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CHARACTERIZATION OF A NOVEL HLA-A*02:1281 ALLELE

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BACKGROUND

A novel HLA-A*02 allele was identified in a renal patient and the HLA-matched sibling donor (MSD) during a living-related kidney transplant workup. The serological specificity and structural implications of this novel allele were evaluated.

METHODOLOGY

- HLA NGS typing: Fastplex HLA NGS assay (One Lambda)
- Surrogate flow cytometric crossmatch
- In silico analysis:
  - DNA and amino acid sequences alignment
  - HLA Allele To Serotype (HATS) prediction of serological specificities
  - Eplet analysis & 3D protein structure modeling (pHLA3D)

HLA typing of patient and MSD

	A*	B*	C*	DRB1*	DRB345*	DQB1*	DQA1*	DPB1*	DPA1*
HR typing (serological equivalent)	02:01 (A2)	13:01 (B13)	03:04	12:02 (DR12)	3*02:02 (DR52)	03:01 (DQ7)	06:01	02:01	02:01
	02new (A?)	55:02 (B55)	04:03	-	-	-	-	14:01	02:02

- Novel A*02 allele detected, closest allele is A*02:03:01:01
- Nucleotide substitution: c.484A>G; Atg>Gtg at exon 3.
- Amino acid substitution: Met138Val (M138V) in the α2 domain.
- HLA-A*02:1281 by WHO Nomenclature Committee in IMGT/HLA version 3.64.0

Sequence alignment of A*02:1281 vs A*02:03:01:01

https://www.ebi.ac.uk/ipd/imgt/hla/alignment/

Coding sequence alignment

Exon 3
c.484A>G

```
AA Codon                  130                 135                 140                 145                 150
A*02:03:01:01  AAA GAG GAC CTG CGC TCT TGG ACC GCG GCG GAC ATG GCA GCT CAG ACC ACC AAG CAC AAG TGG GAG ACG GCC CAT
A*02:1281      --- --- --- --- --- --- --- --- --- --- G-- --- --- --- --- --- --- --- --- --- --- --- --- ---
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Amino acid sequence alignment

M138V

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AA Pos.              110        120        130        140        150        160        170        180        190        200
A*02:03:01:01  CDVGSDWRFL RGYHQYAYDG KDYIALKEDL RSWTAADMAA QTTKHKWETA HEAEQWRAYL EGTCVEWLRR YLENGKETLQ RTDAPKTHMT HHAVSDHEAT
A*02:1281      ---------- ---------- ---------- -------V-- ---------- ---------- ---------- ---------- ---------- ----------
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Serotype of A*02:1281 (HATS classification)

Serotype
A0203 → I Incomplete

The allele differs from the closest serotype's pattern by a single amino acid, so the match is partial rather than exact.

https://www.serotype.org/allele/A*02:1281

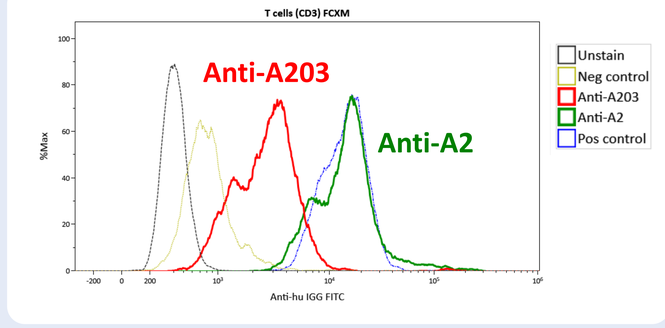
Serotype A0203 — **HATS Defining positions**

	43	62	66	73	107	138	144	145	149	163
A*02:03	Q	G	K	T	W	M	K	H	T	T
A*02:1281	Q	G	K	T	W	V	K	H	T	T

Surrogate FCXM

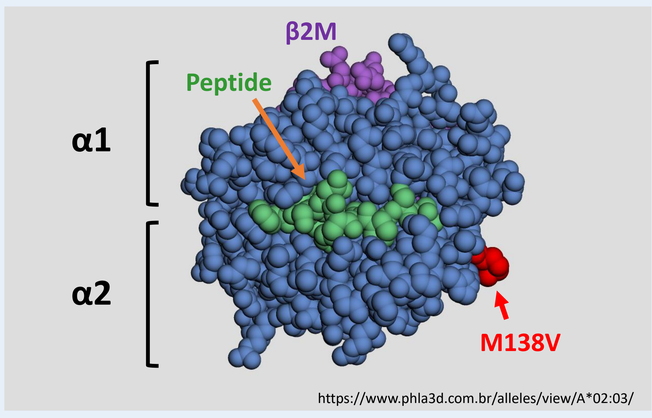
- Matched sibling was recruited for further surrogate FCXM.
- Sera with anti-A2 and -A203 detected by single antigen bead assays and confirmed individually by A2 and A203 donor cells.
- Patient has both A*02:01 and A*02:1281, both anti-A2 and -A203 sera were positive in T cells FCXM.

Serum	Class I specificities	Eplet	MCS (Cut-off > 57)
Anti-A2	**A*02:01**, A*02:02, A802:05, A*68:01, A*68:02, A*69:01	144TKH + 149A	312 (Pos)
Anti-A203	**A*02:03**	144TKH + 149T	137 (Pos)



pHLD3D structure of A*02:1281

- Residue 138V is solvent exposed on the α2 helix.
- A*02:1281 carrier may develop antibodies against the wild-type A203 through recognition of the methionine (138M) residue.



https://www.phla3d.com.br/alleles/view/A*02:03/

CONCLUSIONS

- The serological specificity of A*02:1281 is A203 (Serotype A0203).
- Met138Val is an exposed eplet, potential risk for the development of antibodies against wild-type A203
- Low risk in this case since the potential donor is a MSD.
- Serotype assignment, eplet and structural analyses + Serology tray/FCXM for assessment of immunogenic profile of novel HLA variants.

Osoegawa K, et al. HLA. 2022 Sep;100(3):193-231 (PMID: 35538616) ; Barker DJ, et al. Nucleic Acids Res. 2023 Jan 6;51(D1):D1053-D1060 (PMID: 36350643)
Menezes Teles E Oliveira D, et al. Hum Immunol. 2019 Oct;80(10):834-841 (PMID: 31239187); Marsh SGE, et al. HLA. 2026 Mar;107(3):e70595.(PMID: 41742599)