IARC Meeting 32: March 1st 2019: minutes

The meeting commenced at 22:00 AEDT. AC, MC, and MO were in attendance. William Lees and Corey Watson joined the meeting.

1. The minutes for Meeting 31 were considered, and it was agreed that further work was required to remove consideration of haplotype analysis from the report of the assessment of the IGHV4-59*i01 inference. The haplotype analysis was provided by MC after Meeting 31. This confirms the validity of the affirmation of IGHV4-59*i01, for it is clear that all alignments to the inference are associated with just one chromosome. The allele IGHV4-59*01 is present in both haplotypes, suggesting that either IGHV4-59*i01 or one of the IGHV4-59*01 sequences is present at a different gene location. Of note, no allele of IGHV4-4 has been assigned to the haplotype that carries both IGHV4-59*01 and IGHV4-59*01 T288C. This analysis also demonstrated that many genes were homozygous, such as IGHV1-2, IGHV1-8, IGHV3-11, IGHV3-48, and IGHV3-49. IGHV3-23*01 and IGHV3-23*04 are both associated to both haplotypes suggesting the presence of a gene duplication, presumably IGHV3-23D. At a future meeting, the committee should move to affirm the IGHJ4 polymorphism.
2. Progress with the Frontiers manuscript was outlined, including communications from Menno van Zelm that there would be a reduced charge for the manuscript, and from Felix Breden that he would be asking the Antibody Society to contribute to publication costs.
3. The committee needs to formulate goals for 2019, for presentation to the AIRR Community at the Genoa meeting. A googledoc has been started, and it was agreed that the committee will work together on this document.
4. The committee has been asked to consider whether the IARC should be altered to have a status within the AIRR Community as a Standing Committee. The IARC agreed that a Standing Committee with responsibilities for IARCs should be formed, but considered it inappropriate for the human IARC to be given this responsibility. It was agreed that the definition of the role of the Standing Committee should be a responsibility of the Working Group, and this task will therefore be referred to them at the next meeting of the WG. It was also agreed that the WG should be tasked with defining the terms of appointment of the IARCs, and the time and manner by which the human committee will be periodically renewed.
5. It was noted that Level 0 inferences from the submissions of Davide Bagnara have still not been processed within OGRDB. This requires the submission of the sequences by DB. AC will write to him, to ensure that the process is complete before the Genoa meeting.
6. The committee then considered the submitted IGHV4-31 variant from S0007. The submitted sequence is as follows:

   >IGHV4-31*03+A66G
   CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCC
   CTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGA

TCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGA
GCACCTACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAG
AACCAGTTCTCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACT
GTGCGAGAGA

This sequence represents IGHV4-31*03 A70G in the IMGT numbering system. The committee noted a rearrangement frequency of 0.9%, with 812 alignments including 293 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. There was no alternative allele present in the genotype, but there are published reports (eg Gidoni et al 2019) of a deletion polymorphism involving the IGHV4-31 locus. All members of the committee agreed that the sequence should be accepted as a Level 1 sequence.

This sequence has previously been catalogued by IgPdb as IGHV4-31*p13, though the IgPdb sequence is derived from the S0007 dataset. The S0007 submission noted that haplotyping was not possible, but the haplotype analysis provided by MC (using the IGHJ4 locus) supports the decision of the committee. All alignments to the inference are associated with a single chromosome. In line with previous policy, the submitted sequence will be recognized up to and including nucleotide 319 as follows:

>IGHV4-31*i01
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCC
CTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGA
TCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGTGGGA
GCACCTACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAG
AACCAGTTCTCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACT
GTGCGAGAG

This decision will be recorded in OGRDB, and the haplotype analysis will be made available through the OGRDB.

7. MC noted that care must be taken where a new polymorphism appears to be homozygous within an individual, as is the case with IGHV4-31*i01. The committee discussed that kinds of analyses that could be provided to give added support to such an inference. MC pointed to the value of removing the novel allele from the genotype and re-analysing data to ensure the exclusion of a particular type of false positive candidate novel allele. In these situations an apparently homozygous candidate novel allele, that is present in the genotype at high frequency, can obscure the presence of other alleles of the same gene that are present at lower frequency but are removed during the inferral process due to allelic ratio filtering. Haplotyping analysis, where possible, can provide the best supporting evidence.
8. CW and AC will work together to provide appropriate documentation for IMGT, regarding the seven sequences that have now been affirmed at Level 1.

The next meeting (Meeting 33) will be on Friday March 15th at 22:00 AEDT.

The meeting ended at 23:15 AEDT.