Review

# Cartwright blood group system review

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The Cartwright (Yt) blood group system consists of two antigens, Yt$^a$ and Yt$^b$, that result from point mutations in the acetylcholinesterase gene on chromosome 7q. Yt$^a$ is a high-incidence antigen, whereas its antithetical antigen, Yt$^b$, shows much lower incidence. Anti-Yt$^a$ and anti-Yt$^b$ are relatively rare. Anti-Yt$^a$ is more commonly found in individuals of Jewish descent. Cartwright antibodies are rarely clinically significant; however, cases of in vivo hemolysis have been reported, suggesting that clinical significance should be interpreted on a case-by-case basis. ***Immunohematology* 2012;28:49–54.**

**Key Words:** Cartwright, Yt, AChE

## History

Anti-Yt$^a$ and thus the Yt$^a$ antigen of the Cartwright blood group system were first described in 1956 by Eaton and colleagues.[1] This discovery in the early 1950s came on the heels of the identification of three other antibodies against high-incidence antigens (anti-Tj$^a$, -Vel, and -U). This new antibody was noted to agglutinate the majority of red blood cells (RBCs) of whites and was independent of all other known blood group systems. The antibody was first identified in a woman with a history of four pregnancies complicated by severe hemorrhage at delivery. She received several units of blood after her last delivery. Several years later, she required more transfusions. RBC units were weakly incompatible with her serum by the indirect antiglobulin test (IAT). Blood samples from eight laboratory staff members were also tested with the patient's serum and found to be incompatible. Transfusion was deferred until compatible blood could be obtained. The patient was discharged to home, and her hemoglobin level recovered without transfusion.

Serologic investigations performed on the patient's serum against a panel of RBCs of known phenotype demonstrated no agglutination in saline or albumin, slight but easily dispersible agglutination with trypsin-treated cells, and no reactivity with papain-treated cells. Owing to the weak and variable reactivity, Eaton and colleagues[1] decided to rule out a mixture of antibodies, and repeatedly adsorbed the serum with a number of strongly and weakly reacting cells. Six adsorptions were performed with equal volumes of strongly reacting cells at 37°C. After 1 hour, the antibody titer was reduced from between 32 and 128 to between 2 and 4. The sera after adsorption tested against a panel of cells indicated that only a single antibody was present. The antigen to which this antibody was reacting was provisionally named Yt$^a$. Eaton and colleagues[1] assumed that the antithetical antigen in this system, if discovered, would be called Yt$^b$. Having excluded the presence of more than one antibody, the researchers noted that the observed differing strengths of reactivity could represent a dosage effect, with weak reactors symbolizing heterozygotes. Forty-four members of the laboratory staff were tested. Of those 44, 5 reacted weakly. If those 5 represented heterozygotes, it was calculated that a negative would be encountered in every 250 to 300 random blood samples (0.348%). The goal of these initial investigations was to obtain compatible blood. A total of 1051 group O donors were tested with the patient's serum at two dilutions, 1 in 4 and 1 in 8, by the IAT. Tests were interpreted by the same staff members and were graded as strong, weak, and intermediate. Four negatives were identified and confirmed by repeat testing. The incidence of negatives was calculated as 0.38 percent. Extensive serologic testing demonstrated the independence of this new blood group system from ABO, Rh, and MNS systems. Yt$^a$ was identified on the RBCs of six infants at birth; reactivity was weaker than on adult cells. Further proof of this new blood group system was provided through the identification of additional cases of anti-Yt$^a$ by Race and Sanger,[2] Bergvalds and colleagues,[3] and Dobbs.[4] In 1963, Yt$^a$ was demonstrated to be separate from the Lutheran blood group system by Allen et al.[5] using a detailed family pedigree starting with a mother of six children who was homozygous for both Yt$^a$ and Lu$^a$. Given the significant genetic recombination as evidenced by the varied phenotypes in the children, it was clear that Yt and Lu were not related. The same pedigree demonstrated Yt to be separate from the Rh system.

Giles identified and reported the expected antithetical antigen, Yt$^b$, in 1964.[6,7] The patient was known to have anti-Fy$^b$ and an additional unidentified antibody. This antibody was isolated by adsorption and elution and tested against random blood samples. Nineteen of 229 samples demonstrated reactivity. Six known Yt(a–) RBC samples were tested against an eluate containing only the unknown antibody in the patient's serum. All reacted positively, with presumptive identification of anti-Yt$^b$, adding further evidence of the discovery of the antithetical antigen, Yt$^b$. A second example of anti-Yt$^b$ was

presented by Ikin et al.[8] in a case report of a patient with paroxysmal nocturnal hemoglobinuria (PNH) with aplastic bone marrow. He had been receiving six units of blood two or three times a year since 1957. This group found Yt$^b$ in about 8 percent of random samples, and the incidence of individuals with the Yt(a+b–) phenotype was reported to be as high as 91.4 percent. Given these statistics, it seemed likely that other cases of anti-Yt$^b$ may have passed unnoticed. In 1968, Wurzel and Haesler[9] found another anti-Yt$^b$ in a 76-year-old man who had received many transfusions.

## Nomenclature

The blood group system was named after the patient, Mrs. Cartwright, in whom it was first identified. Eaton and colleagues[1] developed the system's nomenclature by using the last letters of the patient's first and last name (Y and T), since her initials, A and C, already represented well-known blood group antigens. They adopted the idea of using a superscript letter to denote individual antigens within the system, starting with Yt$^a$ and assuming that the antithetical antigen in this system, if discovered, would be called Yt$^b$. The nomenclature across various systems is denoted in Table 1.[10–16]

**Table 1.** Nomenclature

| System Name | | System Symbol | | | Gene Symbol | | |
|---|---|---|---|---|---|---|---|
| Traditional/ISBT | ISBT number | Traditional | ISBT | ISBT number | Traditional | ISBT | ISGN |
| Yt or Cartwright | 011 | Yt | YT | | *Yt* | *YT* | *ACHE* |
| | | Yt$^a$ | YT1 | 011.001 | | | |
| | | Yt$^b$ | YT2 | 011.002 | | | |

ISBT = International Society of Blood Transfusion
ISGN = International System for Gene Nomenclature

## Genetics/Inheritance

The original cases of anti-Yt$^a$ were identified in patients of Jewish ancestry. The National Blood Group Reference Laboratory in Jerusalem identified 14 patients of 4474 referrals with anti-Yt$^a$, which was higher than expected based on prior European data. Once anti-Yt$^b$ became available, this group undertook a survey of Yt groups using both anti-Yt$^a$ and anti-Yt$^b$ on Israeli Jews. They tested 264 blood samples selected at random from the population and found that Yt$^b$ and anti-Yt$^a$ are relatively frequent among Israelis. These discoveries prompted further testing using the Yt system as a useful genetic marker in examining potential variability among different Jewish ethnic groups.[17–19] This same Israeli group looked at 1683 blood samples from Israeli Jews, Arabs, and Druse to determine the incidence of the Yt blood group phenotype and allelic frequencies. These populations had an overall incidence of the Yt(b+) phenotype ranging from 24 to 26 percent, versus a general European incidence of 8 percent. A null phenotype, Yt(a–b–), was not identified. These findings suggested that if blood group antibodies against a high-incidence antigen were detected in an individual of Jewish, Arab, or Druse descent, the probability of anti-Yt$^a$ would be high. Few ethnic groups have been tested for the incidence of Yt blood group system phenotypes and for allelic frequencies; however, individuals of Jewish descent and other Mid-Eastern ethnicities tended to have a lower incidence of Yt$^a$ and a higher incidence of Yt$^b$. Yt$^b$ was not identified in a random sampling of 70 Japanese individuals.[17] The incidence of the Yt(a+b–) phenotype in American blacks and white Canadians was found to be essentially the same as determined in studies of Europeans, as reported by Wurtzel and colleagues[20] in 1968 and Lewis and colleagues[21] in 1987. Overall, Yt$^a$ occurs in approximately 99.7 percent of American and European blood donors, whereas the antithetical Yt$^b$ is found in 8.1 percent of these donors. Yt(a–b–) appears to be transient, and a true inherited Yt(a–b–) phenotype would be extremely rare.[22] The percent occurrences of general phenotypes in Americans and Europeans are summarized in Table 2.[23]

**Table 2.** Yt Phenotypes

| | | % Bloods Reacting With | |
|---|---|---|---|
| Phenotype | % Occurrence | Anti-Yt$^a$ | Anti-Yt$^b$ |
| Yt(a+b–) | 91.9 | 99.7 | |
| Yt(a+b+) | 7.8 | | 8.1 |
| Yt(a–b+) | 0.3 | | |

## Molecular Basis

Even after the Cartwright antigen system was well characterized serologically, the chromosomal location was not known until 1991. In 1987, Lewis et al.[21] looked at linkage between Yt and 42 chromosomally assigned loci, but relationships were not clear. By 1989, Yt was believed to be loosely linked to the Kell system.[24] Linkage was shown to occur between the Yt and Kell loci at a recombination fraction of 28 percent. So when Kell was provisionally assigned to chromosome 7q, the placement of Yt seemed to be the next step. Based on their previous work with loci on chromosome

7, Zelinski and colleagues were able to demonstrate linkage to *COL1A2* and *D7S13* genotypes through paternal meiosis. Because it showed no recombination, Yt was provisionally assigned to chromosome 7, particularly within 7q22.1–q22.3.[25–28] Further studies of chromosome 7 also localized acetylcholinesterase (AChE) to 7q22. AChE plays a crucial role in cholinergic neurotransmission, and is found in the RBC membrane, where its function remains largely unknown. AChE undergoes extensive posttranslational modification, which may leave room for genetic variability.[29–32] A study by Spring et al.[33] provided evidence that Yt blood group antigens are located on erythrocyte AChE. This study identified immune precipitates of human anti-Yt$^a$ and -Yt$^b$ of the same molecular weight as AChE from radioiodinated erythrocytes of appropriate Yt phenotype. The immune precipitates obtained with anti-Yt$^a$ and -Yt$^b$ contained AChE activity. These results indicated that the Yt antigens were derived from an inherited polymorphism of AChE, and in addition to Zelinski's provisional assignment of Yt blood group locus to chromosome 7, gave provisional identification of the location of the *ACHE* gene. Further corroborating the link between Yt and AChE, Bartels et al.[34] discovered that the Yt blood group polymorphism is caused by point mutations in the *ACHE* gene. Further genetic characterization demonstrated that the *YT(ACHE)* gene consists of six exons distributed over 2.2 kbp of genomic DNA. The molecular basis of the Yt antigens is summarized in Table 3.[11]

**Table 3.** Molecular basis of the Yt antigens

| | Yt$^a$ | Yt$^b$ |
|---|---|---|
| Amino acid | His 353 | Asn 353 |
| Nucleotide | C at bp 1057 in exon 2 | A at bp 1057 in exon 2 |
| Additional features | Nucleotide at position 1431 C>T in exon 3 also differentiates Yt$^a$ from Yt$^b$ but does not alter the encoded amino acid. A second silent mutation in exon 5 does not correlate with the Yt polymorphism. | Nucleotide at position 1431 C>T in exon 3 also differentiates Yt$^a$ from Yt$^b$, but does not alter the amino acid. A second silent mutation in exon 5 does not correlate with the Yt polymorphism. |

## Biochemistry

Early studies of the Kell blood group antigen system led to some biochemical parallels between this system and the Cartwright system. Studies of the effect of dithiothreitol (DTT) on Kell and other RBC antigens led to the discovery that all Kell blood group antigens as well as Yt$^a$ are completely denatured after treatment with DTT. Other sulfhydryl reagents did not result in Yt$^a$ denaturation. Yt$^a$ was denatured within the same DTT concentration range as Kell, which led Branch and colleagues[35] to speculate that a biochemical relationship existed between the two systems. They concluded that Yt$^a$ requires at least one disulfide bond for maintenance of antigen integrity, implying a protein backbone. These findings paved the way for further biochemical characterization of the Cartwright antigen system.[36,37] The protein structure of the antigens within the Cartwright system helps to explain their serologic properties. Effects of enzymes and chemicals on Yt antigens are summarized in Table 4.[11,38]

**Table 4.** Effects of enzymes and chemicals on Yt antigens

| Enzyme/chemical | Yt$^a$ | Yt$^b$ |
|---|---|---|
| Ficin/papain | Sensitive (variable) | Sensitive (variable) |
| Trypsin | Resistant | Resistant |
| α-Chymotrypsin | Sensitive | Sensitive |
| Pronase | Sensitive | Sensitive |
| Sialidase | Resistant | Resistant |
| DTT 200 mM/50 mM | Sensitive/weakened | Sensitive/weakened |
| Acid | Resistant | Presumed resistant |

Additionally, Levene and Harel[39] noted that 2-amino-ethylisothiouronium (AET)-treated RBCs, which their laboratory used to detect antibodies to high-incidence antigens, may be helpful in the identification of Cartwright antibodies. Because disulfide bonds are a requirement for Cartwright antigen integrity, AET can reduce these bonds and eliminate reactivity.

In tandem with the molecular studies of the Cartwright antigen system, once a protein backbone was suspected, the study of patients with PNH led to the discovery that the Yt antigens likely resided on a phosphatidylinositol (PI)-anchored protein, as the complement-sensitive (PNH III) erythrocytes of these patients failed to express these antigens. However, the relatively normal constituent of complement-insensitive erythrocytes from the same patients expresses these antigens normally. Other high-incidence antigens showed varying levels of reactivity.[40,41] Human RBCs express a wide variety of PI-anchored proteins, including decay accelerating factor (DAF; CD55), membrane inhibitor of reactive lysis (MIRL; CD59), lymphocyte function associated antigen-3 (LFA-3; CD58), AChE, oxidized nicotinamide adenine dinucleotide (NAD+) glycohydrolase, JMH protein (p76), and others. DAF is known to bear the Cromer blood group antigens. A study in 1993 by Rao and colleagues[22] demonstrated that Yt$^a$ resides on erythrocytes' AChE. This study used RBCs from an individual with a previously uncharacterized Yt(a–b–) phenotype as well as normal Yt(a+) cells to serologically and

biochemically evaluate the relationship between Yt$^a$ and PI-linked erythrocyte proteins. Their work demonstrated that the Yt(a–b–) RBCs expressed normal amounts of all PI-linked proteins except for AChE, which added further proof of the Yt blood group system stemming from AChE.[40] Yt$^a$ is weakly expressed on cord RBCs, whereas Yt$^b$ shows the same level of expression on cord cells as on adult RBCs.[11–13]

In the late 1970s and early 1980s, a number of studies were undertaken to investigate the presence or absence of RBC antigens on various white blood cell fractions. Historically, there was no consensus in the literature regarding this topic.[42,43] In 1984, using flow cytometry, Dunstan[44] demonstrated that Yt$^a$ was not detected on lymphocytes, monocytes, or neutrophils.

## Antibodies

The discovery of the Yt blood group system was dependent on the identification of the antibodies directed against the antigens within the system. There are only two antigens in the Yt blood group system, Yt$^a$ and Yt$^b$, and therefore only two possible antibodies. Both anti-Yt$^a$ and -Yt$^b$ are of the IgG class and are optimally detected at the IAT phase. The incidence of the Yt (a–) phenotype, and hence anti-Yt$^a$, is higher in populations of Jewish descent. The first cases of anti-Yt$^a$ were found in Jewish women who were sensitized by pregnancy or blood transfusion.

Eaton et al.[1] were the first to describe anti-Yt$^a$ and hence Yt$^a$. Race and Sanger[2] reported three additional cases of anti-Yt$^a$ in their book *Blood Groups in Man* in 1962. An additional case of anti-Yt$^a$ was reported by Bergvalds and colleagues[3] in 1965. Their case was that of a Jewish woman who presented for induction of labor at 40 weeks' gestation. She had one previous pregnancy in which no antibodies were identified. She had no history of abortions, miscarriages, or previous blood transfusions. Late in her pregnancy, she was found to have a rising anti-D titer and a second unidentified antibody. After serologic investigation pointed to anti-Yt$^a$, a blood sample was sent to the Blood Group Reference Laboratory in London, England, where the presence of anti-Yt$^a$ was confirmed. Additionally, the patient's RBCs were tested against anti-Yt$^b$, demonstrating that her phenotype was Yt(a–b+) as expected.

In 1968, Dobbs et al.[4] reported clinical experience in three cases of anti-Yt$^a$. Over 3 years this group identified anti-Yt$^a$ in three patients: two were pregnant Jewish women with no evidence of hemolytic disease of the newborn (HDN); the third was a Jewish male patient with pure RBC aplasia who had been sensitized by multiple transfusions. Given the rarity of Yt(a–) blood and the severity of his anemia, this patient was transfused with several units of Yt(a+) blood with no evidence of untoward reaction. Chromium RBC survival studies were performed using an aliquot of transfused incompatible Yt(a+) blood. The study showed a RBC half-life of 30 days (normal is 27 to 30 days), so it appeared that this incompatibility had no effect on RBC survival in this patient. The patient required numerous transfusions and eventually underwent splenectomy and a regimen of steroids.

## Clinical Significance

The clinical significance of Cartwright system antibodies is debatable. There are two main laboratory diagnostic tests to assess clinical significance: the monocyte monolayer assay (MMA), which is used in vitro, and the $^{51}$chromium labeling study, used in vivo.[45,46] Most data regarding the clinical significance of these antibodies have been anecdotal through case studies. Despite evidence that anti-Yt$^a$ and -Yt$^b$ are capable of crossing the placenta, their presence does not necessarily result in HDN, which may in part be explained by the fact that Yt$^a$ generally shows weak expression on cord blood cells. Anti-Yt$^a$ does not generally cause transfusion reactions; however, moderate delayed reactions have been reported. The first evidence of clinical significance of anti-Yt$^a$ came from Bettigole et al.[47] Their group demonstrated rapid in vivo destruction of Yt(a+) RBCs in a patient with anti-Yt$^a$. They conducted an in vivo RBC survival study by transfusing 10 mL of chromium-tagged Yt(a+) RBCs. The half-life of the transfused cells at 12 minutes was estimated to be 3 days. Only about 13 percent of the original radioactivity was detected in vivo, despite 91 percent effectiveness of chromium labeling in vitro. Several years later, Göbel et al.[48] and Ballas and Sherwood[49] identified additional examples of anti-Yt$^a$ with rapid in vivo destruction of Yt(a+) RBCs.

Although chromium studies[50,51] are useful, some antibodies have demonstrated a change in perceived clinical significance as detected with long-term chromium-labeling studies. AuBuchon and colleagues[52] described an anti-Yt$^a$ that initially did not appear to decrease RBC survival; however, 12 weeks after transfusion of Yt(a+) RBCs, the alloantibody was characterized as IgG1 and repeat radiolabeled RBC survival studies demonstrated significant shortening of RBC lifespan as followed for 7 days. This particular case demonstrated a two-component survival curve in which initial rapid destruction is followed by slower removal of remaining cells. The authors attribute this to uneven antigen distribution, exhaustion of antibody, effect of RBC age, or blockade of

macrophage receptors for the complement system. Previous reports suggested the homogeneity of the Yt blood group system. However, an allogeneic anti-Yt$^a$ in a Yt(a+) individual was reported by Mazzi et al.[53] Both parents of the patient typed as Yt(a+). The patient's serum was adsorbed with his father's RBCs. Subsequently, the patient's serum was tested with his mother's RBCs, giving a positive reaction. Although all three parties tested Yt(a+), this pattern of reactivity suggests that a variant Yt$^a$ was present in the propositus and his father that was distinct from the normal Yt$^a$ found in the mother. Overall, recommendations for management of patients with anti-Yt$^a$ must be based on the individual case. A 14-month study of five such patients conducted by Mohandas and colleagues[54] suggested considerable variability in these patients' tolerance of Yt(a+) RBC transfusions.

Little has been reported about the clinical significance of anti-Yt$^b$. Yt$^b$ is expressed normally on cord blood cells; however, little is known about anti-Yt$^b$ in pregnancy, and therefore its potential to cause HDN is unknown. Generally, anti-Yt$^b$ is not believed to cause transfusion reactions. However, Levy et al.[55] both performed $^{51}$chromium-labeling studies in vivo and used MMA studies as an in vitro estimate of clinical significance. Their study found slightly abnormal MMA results and evidence of decreased RBC survival as measured by the $^{51}$chromium-labeling study. This finding was similar to that reported by Baldwin et al.,[56] which examined RBC antibodies of questionable clinical significance (anti-McC$^a$, -JMH, -Kn$^a$, and -Hy).

In summary, the Cartwright blood group system is a small system that demonstrates interesting demographic patterns. The expression of Yt antigens is dependent on intact AChE and a PI backbone. Although antibodies to this system are generally considered clinically insignificant, case reports have demonstrated decreased RBC survival. It would be advisable to consider the clinical circumstances surrounding each case of anti-Yt$^a$ or -Yt$^b$ in making a judgment on the clinical significance of the antibody. In emergency or urgent transfusion, most patients receiving Yt-incompatible blood have fared well; however, the various case reports discussed previously suggest that some cases have demonstrated decreased cell survival such that Yt-compatible blood would be preferable.

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