Alleles

A gene at a given locus on a chromosome may exist in more than one form; that is, it may be allelic. Each person has two alleles for a trait, one is maternally derived and the other is paternally derived. At the simplest level, and for the purpose of explaining the concept, the *ABO* gene locus can be considered to have three alleles: *A*, *B*, and *O* (although genotyping has revealed many variant alleles; see the ABO chapter for additional information). With three alleles, there are six possible genotypes (*A/A*, *A/O*, *A/B*, *B/B*, *B/O*, and *O/O*). Depending on the parental contribution, a person could inherit any combination of two of the alleles and express the corresponding antigens on their red cells. For example, inheritance of *A/A* and *A/O* would result in group A red cells, *A/B* would result in group AB red cells, *B/B* and *B/O* would result in group B red cells, and *O/O* would result in group O red cells.

When identical alleles for a given locus are present on both chromosomes, the person is said to be homozygous for the particular allele. A person who is hemizygous for an allele has only a single copy of an allele instead of the customary two copies; an example is the deletion of one *RHD* in a D+ phenotype. An individual can also be functionally hemizygous if they carry two alleles where one is nonfunctional such as in the case of the *RHD*08N.01* allele (previously referred to as the *RHD* pseudogene or *RHD*Ψ)*. When different (ie, not identical) alleles are present at a particular locus, the person is said to be heterozygous. For example, a person who is homozygous at the *KEL* locus for the allele encoding the k antigen (*KEL*02*) will have K–k+ red cells. A person who is heterozygous for *KEL*01* and *KEL*02* (*KEL*01/02* genotype) will have red cells that are K+k+.

Antigens that are encoded by alleles at the same locus are said to be antithetical (meaning opposite); thus, K and k are a pair of antithetical antigens. It is incorrect to refer to red cells that are, for example, K–k+ or Kp(a–b+) as being homozygous for the k or Kp^b antigen; rather, it should be said that the cells have a double dose of the antigen and that they are from a person who is homozygous for the allele. Genes are allelic, whereas some antigens are antithetical.

The quantity of antigen expressed (antigen density) is influenced by whether a person is heterozygous, homozygous, or hemizygous for an allele; the antigen density is generally greater when a person is homozygous. In some blood group systems, this difference in antigen density is manifested by antibodies giving stronger reactions with cells that have a double dose of the antigen. Red cells with the Jk(a+b–) phenotype, encoded by a *JK*A/A* genotype, have a double dose of the Jk^a antigen and often are more strongly reactive with anti-Jk^a than those that are Jk(a+b+), which have a single dose of the antigen. Similarly, M+N– red cells tend to be more strongly reactive with anti-M than are M+N+ red cells. Weakly reactive antibodies may not be detected if they are tested with red cells expressing a single dose of the antigen. This observable difference in strength of reaction, based on the result of homozygosity or heterozygosity for an allele, is termed the "dosage effect." (See Table 9-2.)

TABLE 9-2. Example of How Genotyping Can Be Used to Determine Zygosity and Antigen Dose

Allelic State	Genotype*	Phenotype	Jk^a Dose	Jk^b Dose
Homozygous	*JK*01/JK*01*	Jk(a+b–)	Double dose	N/A
Heterozygous	*JK*01/JK*02*	Jk(a+b+)	Single dose	Single dose
Hemizygous	*JK*01/JK*01N.01* (null)	Jk(a+b–)	Single dose	N/A

* *JK*01* encodes Jk^a, and *JK*02* encodes Jk^b. *JK*01N.01* is silenced for Jk^a expression.
N/A = not applicable.

Genotype and Phenotype

The genotype of a person is the complement of genes inherited from his or her parents; the term is frequently also used to refer to the set of alleles at a single gene locus. The phenotype is the observable expression of the genes inherited by a person and reflects the biologic activity of the gene(s). Thus, the presence or absence of antigens on the red cells, as determined by serologic testing, represents the phenotype; the phenotype can be predicted by interrogating specific nucleotide variants using DNA-based testing to determine the genotype. In transfusion medicine, a genotype is commonly utilized for the purpose of obtaining the predicted phenotype of a patient or donor. Sometimes the genotype can be predicted from the phenotype; for example, when a person's red cells are reactive with anti-Jk^a and anti-Jk^b, which is a Jk(a+b+) phenotype, a *JK*A/JK*B* genotype can be inferred. Frequently, the phenotype provides only a partial indication of the genotype; for example, red cells that are group B reflect the presence of a *B* gene, but the genotype may be *ABO*B/B* or *ABO*B/O*. For decades, family studies were often used to infer a person's genotype, but now that most antigens and phenotypes can be predicted by the use of molecular methods, family studies to determine genotype can be mostly replaced by DNA analysis. (See "Blood Group Genomics" section below.)

INHERITANCE OF GENETIC TRAITS

A genetic trait is the observed expression of one or more genes. The inheritance of a trait (and red cell antigens) is determined by whether the gene responsible is located on an autosome or on the X chromosome (sex-linked) and whether the trait is dominant or recessive.

Pedigrees

A family study follows the inheritance of a genetic characteristic—for example, an allele encoding the expression of a red cell antigen—as it is transmitted through a kinship. A diagram that depicts the relationship of family members and shows which family members express (are affected), or do not express, the trait under study is termed a pedigree. A review of a pedigree should reveal the pattern or type of inheritance for the trait, or antigen, of interest. The person who first caused the family to be investigated is considered the index case and is often referred to as the proband or propositus/proposita (male singular form or gender unknown/female singular form); propositi is the plural form regardless of gender. Details of the conventions and symbols used for the construction of pedigrees are provided in Figs 9-5 and 9-6.

Autosomal Dominant Inheritance

An antigen (or any trait) that is inherited in an autosomal dominant manner is always expressed when the relevant allele is present, regardless of whether a person is homozygous or heterozygous for the allele. The antigen appears in every generation and occurs with equal frequency in both males and females. A person who carries an autosomal dominant trait trans-

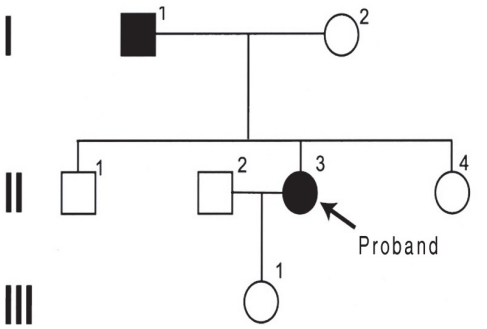

FIGURE 9-5. An example of a pedigree. Males are denoted by squares and females by circles, and each different generation in a pedigree is identified by Roman numerals. Persons in each generation are identified by Arabic numbers; the numbering is sequential from left to right, with the eldest child for each family unit being placed on the left of any series of siblings. Closed symbols represent family members affected by the trait, whereas open symbols are unaffected members.

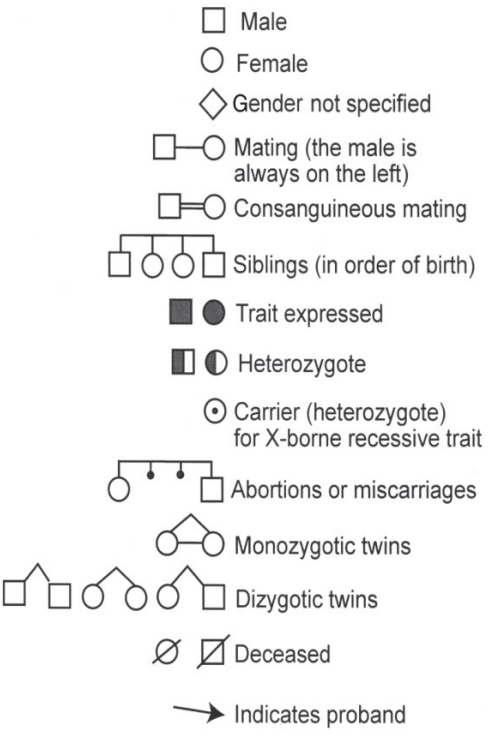

FIGURE 9-6. Symbols, and their significance, used in the construction of pedigrees.

mits it, on average, to half of his or her children. The pedigree in Fig 9-7 demonstrates autosomal dominant inheritance and shows that the *B* allele is dominant over *O*.

Autosomal Codominant Inheritance

Some blood group antigens that demonstrate an autosomal dominant inheritance are members of antithetical antigen pairs and are inherited in a codominant manner—that is, when two different alleles are present (the heterozygous condition), the products of both alleles are expressed. Thus, when red cells have the S+s+ phenotype, the presence of one allele encoding S and another allele encoding s [or an *S/s* (*GYPB*S/s*) genotype] can be inferred.

Autosomal Recessive Inheritance

A trait with autosomal recessive inheritance is expressed only in a person who is homozygous for the allele and has inherited the recessive allele from both parents. When a person inherits a single copy of a recessive allele in combination with a silent or deleted (null) allele—that is, a nonfunctioning allele or one that encodes a product that cannot be detected—the recessive

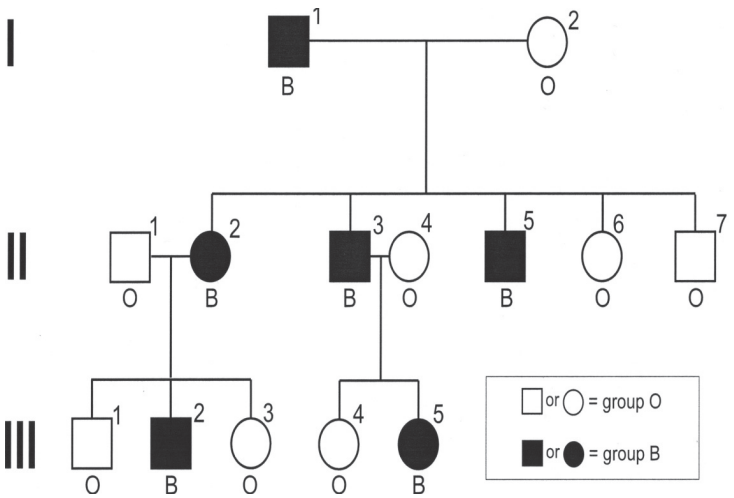

FIGURE 9-7. Autosomal dominant inheritance of the ABO alleles. Based on the ABO groups of his children, I-1 would be expected to have a *B/O* rather than a *B/B* genotype (showing that the B allele is dominant over *O*) because two of his children (II-6 and II-7) are group O and must have inherited an O allele from their father (I-1) in addition to the O allele inherited from their mother (I-2). Similarly, II-2 and II-3 are *B/O*, based on the ABO type of their children, showing the dominance of *B* over *O*.

trait is expressed and the person phenotypically appears to be homozygous for the allele. It is difficult or impossible to distinguish such a combination from homozygosity for the recessive allele through serologic testing, but DNA-based testing can usually make this distinction.

A mating between two heterozygous carriers results in one chance in four that the children will be homozygous for the trait. The parents of a child who is homozygous for a recessive trait are obligate carriers of the trait. If the frequency of the recessive allele is low, the condition is rare and usually found only among siblings (brothers and sisters) of the person and not in other relatives. The condition is not found in preceding or successive generations unless consanguineous mating (ie, between blood relatives) occurs. When a recessive allele is very rare, the parents of an affected person are most likely consanguineous because a rare allele is more likely to occur in blood relatives than in unrelated persons in a random population. When a recessive trait is one that is common, typically having a prevalence of greater than 1%, consanguinity is not a prerequisite for homozygosity; for example, the O allele of the ABO system, although recessive, is not rare, and persons who are homozygous for *O* are easily found in the random population.

In blood group genetics, a recessive trait almost always involves homozygosity for a silenced allele that encodes no product such that the red cells express a null phenotype [eg, the Lu(a–b–) or Rh_{null} or O phenotypes]. Null alleles are also known as amorphs: forms of a gene that do not express a product. The family in Fig 9-8 demonstrates the codominant inheritance of the antithetical antigens Lu^a and Lu^b as well as autosomal recessive inheritance of a null *LU* gene, which in the homozygous state results in the Lu(a–b–) phenotype. The proband, II-3, who received multiple transfusions, developed anti-Lu3 (an antibody to a high-prevalence Lutheran antigen).

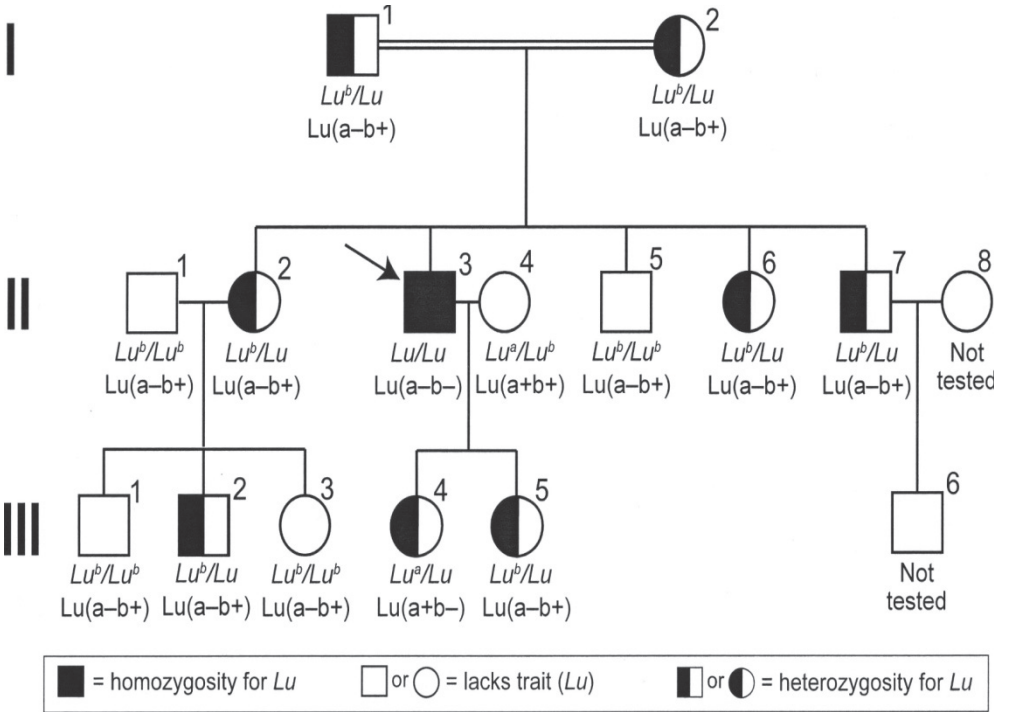

FIGURE 9-8. Autosomal recessive inheritance. The offspring of II-3, the Lu(a–b–) proband, and II-4, his Lu(a+b+) wife, demonstrate that *Lu* (depicting a Lutheran null allele, or *LU*02N*) is recessive to Lu^a (*LU*A*) and Lu^b (*LU*B*) and that the presence of the silenced Lutheran allele is masked by the product of Lu^a (*LU*A*) or Lu^b (*LU*B*) at the phenotype level.