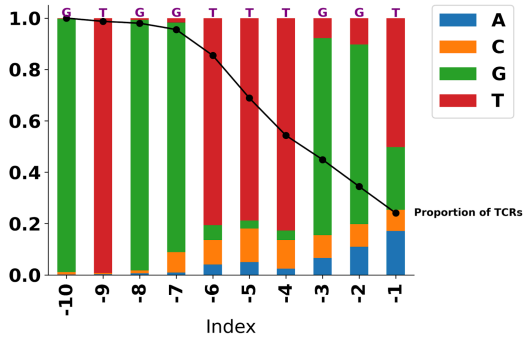
Closest V-REGIONs (evaluated from the V-REGION first nucleotide to the 2nd-CYS codon)

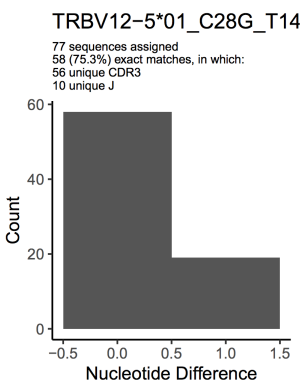
		Score	Identity
X07223	Homsap TRBV12-5*01 F	1362	99.28% (274/276 nt)
X07192	Homsap TRBV12-3*01 F	957	82.97% (229/276 nt)
K02546	Homsap TRBV12-4*01 F	948	82.61% (228/276 nt)
M14264	Homsap TRBV12-4*02 (F)	930	81.88% (226/276 nt)
X07224	Homsap TRBV12-1*01 P	840	78.26% (216/276 nt)

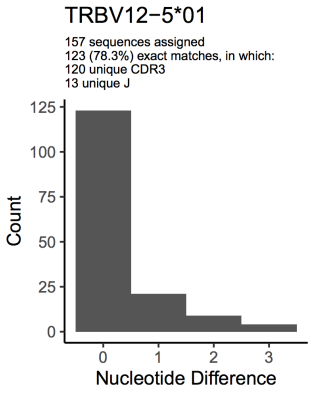


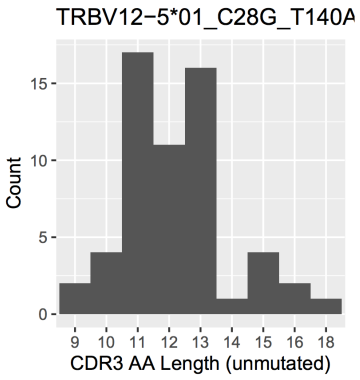
Consensus plot of 3’-end:

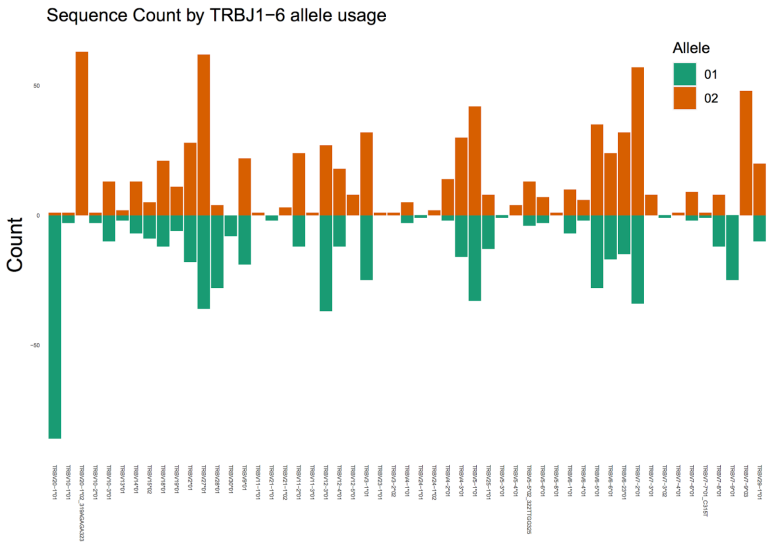
All data:





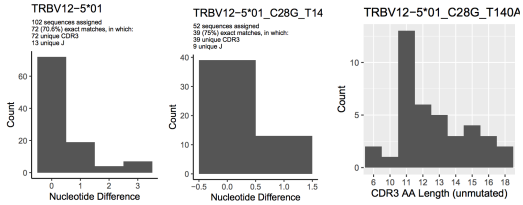






TRBV12-5*01_C28G_T140A is also inferred in VDJbase P4_I9 and P4_I31:

P4_I9



P4_I31: