



## 12. The MNS blood group

The antigens of the MNS blood group are carried on sugar-bearing proteins called glycoporphins. These lie in the red blood cell (RBC) membrane. One end of a glycoporphin is attached to the underlying cell, and the other end bears the sugars and determines a person's MNS blood type.

### At a glance

#### Antigens of the MNS blood group

<b>Number of antigens</b>	<b>42: including M, N, S, and s</b>
<b>Antigen specificity</b>	<b>Protein</b> Amino acid sequence determines the specificity of MNS antigens
<b>Antigen-carrying molecules</b>	<b>Glycophorins</b> Glycophorins are transmembrane, single-pass glycoproteins that contain carbohydrate, mostly in the form of sialic acid. Glycophorins A and B carry the MNS antigens, and they may also serve as receptors for cytokines and pathogens, including the malaria parasite, <i>Plasmodium falciparum</i> .
<b>Molecular basis</b>	<b>Two genes encode the MNS antigens, GYPA and GYPB.</b> Both genes are located on chromosome 4 (4q28.2-q13.1). A third gene, GYPE, may be involved in the creation of variant MNS antigens. GYPA has two codominant alleles, M and N, which result from three SNPs (59C→T, 71G→A, 72G→T), and the corresponding M and N antigens differ by two amino acids (S1L, G5E). The codominant alleles of GYPB, C and c, result from one SNP (143C→T), and the corresponding S and s antigens differ by a single amino acid (T29M).
<b>Frequency of MNS antigens (%)</b>	<b>M:</b> 78% Caucasians, 74% Blacks <b>N:</b> 72% Caucasians, 75% Blacks <b>S:</b> 55% Caucasians, 31% Blacks <b>s:</b> 89% Caucasians, 93% Blacks (1)
<b>Frequency of MNS phenotypes (%)</b>	<b>M+N+S-s+: 22% Caucasians, 33% Blacks</b> <b>M+N+S+s+: 24% Caucasians, 13% Blacks</b> <b>M-N+S-s+: 15% Caucasians, 19% Blacks</b> <b>M+N-S+s+: 14% Caucasians, 7% Blacks</b> <b>M+N-S-s+: 8% Caucasians, 16% Blacks</b> <b>M-N+S+s+: 6% Caucasians, 5% Blacks</b> <b>M+N-S+s: 6% Caucasians, 2% Blacks</b> Less common phenotypes are M+N+S+s- (4% Caucasians, 2% Blacks) and M-N+S+s- (1% Caucasians, 2% Blacks). The phenotypes M+N-S-s-, M+N+S-s-, and M-N+S-s- are rare in Caucasians but are found in ~0.5% of Blacks (1).

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## Antibodies produced against MNS antigens

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<b>Antibody type</b>	<b>IgG and IgM</b> The Ig class depends upon which antigen is targeted.
<b>Transfusion reaction</b>	<b>Uncommon but potentially severe</b> Anti-S and anti-s are among the MNS antibodies implicated in causing transfusion reactions.
<b>Hemolytic disease of the newborn</b>	<b>Uncommon but potentially severe</b> Anti-S is more common than anti-s, but both are capable of causing severe-to-fatal HDN (2).

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## Background information

### History

After the discovery of the first blood group, ABO, in 1900, Landsteiner and his colleagues continued to experiment with blood to identify other blood groups.

MNS was the second blood group, discovered in 1927, after immunizing rabbits with human RBCs. The M and N antigens were identified first, but it was another 20 years before the S and s antigens were named. Now, more than 40 antigens are known in this blood group, but the M, N, S, and s antigens remain the most common.

### Nomenclature

- Number of MNS antigens: 43 (3)
- ISBT symbol: MNS
- ISBT number: 02
- Gene symbols: GYPA and GYPB
- Gene names: Glycoprotein A and Glycoprotein B

Note: A third locus, GYPE, lies adjacent to GYPB and is thought to be involved in the gene arrangements of the GYPB locus that result in the production of variant MNS alleles.

## Basic biochemistry

### Common phenotypes

In Caucasians, the most common phenotypes are M+N+S+s+ (24%), M+N+S-s+ (22%), and M-N+S-s+ (15%). The latter two phenotypes are common in Blacks also, occurring at a frequency of 33% and 19%, respectively (1).

### Uncommon MNS phenotypes

Many of the uncommon MNS antigens result from mutations within the GYPA and GYPB genes. For example, the Mt<sup>a</sup> antigen is produced by a single nucleotide polymorphism (SNP) in GYPA that results in a change of amino acid from threonine to isoleucine at position 58 in the GYPA protein. Likewise, the Vr

antigen arises from a SNP that causes a Ser47Tyr change (4).

Other MNS antigens are created by swapping of DNA between the GYPA and GYPB genes, which lie close together on chromosome 4. The resulting hybrid glycoproteins bear new MNS antigens, e.g. the Stones antigen (St<sup>a</sup>), Dantu antigen, Henshaw antigen (He), Mg, and the Miltenberger antigen (Mi<sup>a</sup>).

The rare blood type En(a-) is characterized by RBC membranes that lack glycophorin A as a result of several different mutations. A deletion of the GYPB gene occurs in individuals with the rare blood type S-s-U- (also known as U-). A deletion of both GYPA and GYPB results in the MkMk phenotype. Such individuals lack expression of both glycophorin A and B on their RBCs.

## Expression of MNS antigens

The MNS antigens are found mainly on RBCs. There are about 1 million copies of glycophorin A per RBC and 0.2 million copies of glycophorin B.

The MNS antigens are also expressed in the kidney (on the renal endothelium) and epithelium.

## Function of the molecules that carry the MNS antigens

Glycophorins A and B may serve as receptors for cytokines, bacteria, and viruses, but the lack of the glycophorins does not result in disease, indicating that their function is not physiologically significant, at least in modern times.

Scientists are interested in these glycophorins because they bear the MNS antigens and because they may act as a receptor for *Plasmodium falciparum*. This is a parasite that causes malaria in humans. Individuals who have rare blood types in which either the glycophorin A or B is absent, e.g., phenotypes En(a-) and S-s-U-, have RBCs that are resistant to invasion by *Plasmodium*.

## Clinical significance of MNS antibodies

### Transfusion reactions

Anti-M and anti-N are not considered to be a cause of transfusion reactions, although rare cases of delayed transfusion reactions have occurred as a result of anti-M (5). Anti-M is fairly common and is thought to mostly be naturally occurring because it is frequently found in children who have never received a blood transfusion.

Mild to moderate transfusion reactions can be caused by the presence of anti-S and anti-s in the patient's serum (6, 7).

Severe transfusion reactions have been attributed to anti-U, anti-Vw, anti-Mur, and anti-En<sup>a</sup> (1, 8, 9).

### Hemolytic disease of the newborn

Of the MNS antibodies, anti-S is more common than anti-s, and both are capable of causing severe hemolysis.

Less common causes of HDN include anti-M, anti-N, anti-U, anti-Mi<sup>a</sup>, anti-Mt<sup>a</sup>, and anti-En<sup>a</sup> (1, 10-15). Other MNS antibodies implicated in HDN are anti-Vw, anti-Mur, anti-Hut, anti-Hil, anti-Mv, anti-Far, anti-s<sup>D</sup>, anti-Or, and anti-MUT. In addition, other antibodies to low-incidence MNS antigens should be considered as potentially harmful (1, 16-20).

## Molecular information

Two genes encode the glycoporphins that carry the antigens of the MNS blood group: GYPA and GYPB. Both are on the long arm of chromosome 4 in the region 4q28.2-q13.1. They are tightly linked, and recombination occurs between them.

A third gene, GYPE, is located next to GYPB and may play a role in the gene arrangements that result in new variant alleles.

GYPA and GYPB are similar, sharing up to 97% sequence homology. In fact, the 5'-GYPA-GYPB-GYPE-3' gene cluster is thought to have originated from a single ancestral gene that underwent two duplications.

### The GYPA locus

The GYPA gene consists of 7 exons that span more than 60 kbp. It has two allelic forms called MNS1 and MNS2, which produce the M antigen and N antigen, respectively. The alleles are identical, except for two amino acid substitutions. The MNS1 allele encodes serine at residue 1 and glycine at residue 5. The MNS2 allele encodes leucine at residue 1 and glutamate at residue 5.

### The GYPB locus

The GYPB gene consists of five exons that span more than 58 kbp. It has two allelic forms called MNS3 and MNS4, which produce the S antigen and the s antigen, respectively. The alleles differ in one amino acid. The MNS3 allele encodes a methionine at residue 29, whereas the MNS4 allele encodes a threonine at this position.

### Protein

Glycophorins A and B are single-pass, transmembrane proteins. Glycophorin A contains abundant sialic acid, which contributes to the negative surface charge of the RBC membrane. It has three main domains: an extracellular domain (70 amino acids), the membrane spanning domain (22 amino acids), and an intracellular domain (39 amino acids). The M and N phenotypes differ from each other by one amino acid at positions 1 and 5 (as described above) in the extracellular N-terminal domain.

Glycophorin B is structurally similar to glycophorin A, also consisting of three domains but with a shorter intracellular domain of six amino acids. The S and s phenotypes differ from each other by one amino acid at position 29 (as described above) (21).

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