Hemophilia A (classic hemophilia) and B (Christmas disease) are the two main types of inherited bleeding disorders that hamper the blood-clotting process. Although they result from mutations in different genes, they have similar clinical courses. Hemophilia A occurs in up to 1:5,000 males around the world, whereas hemophilia B occurs in about 1:20,000 newborn males globally.

During a Biogen Idec–sponsored symposium offered at the 65th Annual Meeting of the National Hemophilia Foundation, experts discussed the genetics of hemophilia A and B and presented talking points that they often share with their patients, including those addressing family planning and the care of pregnant patients with hemophilia. The panel of speakers included Barbara Konkle, MD, Professor of Medicine at the University of Washington School of Medicine, Director of Translational Research, and Medical Director of the Hemostasis Reference Laboratory at the Puget Sound Blood Center in Seattle, Washington; Michelle Alabek, MS, CGC, of Norton Cancer Institute Genetic Counseling Services at Norton Suburban Hospital in Louisville, Kentucky; and Jennifer Maahs, PNP, MSN, of the Indiana Hemophilia and Thrombosis Center (IHTC) in Indianapolis, Indiana.

### THE GENETIC BASIS OF HEMOPHILIA

Congenital deficiencies in factors VIII (FVIII; hemophilia A) and IX (FIX; hemophilia B) result from mutations of the \(F8\) and \(F9\) genes on the X chromosome, respectively. Males have only one X chromosome, so a single altered copy of one of these genes in each cell is enough to cause hemophilia. Females, on the other hand, carry two X chromosomes, so women need a mutation in both copies of the gene—one inherited from their mother and the other from their father—to develop the disease. Consequently, hemophilia is exceedingly rare in females.

Many types of mutations of \(F8\) and \(F9\) can lead to hemophilia. Further, the type of mutation can predict disease severity. Deletion and insertion mutations and mutations that cause premature termination of synthesis usually cause severe disease. Certain missense mutations also can lead to severe hemophilia. More commonly, missense mutations cause mild or moderate disease; in fact, 90% of patients who have mild-to-moderate hemophilia A have missense mutations. The majority of patients with hemophilia B also have missense mutations.

In hemophilia A, the most common genetic mutation is the intron 22 inversion mutation, which accounts for approximately 45% of all cases. This mutation arises from a folding over of the tip of the X chromosome, which leads to a homologous recombination. When the tip unfolds, some exons (nucleotide sequences) are oriented in the opposite direction, or inverted. Interestingly, most inversions originate during male meiosis (ie, in the maternal grandfather). As a result, almost all mothers of patients with inversion mutations are carriers of hemophilia.

### WHO SHOULD BE TESTED AND HOW?

Understanding the most frequently encountered genetic mutations in patients with hemophilia can help to guide diagnostic testing. Patients with a severe FVIII deficiency are first screened for the intron 22 inversion mutation (Figure 1).

If they test negative for this mutation, they undergo gene analysis. Patients with mild disease and hemophilia B undergo gene analysis. Currently, the Medical and Scientific Advisory Committee (MASAC) for the National Hemophilia Foundation recommends that all patients...
with hemophilia have genotype testing. An ongoing initiative is creating a comprehensive de-identified database of these mutations.8

Appropriate family members of hemophilia patients also can undergo carrier testing. Analysis of data from patients undergoing pretesting counseling found that approximately 30% of cases of hemophilia are sporadic.6 Despite this finding, most carriers are unaware of their status and require supportive counseling.

Most carriers are asymptomatic. In unusual circumstances, such as cases of Turner syndrome, some carriers may have low enough levels of a blood factor to cause clinical bleeding. For most patients, though, carrier status only affects preconception counseling.

**Testing a Carrier**

To test a possible carrier, it is best to target a known mutation. If the mutation is unknown, then the approach is similar to that used for testing patients with hemophilia. Patients are first screened for intron 22 inversion mutations, the most common overall cause of unspecified hemophilia.5 If the result is negative, then the whole gene is screened. Once carrier status is confirmed, patients can be counseled regarding family planning options, including preimplantation genetic testing. Patients who are carriers and pregnant with male fetuses need to be followed by a multidisciplinary team of specialists throughout pregnancy to address any possible perinatal testing and ensure a safe delivery.7

**USE OF GENETICS TO GUIDE TREATMENT**

Traditionally, analysis of factor levels and clinical presentation have guided the treatment course for hemophilia. However, a small percentage of patients with severe disease, as defined by coagulation factor level, have a milder clinical presentation.9 Therefore, there has been some interest in using genetic information to help guide management of the disease. For example, based on the results of genetic testing, a healthcare provider may consider inserting a central line earlier in some patients or delaying primary prophylaxis in others.

To take a closer look at the value of genetic testing, Carcao and colleagues8 examined 621 previously untreated patients and classified them according to whether they carried null or non-null mutations. Patients with null mutations experienced their first hemorrhage at a younger age, even though the difference was only 2 months. In the future, genetic characterization may allow individualized treatment.

### Characteristics of Hemophilia A (Classic Hemophilia)

- Caused by a mutation in the gene encoding coagulation factor VIII (F8) on chromosome Xq28
- Clinically heterogeneous, with severity dependent upon plasma levels of factor VIII (FVIII)
  - Mild: FVIII levels 6%–30% of normal; excessive bleeding only after trauma or surgery; experienced by 40% of patients
  - Moderate: FVIII levels 1%–5% of normal; experienced by 10% of patients
  - Severe: FVIII levels < 1% of normal; an average of 20–30 episodes/year of spontaneous and/or excessive bleeding, particularly into the muscles and joints, may occur after minor trauma; experienced by 50% of patients
- Joint involvement causes swelling, pain, decreased function, and degenerative arthritis.
- Muscle involvement causes weakness, contractures, and neuropathy by entrapment.
- Hematuria (occasional) is usually painless.
- Intracranial hemorrhage is uncommon but can occur after mild head trauma and lead to severe complications.
- Persistent bleeding from tongue or lip lacerations may occur.

Source: McKusick and Kniffin1

### Characteristics of Hemophilia B (Christmas Disease)

- Caused by a mutation in the gene encoding coagulation factor IX (F9) on chromosome Xq27.1
- Phenotypically indistinguishable from hemophilia A; on blood testing, however, hemophilia B is associated with a prolonged activated partial thromboplastin time and a normal prothrombin time.
- A distinction has been made between cross-reactive material (CRM)-negative and CRM-positive hemophilia B mutants based on the detection of F9 antigen in plasma even in the presence of decreased F9 activity. About 90% of hemophilia B patients are CRM-negative.
- Treatment for factor IX deficiency involves replacement of the missing factor by transfusion of plasma from a healthy person or infusion of a recombinant factor IX product.
- A subset of patients develops immunoglobulin G antibodies against normal factor IX, which complicates therapy.

Source: McKusick and Harnosh2
Development of Inhibitors

Most patients with the inhibitor phenotype have large alterations of the F8 or F9 gene (eg, large deletions, nonsense mutations, frameshift mutations). A small percentage of patients with the inhibitor phenotype can develop anaphylaxis to replacement factor, a life-threatening, difficult-to-manage clinical situation. 

Thorland et al\(^{10}\) genotyped eight patients with hemophilia B who had experienced anaphylaxis when exposed to FIX therapy and compared them with patients with severe disease. Those who had complete gene deletions were at the highest risk of developing anaphylaxis.

**SUMMARY**

Recognition that patients with hemophilia are at high risk may impact healthcare decisions. For example, patients at high risk of anaphylaxis may need to be infused in the supervised clinic setting instead of receiving treatment at home. Genetic testing remains expensive, but used judiciously, it has the potential to improve the management of patients with hemophilia.

**REFERENCES**