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‘Irish’ Bombay Phenotype: Compound Heterozygosity for Novel *FUT1* Alleles.

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Background

The human blood groups of the ABO, H and Lewis systems are determined by oligosaccharides. α-(1,2)-fucosyltransferases (coded for by *FUT1* and *FUT2*) synthesise the H antigen, which is the precursor molecule of the A and B antigens. The product of *FUT1* is responsible for H expression on red blood cells, while that of *FUT2* is responsible for H expression in secretions. H-deficient phenotypes arise due to inactivating mutations in *FUT1* and *FUT2* genes. The H- phenotype is called the O_h (Bombay) phenotype. Transfusion support for patients with the O_h phenotype is problematic due to the presence of anti-H in their plasma, the ubiquity of H antigen in donors and the rarity of O_h phenotype donors.

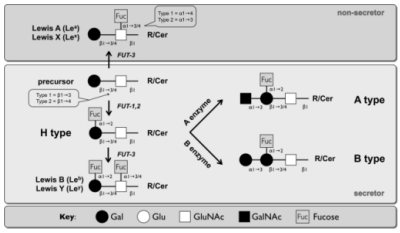

Fig 1. Synthesis of Oligosaccharide Blood Groups

We investigated a 57 year old male patient with a history of bladder carcinoma, who required blood for a transurethral resection of the prostate. Samples were referred for investigations as he grouped O RhD+ with a suspected allo-antibody to a high frequency antigen. There was no known history of transfusion. The patient’s two brothers were also investigated.

Methods

Initial ABO typing was performed by AutoVue Innova. Further phenotyping was performed by direct agglutination tube methods. Antibody investigation was performed by standard BioRad and LISS tube IAT using untreated and papain-treated cells. Adsorption-elution tests were carried out using high-titre immune anti-A and anti-B (1/1048 and 1/512 respectively) and anti-H. Elution was performed with Immucor Elu-Kit II. The coding regions of *FUT1* (exon 4) and *FUT2* (exon 2) were sequenced using Sanger sequencing.

Results

The patient’s cells were negative with all examples of anti-A, anti-B and anti-A,B tested and were negative with anti-H from O_h individuals and also *Ulex europaeus* lectin. Anti-H was detected in the patient’s plasma, reacting by IAT and direct agglutination methods, with all panel cells. Only O_h phenotype cells (n=6) were compatible. Anti-A, anti-B and anti-H were not present in eluates prepared from the patient’s cells following adsorption with the respective antibodies.

FUT1 sequencing revealed compound heterozygosity for two novel mutations: c.310C>T (p.Q104X) and c.496G>T (p.G166C). *FUT2* sequencing revealed homozygosity for mutations associated with the *FUT2*01N.02* allele. The same mutations were found in samples from both brothers and they were confirmed to have the O_h phenotype and anti-H in their plasma.

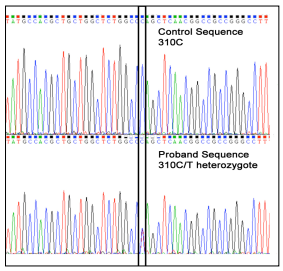

Fig. 3. *FUT1* Sequencing identifying 310C>T

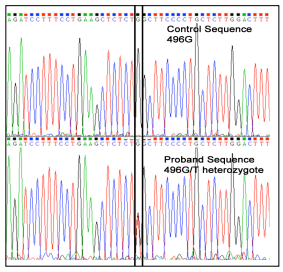

Fig. 4. *FUT1* Sequencing identifying 496G>T

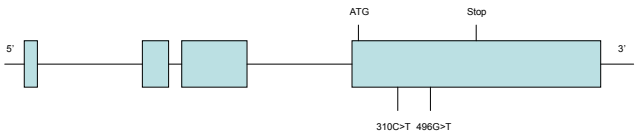

Fig 5. Schematic view of *FUT1* gene arrangement showing novel mutations in the protein coding region of exon 4.

Conclusion

We identified a patient and his two brothers, with apparent compound heterozygosity for two novel *FUT1* mutations: c.310C>T introducing a stop codon at residue 104, and c.496G>T changing glycine to cysteine at position 166. Both mutations are predicted to produce non-functional enzymes since no A, B or H antigens could be detected on their red cells. Due to the lack of O_h donors in Ireland, the patient’s brothers have been assessed as donors.

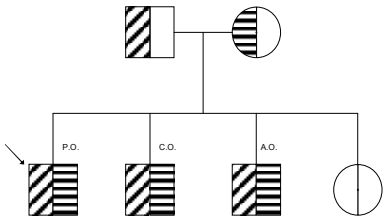

Fig 6. Family Tree Representing *FUT1* alleles. Proband’s sister was not investigated.

Additional Data

Since submitting this abstract our laboratories have identified an antenatal patient as having O_h with anti-H. The patient appeared to be unrelated to this case, although living less than 35 Km apart.

FUT1 and *FUT2* sequencing has identified this patient as having the same *FUT2* mutations characteristic of *FUT2*01N*. More interestingly she also has compound heterozygosity for the same *FUT1* mutations. We assume that one variant *FUT1* allele has been inherited from each parent. However, the possibility exists that both novel mutations are carried on the same allele, although this would not explain the non-functional *FUT1* product. Parental samples are required to confirm this.

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