Molecular genetic analysis of weak ABO subgroups in the Chinese population reveals ten novel ABO subgroup alleles

Haobo Huang[1,3], Sha Jin [2], Xi Liu[2], Zhongying Wang[2], Qiong Lu[2], Liangfeng Fan[2], Wei Shen[2], Hang Lei[1], Chengrui Qian[2], Xuefeng Wang[1], Dong Xiang[2], Xiaohong Cai[1]

[1]Blood Transfusion Department, Ruijin Hospital, Medical School of Shanghai, Jiao Tong University, Shanghai; [2]Blood Group Reference Laboratory, Shanghai Institute of Blood Transfusion, Shanghai Blood Centre, Shanghai; [3]Fujian Medical University Union Hospital, Fuzhou, China

Background. A weak ABO subgroup is one of the most important causes of an ABO blood grouping discrepancy. Here, we investigated the distribution of weak ABO subgroups in the Chinese population and identified ten novel weak ABO subgroup alleles.

Material and methods. We performed phenotype investigations by serological studies, analysed the DNA sequence of the *ABO* gene by direct sequencing or sequencing after cloning, and evaluated the role of glycosyltransferase mutations by *in silico* analysis and *in vitro* expression assay.

Results. Three hundred and fifty-one individuals with a weak ABO subgroup were detected among 1.45 million blood-typed subjects. Ten novel weak ABO subgroup alleles were identified. Molecular modelling and analysis of GTA mutation p.L339P suggested that the mutation may change the local conformation of GTA and reduce its stability. The *in vitro* expression assay showed that A antigen expression and agglutination of HeLa cells transfected with GTA mutant p.L339P decreased significantly compared to those of cells transfected with wild-type GTA.

Conclusion. Ten novel weak ABO subgroup alleles were identified in the Chinese population. GTA mutant p.L339P may lead to a weak A phenotype by changing the local conformation of GTA and reducing its stability.

Keywords: ABO, subgroup, phenotype, novel allele.

Introduction

The ABO blood group was discovered by Karl Landsteiner in 1900 and is the most important blood group system in transfusion medicine. Blood group A and B antigens have been defined by trisaccharide determinants, GalNAcα1→3(Fucα1→2)Galβ1→R and Galα1→3(Fucα1→2)Galβ1→R respectively, which are synthesised by the respective glycosyltransferase (GT) products of the *A* and *B* alleles at the *ABO* locus[1]. The *ABO* gene, located on chromosome 9q34.1-q34.2, is 19.5 kb long and contains a 1062 bp coding region from seven exons[2]. The common ABO alleles, *ABO*A1.01*, *ABO*B.01* and *ABO*O.01*, differ by only a few single-nucleotide polymorphisms. GTB is distinguished from GTA by four amino acid changes (p.R176G, p.G235S, p.L266M, p.G268A), which were shown to confer the specificity and activity of the enzyme[3]. Both GTA and GTB are type II transmembrane proteins with short cytoplasmic and transmembrane domains, a stem region, and a catalytic domain[4].

In addition to the common ABO phenotypes, numerous hereditary phenotypes with weak expression of A or B on the red cells (weak ABO subgroups) have been found. Although weak ABO subgroups are rare, they are one of the most important causes of ABO blood grouping discrepancy. Most weak ABO subgroups result from the inheritance of a rare allele at the *ABO* locus, usually involving missense mutations, insertions, or deletions in the coding region, splicing sites, or regulatory elements[5-10]. However, the molecular mechanisms underlying some weak ABO subgroups remain unclear.

In our previous study, we found that the detection rate of weak ABO subgroups in the Chinese population was approximately 0.015%[11] and reported that promoter abnormality was involved in the formation of weak ABO phenotypes by reducing transcriptional activity[9]. In this report, we describe ten novel mutations and explore the possible mechanism through which they produce weak ABO subgroups.

Materials and methods

Samples

Peripheral venous blood samples, anticoagulated in EDTK-K2, were collected from the following groups: (i) Chinese blood donors (n=1,400,138) at Shanghai Blood Centre between June 2009 and May 2014; (ii) blood typing samples (n=50,964) from Ruijin Hospital between July

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2014 and November 2016; (iii) samples with ABO blood grouping discrepancies (n=10) referred to the Transfusion Department of Ruijin Hospital. Samples were collected from apparently healthy random Chinese donors (n=120) as normal controls. Informed consent was obtained, and the study was approved by the local ethics committees of Shanghai Blood Centre and Ruijin Hospital.

All the individuals found to have weak subgroups were without identifiable risk factors for acquired variant ABO phenotypes such as infants within the first 6 months of life, pregnant women, or subjects with infection, haematological disorders or an ABO incompatible transfusion within the preceding month.

Serology

ABO phenotypes of the blood donors and patients in Ruijin Hospital were first determined by the Galileo (Immucor, Norcross, GA, USA) and Ortho BioVue (Ortho-Clinical Diagnostics, Raritan, NJ, USA) systems, respectively. The samples with ABO blood grouping discrepancies, as well as those referred to the reference laboratory and Transfusion Department, were identified by tube agglutination and adsorption-elution tests according to modern standard methods[12] and a serological diagnostic classification[13]. The following commercially available reagents were used: monoclonal anti-A, anti-B, anti-AB, anti-H (Shanghai Hemo-Pharmaceutical & Biological Co. Ltd, [SHPBC], Shanghai, China), polyclonal anti-A, anti-B, anti-AB (Blood Group Reference Laboratory, Shanghai, China), *Dolichos biflorus* for anti-A1 (SHPBC) and an ABO red blood cell kit for reverse typing (SHPBC).

ABO gene sequence analysis

Genomic DNA extraction, primer design and polymerase chain reaction amplification of the *ABO* gene exons 1 to 7 sequences and their boundary area, the promoter region and an enhancer element located −3.8 kb upstream were performed as previously described[14]. The polymerase chain reaction products were purified and sequenced. The gel-purified products containing the mutation sites were cloned and then sequenced to confirm the haplotypes. Novel mutations were confirmed by a second independent polymerase chain reaction and sequencing. The novel variation sites were also amplified and then sequenced from 120 random, apparently healthy Chinese donors.

Nomenclature of mutations and ABO alleles

The *ABO* mutations and alleles were named according to the nomenclature used by the International Society of Blood Transfusion (ISBT). If an ISBT allele name was not available, a name in the original literature was used in square brackets.

Modelling of the three-dimensional structure of GTA

An unliganded x-ray structure of GTA (PDB ID 4C2S) was used as the template to construct the initial molecular model. An *in silico* mutation was modelled using the Chimera software (version 1.11.2, University of California, San Francisco, CA, USA)[15]. The structural figures were generated in PyMol (DeLano, W.L. The PyMOL Molecular Graphics System [2003-2011], version 1.4.1, DeLano Scientific, San Carlos, CA, USA) or prepared by VMD (visual molecular dynamics)[16].

Predicted protein stability changes upon GTA mutation

To examine the effect of the mutation on protein stability, the empirical protein design FoldX force field in SNPeffect[17] was used to calculate the difference in free energy of the mutation: ddG (ΔΔG) based on GTA

Table I - Ten novel ABO subgroup alleles in this study.

N.	Allele	Critical nt change(s) †	Corresponding aa change(s)	Individuals	Phenotype	Genotype	Genbank n.
1	A^{var-1}	c.595C>T	p.R199C	1	A_xB	$A^{var-1}/B.01$	MH212230
2	A^{var-2}	c.700C>A	p.P234T	1	A_x	$A^{var-2}/O.01$	KF661390
3	A^{var-3}	c.940A>C	p.K314Q	1	A_m	$A^{var-4}/O.01$	MH197137
4	A^{var-4}	c.963insC	322fs+34aa	1	A_{el}	$A^{var-5}/O.01$	KJ026764
5	A^{var-5}	c.964G>A	p.E322K	1	A_{end}	$A^{var-6}/O.01$	KF661392
6	A^{var-6}	c.1016T>C	p.L339P	1	A_xB	$A^{var-7}/B.01$	KF771180
7	B^{var-1}	c.523G>A, c.746G>A	p.V175M, p.R249Q	5	B_x	$B^{var-1}/O.01$	KF954702
8	B^{var-2}	c.586T>C	p.C196R	1	B_{el}	$B^{var-2}/O.01.$	MH212231
9	B^{var-3}	c.646T>A	p.F216I	1	AB_3	$B^{var-3}/A1.02$	KF661391
10	B^{var-4}	c.664G>A	p.V222M	3	B_xB_3	$B^{var-4}/O.01$	KF727687

† Nucleotide (nt) and amino acid (aa) changes of *A* and *B* alleles are given in comparison to the consensus *A1.02* (n.1-n.4, n.6), *A1.01* (n.5), and *B.01* (n.7-n.10) alleles, respectively.

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enzymes (PDB code, 4C2S). If the mutation destabilised the structure, ΔΔG was increased, whereas stabilising mutations decreased the ΔΔG. Since the FoldX error margin was around 0.5 kcal/mol, changes in this range were considered insignificant.

In vitro expression of GTA and the mutant p.L339P

A full-length *ABO*A1.01*cDNA (Fulengene, Guangzhou, China) was cloned into mammalian expression vector pcDNA3.1 containing the green fluorescent protein reporter gene. Mutation p.L339P was introduced by site-directed mutagenesis. HeLa cells (5×10^5) maintained in Dulbecco's modified Eagle's medium containing 10% foetal calf serum were transiently transfected with 1 μg of expression vector using transfection reagent (Lipofectamine 2000, Invitrogen, Thermo Fisher Scientific, Waltham, Massachusetts, USA) according to the manufacturer's instructions. Seventy-two hours after transfection, the transfected cells were analysed using polyethylene glycol-conjugated immunoglobulin G anti-A antibody (BGRL, Bristol, England) on a flow cytometer (BD FACS Calibur, Becton Dickinson, San Jose, CA, USA). The HeLa cells that expressed green fluorescent protein were gated[18] and three independent transfections were performed. The median fluorescence index (MFI) and the relative percentage of antigen-expressing cells (AEC%) were determined using Graphpad Prime (Graphpad Software Inc., San Diego, CA, USA), and a one-way analysis of variance (ANOVA) was used for statistical studies. The agglutination of suspended HeLa cells was also examined with an IgM monoclonal anti-A antibody (SHPBC). The transfected HeLa cells were incubated with anti-A antibody, and cell agglutination was observed using a phase contrast microscope.

Results

Phenotype and genotype identification of weak ABO subgroups

A total of 351 weak ABO subgroup cases were detected among approximately 1.45 million samples that underwent blood typing. DNA analysis of the *ABO* gene was carried out in 326 individuals with weak ABO subgroups. Forty-four weak ABO subgroup alleles were found in 227 subjects, including 34 known alleles (*Online supplementary content Table SI*) and ten unknown alleles (Table I). All the alleles were detected in Chinese subjects. *ABO*BA.04, BA.02* and *cisAB.01* alleles were commonly present in the Chinese weak subgroup population. The novel alleles were not found in 120 random, apparently healthy Chinese donors with common ABO blood groups. Except for the c.963insC mutation in $A^{var\text{-}4}$ that caused a frameshift starting at codon 322 and produced a GTA product with an extra 34 amino acids at the C-terminus, the other nine novel mutations were associated with amino acid substitutions in the catalytic domain of GT.

No mutations were found in the sequenced regions in the remaining individuals with weak ABO subgroups (n=99). Among these, nine individuals were suspected to be blood group chimeras because we detected three ABO alleles in the individuals by DNA sequencing after cloning. Seventeen samples were suspected to be blood group micro-chimera because weak A/B antigen was detected by adsorption-elution tests, but the corresponding A/B alleles could not be found in these individuals, possibly because of a low level of DNA below the range of detection.

Three-dimensional structural analysis of the GTA p.L339P mutant

Of all the amino acid residues encoded by the novel *ABO* subgroup alleles identified in this study, only the GTA L339 mutation site had not been reported in GTA or GTB. We, therefore, generated three-dimensional molecular models of the novel GTA mutant p.L339P. L339 is located far from the active cleft of GTA (Figure 1A). The overall structure of the p.L339P mutant GTA is predicted to be similar to that of the wild-type

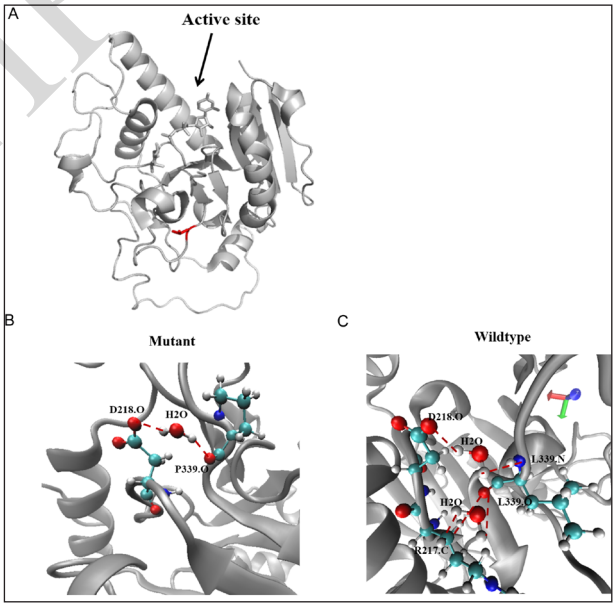


Figure 1 - p.L339P in GTA was predicted to destroy a local hydrogen-bond framework.

(A) Ribbon drawing of the overall GTA structure showing the site of the p.L339P mutation. (B) The local residues are represented by balls and sticks. O, C, N, and H atoms are represented by red, bluish green, blue and grey balls, respectively. The red dotted line indicates a hydrogen bond. In the wild-type GTA, a hydrogen bond framework was formed by L339.O-R217.C, L339.O- H2O-R217.C and L339.N-H2O-D218.O. (C) In the GTA p.L339P mutant, the former hydrogen bond framework disappeared and two new hydrogen bonds were formed between P339.O-H2O-D218.O.

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GTA, suggesting that this mutation may not affect the recognition and binding of the donor UDP-NAc and the acceptor substance H-antigen. However, the p.L339P mutation was predicted to destroy a hydrogen-bond framework formed by L339.O-R217.C, L339.O-H2O-R217.C, and L339.N-H2O-D218.O (Figure 1B), and two new hydrogen bonds were formed between P339.O-H2O-D218.O (Figure 1C). The hydrogen bonds damaged by the p.L339P mutation may change the local conformation of GTA.

Prediction of the stability of the GTA p.L339P mutant protein

Protein stability is believed to be affected by amino acid substitutions because of alterations in the number of hydrogen bonds, disruption of salt bridges, or other changes in protein folding[19]. Based on a three-dimensional structure analysis, a hydrogen-bond framework may disappear and fewer hydrogen bonds would be formed in the presence of the GTA mutant p.L339P. Thus, GTA stability may be affected by the mutation. To evaluate the effect of the p.L339P mutation on GTA stability, we calculated the protein thermodynamic stability changes of the mutant GTA. We built a homology model starting from 4C2S PDB using FoldX. The mutation from LEU to PRO at position 339 resulted in a ΔΔG of 2.92 kcal/mol. This result implies that the p.L339P mutation reduces GTA protein stability, which is consistent with the finding in the three-dimensional modelling analysis that local conformation was destroyed by this mutation.

In vitro expression of the GTA p.L339P mutant

We constructed GTA wild-type and p.L339P mutant expression vectors, which were transfected into HeLa cells, respectively. Fluorescence-activated cell sorting showed that there was a 65.0% reduction of MFI and a 53.0% decrease of AEC% in GTA mutant p.L339P transfected HeLa cells (Figure 2 A, B). The agglutination of HeLa cells transfected with GTA mutant p.L339P was remarkably decreased compared with that of cells transfected with the wild-type GTA expression vector (Figure 2 C-E).

Discussion

In the present study, 44 weak ABO subgroup alleles, including ten novel ones, were found in 227 Chinese subjects detected during blood typing of approximately 1.45 million samples. *ABO*BA.04, BA.02* and *cisAB.01* were commonly present in the Chinese weak ABO

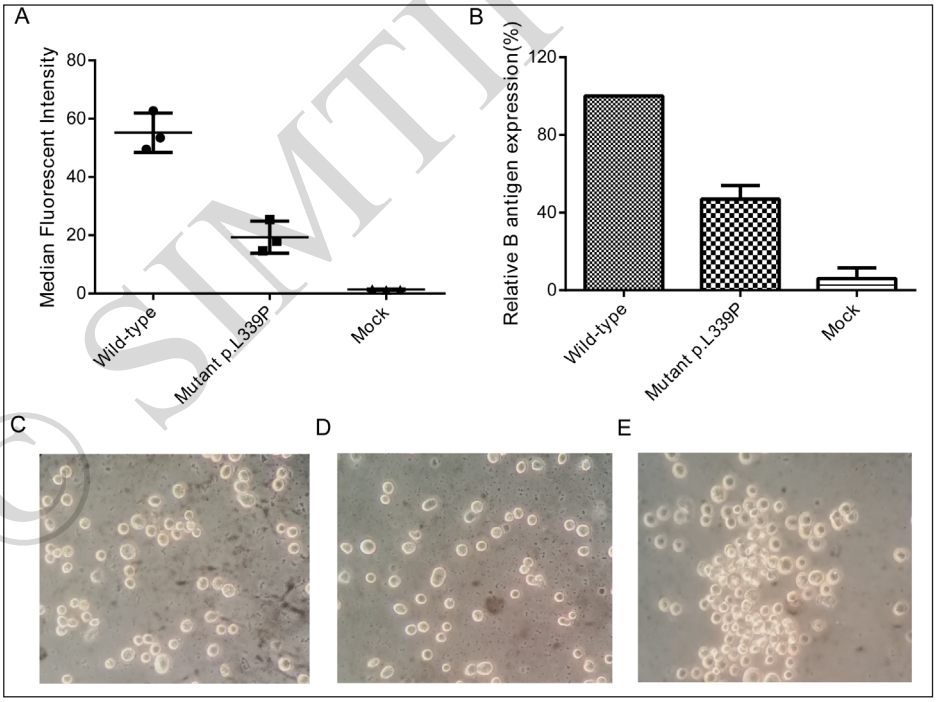


Figure 2 - *In vitro* expression studies showed that the p.L339P substitution affects A antigen expression.

(A) The median fluorescence index (MFI) of HeLa cells after transfection with wild-type GTA, the p.L339P mutant, or a control construct. (B) The relative percentage of antigen-expressing cells (AEC%) of HeLa cells after transfection with wild-type GTA, the p.L339P mutant, or a control construct. (C-E), The transfected HeLa cells were incubated with anti-A antibody and cell agglutination was observed using a phase contrast microscope. The aggregation of cells transfected with the mutant p.L339P construct (C), a control construct (D), or wild-type GTA construct (E) is shown.

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subgroup population. With regards to the ten novel alleles, about half of the related phenotypes were "x" types (5/11), suggesting that "x" types have a very heterogeneous molecular background. The novel allele $B^{var\text{-}4}$ was associated with two phenotypes, B_x and B_3. It is a common phenomenon that one allele corresponds to a variety of phenotypes, presumably because of allelic competition or enhancement[20,21] or differences between the reagent anti-serum. B(A) and cisAB are also related to many phenotypes as reported in Chinese and Korean populations[9,22]. It is noteworthy that five unrelated B_x individuals had the $B^{var\text{-}1}$ allele, suggesting that the frequency of this allele may be relatively high among Chinese subjects with weak ABO subgroup. Two missense mutations, p.V175M and p.R249Q, were found in this allele. The p.V175M mutation is a disputable amino acid substitution that has been reported both in the ABw subgroup (*BW.14*)[5,9] and normal AB and B groups[9,23]. The mechanism underlying this phenomenon is unclear and further *in vitro* study of the enzymes may be required. Furthermore, p.V175M also existed in the A subgroup (*AW.11*), together with another mutation p.R241W[24]. The p.R249Q mutation is a novel amino acid replacement, although p.R249W had been found in the *A3.07* allele in relation to the A_3 phenotype, which suggests that R249 may play an important role in enzyme function or biosynthesis.

In this study, the ten novel weak ABO subgroup alleles contained one insertion and nine point mutations. The insertion is related to the A_{el} subgroup indicating only a trace of A or B antigen expression on red blood cells. It leads to a frameshift 322fs+34aa and disrupts the C-terminus of GTA. In our previous study, we found that the highly flexible C-terminal carboxyl (amino acids 345-354) may play an important role in the catalysis of GT by interacting with some amino acids in the internal disordered loop[25]. The replacement and elongation of the C-terminus may, therefore, affect the function of GT and lead to a very weak ABO subgroup.

Most amino acid substitutions resulting from our newly found alleles are in locations in which other substitutions have been previously detected or the same substitutions have been found in different A or B subgroup alleles[9,26-29]. Only the p.L339P mutation occurred in a GT site that has not been previously found in weak ABO subgroup individuals. Leucine is one of the three amino acids with a branched hydrocarbon side chain, and it is hydrophobic and generally buried in folded proteins, while proline is the only cyclic amino acid which is formally an amino acid without a hydrogen on the α amino group. The modelling studies showed that a hydrogen-bond framework may be destroyed and fewer hydrogen bonds would be formed in the presence of the mutant P339. We calculated the thermodynamic stability change of the p.L339P mutant GTA, which was predicted to be less stable than the wild-type GTA and may, therefore, be responsible for the reduction of A antigen expression. Furthermore, the *in vitro* expression assay showed that A antigen expression and agglutination of HeLa cells transfected with GTA mutant p.L339P decreased significantly compared to those of cells transfected with wild-type GTA. These findings suggest that GTA 339L is essential to maintain the protein's function, and GTA mutant p.L339P may cause the inadequate conversion of H antigen and lead to a weak A phenotype.

Conclusions

In conclusion, we explored weak ABO subgroup distribution in the Chinese population and identified ten novel ABO subgroup alleles. GTA mutant p.L339P may result in a weak A subgroup by changing the local conformation of GTA and reducing its stability. Further investigation is needed to study the relationship between gene mutations and protein function.

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Authorship contributions

HH and SJ contributed equally to this work.

Conception and development of the experiments: XC, DX and XW; phenotype identification: SJ, XL, QL, LF, ZW, WS and CQ; execution and analysis of the *in vitro* experiments: HH and HL; execution and analysis of the molecular modelling and MD simulations: XC and ZW; writing and editing of the manuscript: HH and XC.

The Authors declare no confllict of interests.

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Correspondence: Xiaohong Cai
Ruijin Hospital,Medical School of Shanghai
Jiao Tong University
No.197 Ruijin 2nd Road
Shanghai, 200025, China
e-mail: cxh8407@shsmu.edu.cn

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