IARC Meeting 45: November 18th 2019: minutes

The meeting commenced at 10:30 UTC. AC, MC, CS, MO and WL were in attendance. CS left the meeting at 11:00 UTC. Davide Bagnara joined the early part of the meeting.

1. The minutes of meeting 44 were accepted.
2. The committee commenced the evaluation of inferences in S00010. These sequences were parts of the genotypes previously submitted as S00004 and S00006. However these particular sequences, although assessed during Meetings 7-12, had not been assigned as new inferences in these OGRDB submissions. The current submission was made after submission of sequences to Genbank and select sets to SRA, and has now been reported as part of a new IgDiscover analysis.

    - The committee considered IGHV2-70*01_S6619 (A124G) of Genotype B12, which was previously evaluated as IGHV2-70*01_S4660 at Meeting 8. It was affirmed as a Level 0 sequence at that time. The submitted sequence is as follows:

      >IGHV2-70*01_S6619
      CAGGTCACCTTGAGGGAGTCTGGTCCTGCGCTGGTGAAACCCACAC
      AGACCCTCACACTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACT
      AGTGGAATGTGTGTGAGCTGGGTCCGTCAGCCCCCAGGGAAGGCC
      CTGGAGTGGCTTGCACTCATTGATTGGGATGATGATAAATACTACAG
      CACATCTCTGAAGACCAGGCTCACCATCTCCAAGGACACCTCCAAAA
      ACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGC
      CACGTATTACTGTGCACGGATAC

      The sequence was seen in just 0.05% of all unmutated rearrangements, with 296 sequences including 93 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. Two other alleles were present in the genotype, and it is possible that one of these three sequences is an IGHV2-70D sequence. Haplotype data is supportive of the inference, but in light of the very low frequency of rearrangements seen and the complicated haplotype of this subject, it was affirmed as a Level 0 sequence. The sequence was affirmed up to and including nucleotide 319 even though alleles of IGHV2-70/IGHV2-70D in general extend up to and including base 322. However, the nucleotide composition of the final three bases of genes associated to this inferred allele did not support their inference. It is however likely that three additional 3' nucleotides are present in the sequence, and this will be indicated in IARC and OGRDB publications by three dots at the end of the sequence.

The affirmed sequence is as follows:

>IGHV2-70*01_S6619
CAGGTCACCTTGAGGGAGTCTGGTCCTGCGCTGGTGAAACCCACAC
AGACCCTCACACTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACT
AGTGGAATGTGTGTGAGCTGGGTCCGTCAGCCCCCAGGGAAGGCC
CTGGAGTGGCTTGCACTCATTGATTGGGATGATGATAAATACTACAG
CACATCTCTGAAGACCAGGCTCACCATCTCCAAGGACACCTCCAAAA
ACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGC
CACGTATTACTGTGCACGGA…

It will be given the name IGHV2-70*i01.

- The committee considered IGHV1-69*14_S5279 (G163A) of Genotype B12, which was previously evaluated as IGHV1-69*14_S3451 at Meeting 8. It was affirmed as a Level 0 sequence at that time. The submitted sequence is as follows:

  >IGHV1-69*14_S5279
  CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG
  TCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCA
  GCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGA
  GTGGATGGGAAGGATCATCCCTATCTTTGGTACAGCAAACTACGCAC
  AGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAG
  CACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC
  GTGTATTACTGTGCGAGAGA

  The sequence was seen in 2.29% of all unmutated rearrangements, with 11,849 sequences including 3889 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. Three other alleles were present in the genotype (none of which carries the allele-differentiating base A163), with IGHV1-69*13 also being present in the haplotype with this allele. In the earlier analysis (Meeting 8), an additional allele was reported. Haplotype data is supportive of the inference considering the existence of the IGHV1-69 gene, but in light of the complex structural variation seen in this individual, the sequence was affirmed as a Level 0 sequence. In line with IARC policy, the submitted sequence was recognized up to and including nucleotide 319. It is likely that one additional 3’ nucleotide is present in the sequence, and this will be indicated in IARC and OGRDB publications by one dot at the end of the sequence.

The affirmed sequence is as follows:

>IGHV1-69*14_S5279
CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG
TCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCA
GCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGA
GTGGATGGGAAGGATCATCCCTATCTTTGGTACAGCAAACTACGCAC
AGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAG
CACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC
GTGTATTACTGTGCGAGAG.

It will be given the name IGHV1-69*i01.

- The committee considered IGHV4-61*01_S7407 (C93T, C136G, A138C) of Genotype B12, which was previously evaluated as IGHV4-61*01_S9594 at Meeting 10. It was affirmed as a Level 0 sequence at that time. The submitted sequence is as follows:

  >IGHV4-61*01_S7407
  CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG
  GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCGTCAGTA
  GTGGTAGTTACTACTGGAGCTGGATCCGGCAGCCCGCCGGGAAGG
  GACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAACTAC
  AACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAA
  GAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACG
  GCCGTGTATTACTGTGCGAGAGA

  The sequence was seen in 0.93% of all unmutated rearrangements, with 5928 sequences including 1572 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. Two other alleles were present in the genotype, with IGHV4-61*01 and IGHV4-61*02 also being present in the haplotype with this allele. Haplotype data is generally supportive of the inference, but in light of the complex structural variation seen in this particular individual, such a duplication is not an unlikely event. However based on this complexity and the similarities of IGHV4-4, IGHV4-59 and IGHV4-61 sequences, the sequence was affirmed as a Level 0 sequence. In line with IARC policy, the submitted sequence was recognized up to and including nucleotide 319. It is likely that one additional 3' nucleotide is present in the sequence, and this will be indicated in IARC and OGRDB publications by one dot at the end of the sequence.

  The affirmed sequence is as follows:

>IGHV4-61*01_S7407
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG
GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCGTCAGTA
GTGGTAGTTACTACTGGAGCTGGATCCGGCAGCCCGCCGGGAAGG
GACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAACTAC
AACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAA
GAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACG
GCCGTGTATTACTGTGCGAGAG.

It will be given the name IGHV4-61*i01.

- The committee considered Genotype B16, for evidence of IGHV1-58*01_S8523 which had been seen at low frequency in submission S00006, and was affirmed as a Level 0 sequence at Meeting 9. The sequence was however not seen in the new IgDiscover analysis (S00010), and this sequence will receive no further consideration and it will not be entered into OGRDB.

- The committee considered IGHV4-61*01_S5549 (C136G A138G) of Genotype B16, which was previously evaluated as IGHV4-61*01_S0787 at Meeting 12. It was affirmed as a Level 0 sequence at that time. The submitted sequence is as follows:

  >IGHV4-61*01_S5549
  CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG
  GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCGTCAGCA
  GTGGTAGTTACTACTGGAGCTGGATCCGGCAGCCCGCCGGGAAGG
  GACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAACTAC
  AACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAA
  GAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACG
  GCCGTGTATTACTGTGCGAGAGA

  The sequence was seen in 1.68% of all unmutated rearrangements, with 11,785 sequences including 4732 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. No other allele of IGHV4-61 was present in the genotype. Haplotype data is supportive of the inference, with the sequence being strongly associated with one haplotype. However, two alleles of IGHV4-4 (a gene closely related to IGHV4-61) were present on the other haplotype, highlighting the possibility that one of these alleles might be an allele of IGHV4-61. There was strong support for the sequence being

affirmed up to and including nucleotide 319, in line with IARC policy, as a Level 1 sequence, with one additional 3’ nucleotide being likely present in the sequence. A final decision on this sequence will be made after consultation with CS.

The affirmed sequence is as follows:

>IGHV4-61*01_S5549
CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCG
GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCGTCAGCA
GTGGTAGTTACTACTGGAGCTGGATCCGGCAGCCCGCCGGGAAGG
GACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAACTAC
AACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAA
GAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACG
GCCGTGTATTACTGTGCGAGAG.

It will be given the name IGHV4-61*i02.

- The committee considered IGHV1-69*01_S7220 (G163A) of Genotype B16, which was previously evaluated as IGHV1-69*01_S5096 at Meeting 10. It was affirmed as a Level 0 sequence at that time. The submitted sequence is as follows:

  >IGHV1-69*01_S7220
  CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG
  TCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCA
  GCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGA
  GTGGATGGGAAGGATCATCCCTATCTTTGGTACAGCAAACTACGCAC
  AGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAG
  CACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC
  GTGTATTACTGTGCGAGAGA

  The sequence was seen in 8.02% of all unmutated rearrangements, with 53668 sequences including 22586 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. Three other alleles were present in the genotype, with IGHV1-69*02 also being present in the haplotype with this allele, likely a consequence of the presence of the IGHV1-69D gene in the haplotype in question. The inferred sequence includes six differences to the *02 allele. Haplotype data is supportive of the inference. There was strong support for the sequence being affirmed up to and including nucleotide 319, in line with IARC policy, as a Level 1 sequence, with one additional 3’ nucleotide

being likely present in the sequence. It is noted that this sequences represents a 5'- and a 3'-extension of the partial allele IGHV1-69*07 already recognized by IMGT. A final decision on this sequence will be made after consultation with CS.

>IGHV1-69*01_S7220
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG
TCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCA
GCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGA
GTGGATGGGAAGGATCATCCCTATCTTTGGTACAGCAAACTACGCAC
AGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAG
CACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC
GTGTATTACTGTGCGAGAG.

It will be given the name IGHV1-69*i02.

- The committee considered IGHV2-70*04_S4496 (C6T) of Genotype B16, which was previously evaluated as IGHV2-70D*04_S2803 at Meeting 11. It was affirmed as a Level 0 sequence at that time. The submitted sequence is as follows:

  >IGHV2-70*04_S4496
  CAGGTTACCTTGAAGGAGTCTGGTCCTGCGCTGGTGAAACCCACAC
  AGACCCTCACACTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACT
  AGTGGAATGCGTGTGAGCTGGATCCGTCAGCCCCCAGGGAAGGCC
  CTGGAGTGGCTTGCACGCATTGATTGGGATGATGATAAATTCTACAG
  CACATCTCTGAAGACCAGGCTCACCATCTCCAAGGACACCTCCAAAA
  ACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGC
  CACGTATTACTGTGCACGGATAC

  The sequence was seen in just 0.09% of all unmutated rearrangements, with 687 sequences including 252 perfect matches to the inferred allele. There was abundant variation in the CDR3 regions of the aligned sequences. One other IGHV2-70 sequence was present in the genotype, and haplotype data suggests that both these sequences are carried on a single chromosome, one of them possibly located to IGHV2-70D. The rearrangement frequency was above the agreed threshold (0.05%), but In light of the very low frequency of rearrangements seen and the complicated haplotype profile, there was debate about whether the sequence should be affirmed as Level 0 or Level 1. A final decision on this sequence will be made after consultation with CS.

>IGHV2-70*04_S4496
CAGGTTACCTTGAAGGAGTCTGGTCCTGCGCTGGTGAAACCCACAC
AGACCCTCACACTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACT
AGTGGAATGCGTGTGAGCTGGATCCGTCAGCCCCCAGGGAAGGCC
CTGGAGTGGCTTGCACGCATTGATTGGGATGATGATAAATTCTACAG
CACATCTCTGAAGACCAGGCTCACCATCTCCAAGGACACCTCCAAAA
ACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGC
CACGTATTACTGTGCACGGA...

It will be given the name IGHV2-70*i02.

3. The next meeting (Meeting 46) will be held on December 2nd at 10:30 UTC, subject to email confirmation.

The meeting ended at 11:05 UTC.