

RH FACTOR (RHESUS FACTOR)

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1. Core Definition and Antigenic Structure

The **Rh factor**, scientifically known as the **Rhesus factor**, constitutes one of the most clinically significant human blood group systems, second only to the ABO system. Fundamentally, the Rh factor refers to a complex system comprising at least 50 distinct red blood cell (RBC) surface antigens that are genetically determined. These antigens are lipoprotein complexes embedded in the outer layer of the erythrocyte membrane. The clinical importance of this system is overwhelmingly attributed to five principal antigens: D, C, c, E, and e. The presence or absence of the D antigen is the primary determinant used for classifying an individual as **Rh-positive** or **Rh-negative**, a critical distinction in clinical medicine, particularly in blood transfusions and obstetrics. Unlike the ABO system, where naturally occurring antibodies often develop against missing antigens, antibodies to the Rh factor (known as anti-D, anti-C, etc.) are typically acquired only after exposure to foreign Rh-positive blood, usually through transfusion or pregnancy, leading to **alloimmunization**.

The proteins responsible for carrying the Rh antigens are highly hydrophobic, meaning they are primarily integrated into the lipid bilayer of the RBC membrane. These proteins, known as Rh polypeptides, function as transporters or structural components, although their exact physiological role remains under extensive research. They are crucial for maintaining the structural integrity of the red cell and are often associated with other membrane proteins, forming a complex macrostructure. The density of these antigens on the erythrocyte surface varies considerably; for instance, a single Rh-positive red cell can bear approximately 10,000 to 30,000 copies of the D antigen. The powerful immunogenicity of the D antigen--meaning its capacity to provoke an immune response--makes it the cornerstone of Rh grouping, necessitating strict monitoring in sensitive clinical scenarios.

The definition provided in early literature emphasizes that the Rh factor relates to antigens "affixed to the outer layer of an individual's red blood cells." While accurate, modern understanding confirms that these are not merely affixed but are integral structural components encoded by highly polymorphic genes. The overall complexity of the Rh system means that while the D antigen dictates the general Rh status, compatibility requires considering the full array of Rh antigens (C, c, E, e) in specific clinical cases, especially for patients requiring repeated transfusions, such as those with thalassemia or sickle cell disease, to prevent the formation of multiple alloantibodies.

2. Etymology and Historical Discovery

The discovery of the Rh factor was a pivotal moment in the history of transfusion medicine, immediately following the elucidation of the ABO system by Karl Landsteiner. The initial identification occurred in 1937 when Karl Landsteiner and Alexander S. Wiener reported the presence of an unknown antigen in the blood of 85% of Caucasian individuals. This antigen was detected using an antibody produced by rabbits and guinea pigs after immunization with the red blood cells of **Rhesus monkeys** (*Macaca mulatta*). The original source content correctly notes that the use of these monkeys in early testing is what resulted in the designation **Rh factor**, short for Rhesus factor. This designation, though now considered slightly misleading due to subsequent discoveries showing that the human Rh antigen is not genetically identical to the original Rhesus monkey antigen (now known as LW antigen), has been retained due to historical convention and widespread clinical use.

Further critical developments occurred in 1940 when Landsteiner and Wiener demonstrated that the serum of women who had delivered infants suffering from Hemolytic Disease of the Newborn (HDFN), or patients who had experienced transfusion reactions, contained a similar antibody that reacted with the same antigen present in most human red cells. They named this antigen the Rh factor. This discovery immediately explained many previously mysterious and fatal blood transfusion reactions that occurred even when ABO matching had been meticulously performed. Prior to 1940, unexplained reactions were common, highlighting the crucial nature of this newly identified blood group system.

Following the initial findings, the complexity of the system became apparent. In 1941, Philip Levine and Rufus Stetson confirmed the clinical relevance of the Rh antibody in pregnancy complications. Subsequent research led to two competing nomenclature systems: the Rh-Hr terminology developed by Wiener, which treats the Rh locus as encoding a single antigen complex, and the CDE nomenclature (Fisher-Race terminology), which proposes that the antigens are determined by three closely linked gene loci (D, C/c, and E/e). Although the Fisher-Race system is more widely used clinically due to its simplicity in predicting antigen inheritance, both systems are recognized, underscoring the genetic complexity inherent to the Rhesus system.

3. Genetic Basis of the Rh System

The genetics of the Rh blood group system are governed primarily by two adjacent genes located on the short arm of Chromosome 1: the **RHD gene** and the **RHCE gene**. These genes are highly homologous and are inherited in a Mendelian fashion. The RHD gene determines the presence or absence of the highly immunogenic D antigen. Individuals who are Rh-positive typically possess at least one copy of the functional RHD gene, while Rh-negative individuals usually have a complete deletion of the RHD gene on both chromosomes (a homozygous deletion), particularly in Caucasians.

The RHCE gene is responsible for coding the C, c, E, and e antigens. Crucially, the RHCE gene produces two distinct products via alternative splicing: RhCe or RhcE proteins, which present the C/c and E/e antigens in various combinations (CE, Ce, cE, or ce). Thus, the combination of RHD status and the particular RHCE haplotype dictates the individual's complete Rh phenotype. For example, the common haplotype R1 is defined as DCe, while the r' haplotype is defined as Cde. The co-expression of these two genes is necessary for the proper insertion and function of the Rh proteins in the red cell membrane, and defects in either gene can lead to complex or rare phenotypes.

The inheritance pattern is particularly important for predicting risks in pregnancy. Since the D antigen is inherited independently of the C, c, E, and e antigens, a mother may be Rh-negative (lacking the D antigen) but possess C, E, c, or e antigens. If she is carrying an infant who has inherited the D antigen from the father, the mother's immune system may become sensitized to the fetal D antigen. Genetic counseling and prenatal testing rely heavily on understanding these inheritance patterns to calculate the probability of the fetus being Rh-positive and therefore at risk for HDFN. The development of molecular testing methods, which analyze the DNA directly, has provided definitive genotyping, especially critical for resolving complex or ambiguous serological results.

4. Key Phenotypes and Clinical Classification

Clinical classification within the Rh system centers predominantly on the D antigen. An individual is categorized as **Rh-positive (RhD+)** if the D antigen is present on their red blood cells, and **Rh-negative (RhD-)** if the D antigen is absent. Globally, the distribution of Rh status varies significantly by ethnicity. For example, over 85% of Caucasians are Rh-positive, while the prevalence among some East Asian populations approaches 99%. The remaining Rh antigens (C, c, E, e) are referred to as "minor" or "non-D" antigens, but they still carry significant immunogenic potential and must be considered in patients requiring chronic transfusions.

The primary phenotypes are often simplified into eight common combinations, derived from the possible combinations of the D, C/c, and E/e alleles. These combinations are represented using the Fisher-Race nomenclature (e.g., DCe, dce, Dce, dCE). The most common Rh-positive phenotype in Caucasians is R1 (DCe/dce), and the most common Rh-negative phenotype is r (dce/dce). Understanding the full phenotype is vital because, while anti-D is the most potent and clinically significant antibody, antibodies against C, c, E, or e can also cause severe transfusion reactions and HDFN, albeit less frequently than anti-D.

A particularly challenging group of phenotypes are the **D variants**, which include D weak (formerly Du) and partial D antigens. Individuals with the D weak phenotype possess the D antigen, but it is expressed weakly on the cell surface due to quantitative or structural changes in the RHD protein.

Clinically, D weak individuals are often treated as Rh-positive when donating blood, but as Rh-negative when receiving blood, to prevent potential sensitization. Partial D individuals have a structurally altered D antigen lacking certain epitopes. If a partial D patient is exposed to normal D+ blood, they can produce anti-D antibodies targeting the missing epitopes, potentially leading to transfusion reactions. These variant cases necessitate specialized laboratory testing to accurately determine the risk profile for transfusion and pregnancy management.

5. Clinical Significance in Transfusion Medicine

The Rh factor's primary clinical significance lies in its role in ensuring safe blood transfusions. Due to the high immunogenicity of the D antigen, meticulous matching of Rh status between donor and recipient is mandatory. Failure to match Rh status in a transfusion--for instance, administering **Rh-positive blood** to an **Rh-negative recipient**--will highly likely result in the recipient developing potent anti-D antibodies, a process called alloimmunization. While the first mismatched transfusion may not cause an immediate severe reaction (as the antibodies take time to form), subsequent exposures to D+ blood will trigger a rapid and potentially fatal **acute hemolytic transfusion reaction (AHTR)**, where the newly formed antibodies destroy the transfused red cells.

The standard protocol in transfusion medicine is to administer Rh-negative blood components to Rh-negative patients, particularly women of childbearing potential, regardless of their immediate need, to prevent sensitization that could jeopardize future pregnancies. In emergency situations where Rh-negative blood is unavailable, or for elderly male recipients, the risk-benefit analysis may permit the use of Rh-positive blood, provided the patient is carefully monitored and has no history of prior sensitization. However, such instances are exceptions rather than the rule, underscoring the stringent guidelines governing Rh compatibility.

Furthermore, for individuals requiring chronic transfusions--such as patients with inherited hemoglobinopathies like sickle cell anemia or thalassemia--matching for the full complement of Rh antigens (C, c, E, e) becomes increasingly important. These patients receive blood frequently, significantly increasing their lifetime risk of developing multiple non-D alloantibodies. To mitigate this risk, blood banks often employ extended antigen matching strategies, providing phenotypically matched units that are negative for the specific non-D antigens that the recipient lacks, thereby minimizing the chance of developing clinically significant antibodies that could complicate future transfusions.

6. Pathophysiology: Hemolytic Disease of the Fetus and Newborn (HDFN)

The most severe complication associated with Rh incompatibility is **Hemolytic Disease of the Fetus and Newborn (HDFN)**, historically known as erythroblastosis fetalis. This condition arises when an Rh-negative mother carries an Rh-positive fetus. During pregnancy or, more commonly,

at delivery, fetal red blood cells carrying the D antigen can enter the maternal circulation, typically due to minor placental hemorrhages or trauma. The mother's immune system recognizes the fetal D antigen as foreign and begins synthesizing anti-D antibodies (IgG class), a process known as **maternal alloimmunization**.

These IgG antibodies are small enough to cross the placenta and enter the fetal circulation. If the mother has already been sensitized (usually during a previous pregnancy with an Rh+ baby or prior incompatible transfusion), high levels of anti-D antibodies are rapidly produced during a subsequent pregnancy with an Rh+ fetus. These antibodies bind to the fetal Rh+ red blood cells, marking them for destruction by the fetal reticuloendothelial system, leading to chronic hemolysis. This destruction results in severe fetal anemia, hyperbilirubinemia, and, in its most severe form, **hydrops fetalis** (widespread fluid accumulation and heart failure), which can be fatal *in utero*.

The successful prevention of HDFN stands as one of the great triumphs of modern medicine. The primary preventive measure involves administering **Rh immune globulin (RhIG)**, commonly known by the trade name **RhoGAM**. RhIG is an injectable pharmaceutical preparation containing purified anti-D antibodies. When administered to the Rh-negative mother at strategic points (typically around 28 weeks gestation and again immediately post-delivery if the baby is Rh-positive), the exogenous anti-D antibodies effectively bind to and clear any fetal Rh+ red cells that have entered the maternal circulation before the mother's own immune system can initiate a primary immune response and produce memory B cells. This crucial intervention has dramatically reduced the incidence of severe Rh-D HDFN worldwide.

7. Rare and Variant Rh Phenotypes

While the vast majority of individuals are classified straightforwardly as Rh-positive or Rh-negative, the Rh system exhibits considerable genetic polymorphism, leading to several rare and clinically challenging phenotypes that require specialized management in transfusion services.

D Weak (Dw): This phenotype involves a quantitative reduction in the expression of the D antigen, typically due to inherited variations in the RHD gene promoter or minor amino acid substitutions that impair the protein's stability or insertion efficiency. Though weakly reactive in standard typing tests, D weak individuals generally do not produce anti-D when transfused with standard D+ blood, making their distinction from true Rh-negative status crucial for conservation of Rh-negative blood stocks.

Partial D: Individuals with partial D have a structurally altered D antigen where certain epitopes are missing. If transfused with normal D+ blood, they can generate an alloantibody targeting the missing epitope(s), which is functionally similar to anti-D and can cause HDFN or transfusion reactions. Differentiation between D weak and Partial D requires molecular genotyping, as only Partial D patients are at risk of immunizing against D.

Rhnull Syndrome: This is an extremely rare but highly significant phenotype characterized by the complete absence of all Rh antigens (D, C, c, E, e) on the red blood cell surface. This condition is caused either by mutation in the RHCE gene combined with RHD deletion (the amorph type) or by a defect in the RHAG gene (regulator type), which codes for the Rh-associated glycoprotein essential for the assembly of the Rh complex. Individuals with **Rhnull** blood often suffer from a mild to moderate hemolytic anemia and stomatocytosis (abnormal RBC shape) because the lack of Rh proteins compromises the structural integrity of the cell membrane. These patients can only receive blood from other Rhnull donors, requiring international registries for blood sourcing.

Rh Mod: Similar to Rhnull but less severe, Rh Mod individuals express severely weakened Rh antigens due to partial defects in the RHAG gene. They often require the same specialized transfusion support as Rhnull patients.

Further Reading

[Rh Blood Group System \(Wikipedia\)](#)

[The Rhesus Blood Group System \(NCBI Bookshelf/StatPearls\)](#)

[Karl Landsteiner Biography](#)

[Rh Immune Globulin \(RhoGAM\) Clinical Information](#)