

Genetic Testing for Immune Deficiencies and Autoimmune Disorders: A Patient Primer

As genetic testing becomes more available, it is helpful for patients to understand what options are available and their benefits and risks.

By Troy R. Torgerson, MD, PhD

THE FIRST REPORT of a gene mutation causing an immune deficiency was published just more than 25 years ago. Since this initial report, there has been a rapid increase in the pace of new immunodeficiency-associated gene discoveries. At present, mutations in more than 400 different genes have been associated with disorders of the immune system. This growing number of identified gene defects has created hope among immunologists that they may eventually be able to provide a genetic diagnosis to virtually every patient who presents with a significant immune problem. The result is that gene sequencers have taken their place alongside the stethoscope and the CT scanner as critical tools of the trade for clinical immunologists.

The growing number of gene defects associated with immune disorders has broadened the scope of what is now considered to be an “immune deficiency.” Traditionally, the term was used to describe patients who had frequent, severe or unusual infections. Defects in the immune system were primarily in the cells or proteins required to attack invading bacteria, viruses or fungi. Over time, we have come to realize there are a growing number of genetic immunodeficiencies in which the main clinical problem is not infections, but severe, early-onset or unusual autoimmunity or inflammatory disease. The immune defects in these patients mostly affect the parts of the immune system that control the potency of an immune response or how long the response lasts. Without these control mechanisms in place, the immune system may react too strongly or may attack more than the invading viruses or bacteria, leading to autoimmunity and inappropriate inflammation.

Background and Definitions

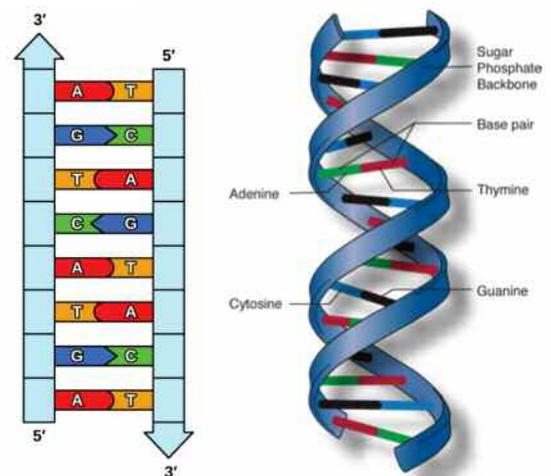
Before proceeding with a more detailed discussion of genetic testing, its use in the immunology clinic and its risks and benefits, it will help to furnish some definitions that provide the background to understand this very useful tool.

- A – Adenine**
- T – Thymine**
- G – Guanine**
- C – Cytosine**

DNA. DNA is made up of four nucleotides or “bases” represented by the letters A (adenine), T (thymine), G (guanine) and C (cytosine). The A, T, G and C bases are linked together to form the structure of DNA that is shaped like a very long ladder. Each side rail of the ladder is created as the A, T, G and C bases are connected to one another to form long strands. The sequence in which the bases are connected to one another “spells out” the genes and creates the genetic code. The rungs of the ladder are made as the bases on each of the side rails link to one another in a specific way: A linking to T (A-T) and C linking to G (C-G). If grasped at the ends and stretched out, the ladder of DNA in a single cell would be about 6 feet long. In order to stuff this into the nucleus of a tiny cell, the ladder is twisted into a helix and wound around proteins like thread around a series of spools to form chromosomes.

Chromosomes. The 6 feet of DNA from a single cell is divided into 46 pieces that are each packaged to become a chromosome by winding around a series of protein “spools” so they can all fit into the nucleus of a tiny cell. Each human cell has 46 chromosomes, 23 inherited from the father and 23 inherited from the mother. One of the chromosomes from each parent is an “X” or a “Y” chromosome that carries DNA sequences that determine the sex of the individual.

DNA is Made of 4 Nucleotides (Bases, Letters)



These are called the “sex” chromosomes. Females have two X chromosomes and males have one X and one Y chromosome.

Genome. The term “genome” refers to the DNA sequence that is included in one complete set of 46 chromosomes contained in a single human cell. The human genome consists of about 3.2 billion bases or “letters” that are linked together to form those 6 feet of DNA. To put this in perspective, this is the same number of letters contained in 1,000 copies of the English translation of Leo Tolstoy’s *War and Peace*, considered by most to be a very long novel. Mercifully, DNA is a much more efficient means of storing information than the printed page; otherwise, a single human cell would be enormous in both size and weight. When we refer to “whole genome sequencing,” it means the sequence of all 3.2 billion letters of DNA in the individual is determined.

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Exome. Interestingly, it turns out only 1 percent of the human genome (10 copies of *War and Peace*) actually contains all of the sequences that make up the genes. These are contained in blocks of DNA sequence called “exons” that are linked together by intervening stretches of DNA that are not part of the genes. Originally thought to be “junk” DNA or stuffing DNA, we now know these intervening sequences contain all of the instructions that tell the cell whether or not to make a specific gene and how much of each gene to make, almost like a computer program provides the instructions to tell the computer hardware what to do. When we refer to “whole exome sequencing,” it means only the 1 percent of the genome that actually encodes the genes (the exons) is sequenced.

Genes. Typically, one gene in the human genome includes the blueprint or sequence of letters that provide the instruc-

tions to make one particular protein in a cell. Each protein works like a tiny machine within the factory-like environment of a cell to carry out specific tasks that contribute to the survival and function of that cell. The human genome has about 20,000 different genes that can encode at least that many proteins. Different types of cells may “express” or make the proteins from only a subset of those 20,000 genes at any one time, and since there are estimated to be 200 different types of cells in the human body, the subset of proteins expressed by a cell determines whether that cell becomes a skin cell, blood cell, nerve cell or other cell type. When we refer to “single-gene sequencing,” it means the sequence of only one gene is determined. Sometimes, a number of single genes that may all be related to the same disease (like common variable immunodeficiency [CVID]) may be sequenced at the same time as a “panel.”

Genetic Testing Options Available to Physicians and Patients

As previously mentioned, there are now a number of different approaches by which patients and providers can have genetic testing performed, including single-gene sequencing, sequencing of a panel of immunodeficiency-related genes, whole exome sequencing and whole genome sequencing. As the costs of sequencing technologies have decreased, these have become increasingly affordable, now ranging from a few hundred dollars to a few thousand dollars, depending on the approach used. The decision of which approach to use depends on each patient’s symptoms and laboratory abnormalities and should be made in consultation with an immunologist, clinical geneticist or genetic counselor. Direct-to-consumer genetic testing options like those currently available through 23andMe, Ancestry.com and others are typically not helpful in identifying the cause of immune-related diseases, simply because the genes that cause these diseases are not included among those for which these services test.

Insurance coverage for genetic testing varies tremendously among carriers. There continue to be some insurance carriers that will not pay for any genetic testing, requiring patients to pay out of pocket. There are others that will pay for one type of genetic testing but not others (i.e., they will pay for a gene panel but not whole exome sequencing), and still others such as Cigna and Aetna that have developed and published criteria for obtaining coverage for whole exome sequencing so patients can determine whether they would be able to obtain coverage.

The likelihood of finding a genetic explanation for a disease depends on how well-defined the clinical picture is. For instance, when symptoms and laboratory testing strongly suggest a classical immune deficiency like X-linked agammaglobulinemia or Wiskott-Aldrich syndrome, the likelihood of finding a mutation in the causative gene is very high. However, in less well-defined diseases like CVID, the likelihood of finding a genetic cause is much lower, recently reported to be 20 percent to 30 percent in those patients with CVID who also have autoimmunity or inflammatory disease.

Benefits of Genetic Testing

There are several potential benefits that arise from identifying the specific genetic cause of a disease:

Making a definitive diagnosis. Many patients have expressed frustration to their providers that they don't really know for sure what they have. They know they get sick frequently with infections or they have a variety of autoimmune or inflammatory disorders, but putting a specific diagnostic name to their disorder is difficult. As a result, it may be labeled as "CVID," "combined immune deficiency" or "multisystem autoimmune disorder." Unfortunately, these generic labels make it difficult to provide specific or useful information about prognosis of the disorder, risk for other family members such as children developing the disorder, or even the optimal course of treatment. Identifying a specific genetic disorder can provide a sense of control. After informing patients that we have identified the genetic cause of their disorder, many have expressed some version of the following sentiment: "I'm not particularly happy to hear that I have a genetic disease, but at least I know what I have and that will help me know how to move forward!"

Family planning. Many patients want to know what the risk level is for other family members to have the same disorder or what the risk is for passing the disorder on to their children. Without knowing the genetic cause of the disorder, the risks that are quoted are usually just a guess. Identification of a gene mutation makes it possible to test other family members who might have similar symptoms, and it allows providers and genetic counselors to give patients an estimate of the specific risk of passing the disease to their children. In addition, knowing the genetic cause of disease makes prenatal testing of a developing fetus possible so families can make informed decisions and providers can plan ahead for the care of the child if he or she has the same disorder. It also allows parents

the option of taking advantage of modern reproductive technologies such as in vitro fertilization with preimplantation genetic diagnosis so they may be able to selectively implant only those embryos that lack the mutation.

Insurance justification. It is often much more straightforward to justify to an insurance company why it needs to pay for a particular diagnostic test, procedure or treatment if a patient is known to have a specific genetic disorder.

Treatment planning. Identifying a specific genetic disorder often helps to facilitate or guide treatment decisions in at least three ways.

First, a growing number of U.S. Food and Drug Administration-approved medications, developed to treat various conditions, can target specific proteins or signaling pathways in the cell. And, there are some genetic immunodeficiencies or autoimmune disorders caused by mutations in some of the proteins that are targeted by these medications. So, these medicines can be particularly effective in controlling the symptoms of that genetic disease — almost as if a designer drug had been developed for that specific disorder. Often, that particular medication would not have been considered for treating the disease without knowledge of the gene mutation.

Second, identifying a gene mutation may also facilitate bone marrow transplant in cases that it may be indicated. In the absence of knowing the genetic cause of a patient's disorder, there is often a delay in treating a patient with a bone marrow transplant, even if it may be indicated, because without knowing what the specific disease is, it is difficult to know whether it will respond to this aggressive treatment option. As a result, transplant becomes a last-ditch option. It also makes bone marrow transplanters hesitant to use siblings as bone marrow donors since they don't know if the sibling may have the same disorder but may not yet be manifesting symptoms. Knowing the gene mutation allows providers to recommend transplant earlier in the course of disease before patients become more ill and develop more problems. It also allows transplanters to test siblings to determine if they can be safely used as bone marrow donors.

Third, knowing the genetic cause of disease is absolutely essential to determine whether a patient may be eligible for newer therapies such as gene therapy or gene editing in which knowing which gene is mutated is essential before attempting to replace or repair it.

Hizentra®

Immune Globulin Subcutaneous
(Human) 20% Liquid

1st and only Self-administered Ig for CIPD Maintenance

#1 Ig Prescribed for PI

**My Life,
My Way
With
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Hizentra is an Ig* therapy that provides proven protection for PI and CIPD with the convenience of self-administration, so you can focus on everyday living

*Ig=immunoglobulin

Important Safety Information

WARNING: Thrombosis (blood clots) can occur with immune globulin products, including Hizentra. Risk factors can include: advanced age, prolonged immobilization, a history of blood clotting or hyperviscosity (blood thickness), use of estrogens, installed vascular catheters, and cardiovascular risk factors.

If you are at high risk of blood clots, your doctor will prescribe Hizentra at the minimum dose and infusion rate practicable and will monitor for signs of clotting events and hyperviscosity. Always drink sufficient fluids before infusing Hizentra.

See your doctor for a full explanation, and the full prescribing information for complete boxed warning.

Hizentra is a prescription medicine used to treat:

- Primary immune deficiency (PI) in patients 2 years and older
- Chronic inflammatory demyelinating polyneuropathy (CIPD) in adults

Treatment with Hizentra might not be possible if your doctor determines you have hyperprolinemia (too much proline in the blood), or are

IgA-deficient with antibodies to IgA and a history of hypersensitivity. Tell your doctor if you have previously had a severe allergic reaction (including anaphylaxis) to the administration of human immune globulin. Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Inform your doctor of any medications you are taking, as well as any medical conditions you may have had, especially if you have a history of diseases related to the heart or blood vessels, or have been immobile for some time. Inform your physician if you are pregnant or nursing, or plan to become pregnant.

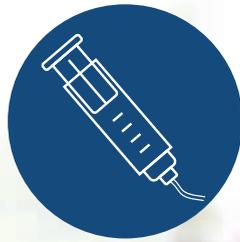
Infuse Hizentra under your skin *only*; do not inject into a blood vessel. Self-administer Hizentra only after having been taught to do so by your doctor or other healthcare professional, and having received dosing instructions for treating your condition.

Why Choose Hizentra?



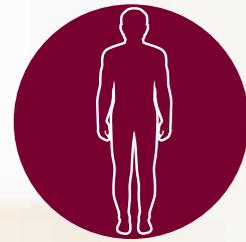
Choose where you infuse

Self-administration with Hizentra means you and your doctor can decide where you can infuse. Convenient dosing routines mean you won't have to adjust or cancel your plans due to IV infusion appointments.



No IV infusions

IV infusions can be challenging for people who have hard-to-find or damaged veins. Hizentra allows you to infuse just under the skin, not into a vein, after training from your doctor.



Proven safety

Hizentra has an established safety profile and demonstrated tolerability. In clinical trials, the most common side effects were redness, swelling, itching, and/or bruising at the infusion site; headache, chest, joint or back pain; diarrhea; tiredness; cough; rash; itching; fever, nausea, and vomiting. These are not the only side effects possible.

Discover all the benefits Hizentra has to offer at Hizentra.com

Immediately report to your physician any of the following symptoms, which could be signs of serious adverse reactions to Hizentra:

- Reduced urination, sudden weight gain, or swelling in your legs (possible signs of a kidney problem).
- Pain and/or swelling or discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, or numbness/weakness on one side of the body (possible signs of a blood clot).
- Bad headache with nausea; vomiting; stiff neck; fever; and sensitivity to light (possible signs of meningitis).
- Brown or red urine; rapid heart rate; yellowing of the skin or eyes; chest pains or breathing trouble; fever over 100°F (possible symptoms of other conditions that require prompt treatment).

Hizentra is made from human blood. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

The most common side effects in the clinical trials for Hizentra include redness, swelling, itching, and/or bruising at the infusion site; headache; chest, joint or back pain; diarrhea; tiredness; cough; rash; itching; fever, nausea, and vomiting. These are not the only side effects possible. Tell your doctor about any side effect that bothers you or does not go away.

Before receiving any vaccine, tell immunizing physician if you have had recent therapy with Hizentra, as effectiveness of the vaccine could be compromised.

Please see brief summary of full prescribing information for Hizentra on adjacent page. For full prescribing information, including boxed warning and patient product information, please visit Hizentra.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

IgIQ: Support Programs to Help You Get Started

Call IgIQ to find out about programs such as:



Free 1-month supply of Hizentra and free at-home nurse visits



Most patients with commercial insurance pay \$0 out-of-pocket*



Protection if you lose insurance*



Your single source for Ig solutions

1-877-355-IGIQ (4447)

*Other terms and conditions apply. Call IgIQ to learn more.

HIZENTRA®, Immune Globulin Subcutaneous (Human), 20% Liquid
Initial U.S. Approval: 2010

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HIZENTRA safely and effectively. See full prescribing information for HIZENTRA.

WARNING: THROMBOSIS

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including HIZENTRA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis, administer HIZENTRA at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

INDICATIONS AND USAGE

HIZENTRA is indicated for:

*Treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years and older.

* Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to prevent relapse of neuromuscular disability and impairment.

-Limitation of Use: Maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Continued maintenance beyond these periods should be individualized based on patient response and need for continued therapy.

For subcutaneous infusion only.

DOSAGE FORMS AND STRENGTHS

0.2 g per mL (20%) protein solution for subcutaneous injection

CONTRAINDICATIONS

- Anaphylactic or severe systemic reaction to human immune globulin or components of HIZENTRA, such as polysorbate 80
- Hyperprolinemia (type I or II) (HIZENTRA contains the stabilizer L-proline)
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity

WARNINGS AND PRECAUTIONS

- IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions.
- Thrombosis may occur following treatment with immune globulin products, including HIZENTRA.
- Aseptic meningitis syndrome has been reported with IGIV or IGSC, including HIZENTRA treatment.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of acute renal failure.
- Monitor for clinical signs and symptoms of hemolysis.
- Monitor for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI])
- HIZENTRA is made from human plasma and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

ADVERSE REACTIONS

The most common adverse reactions observed in ≥5% of study subjects were local infusion site reactions, headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, upper respiratory tract infection, rash, pruritus, vomiting, abdominal pain (upper), migraine, arthralgia, pain, fall and nasopharyngitis.

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

The passive transfer of antibodies may interfere with the response to live virus vaccines, and lead to misinterpretation of the results of serological testing.

Based on March 2018 revision

Risks of Genetic Testing

One of the most frequent concerns expressed by patients regarding genetic testing is whether it will impact their ability to obtain or keep insurance or whether their employer may discriminate against them if a gene mutation is identified. Fortunately, in the United States, the Genetic Information Nondiscrimination Act (GINA) was signed into law in 2008. This law makes it illegal to discriminate against patients with a genetic disease for employment, healthcare and health insurance. GINA does, however, have limitations. It doesn't apply to employers that have fewer than 15 employees, does not protect against discrimination in other forms of insurance such as life, disability or long-term care insurance, and does not cover individuals serving in the military or those who receive benefits from the Veterans Administration or Indian Health Service. That said, the increasing use of genetic testing in all aspects of medicine and the acknowledgement of the value it provides make it less likely genetic discrimination would be tolerated.

The other concern raised by patients, in light of recent reports of "cold" crime cases being solved by DNA evidence available in public databases, is whether genetic testing could subject them or a family member to be convicted of a crime. In each of these cases, the link between the crime and the perpetrator was made because genetic information was accessed on publicly available websites. Genetic testing performed on a clinical basis is never made available on publicly accessible websites without the patient's consent, so this information should not be available in a manner that could be linked to an individual or his or her family members.

Other Recommendations

It is strongly recommended that if patients have genetic testing performed, they should obtain a copy of that testing for their own records so they have it readily available in case they need to seek care in an urgent care setting or emergency room or if they transfer care to a new provider. In the case of exome and genome sequencing, patients should try to obtain a copy of the actual sequencing data on a hard drive or memory stick for themselves. One reason for this is that because of the massive amount of data included in an exome or genome sequence, it is possible to miss a causative mutation buried within the data. Having the actual data files available would allow that to be reanalyzed over time with new computer algorithms that may be able to identify the causative mutation.

In addition, it is likely patients will encounter other non-immune medical issues as they age, and there may be genetic predispositions for those disorders that can be gleaned from that data and that may be helpful in choosing future therapies, etc.

Identification of a gene mutation makes it possible to test other family members who might have similar symptoms, and it allows providers and genetic counselors to give patients an estimate of the specific risk of passing the disease to their children.

Consultation Is Advised

Genetic testing is becoming increasingly accessible to patients with immune disorders, and the growing number of identified gene defects associated with immunodeficiency or autoimmunity has made it increasingly likely that a genetic cause for a particular disease can be identified. While there are clear risks and benefits to genetic testing, consultation with a trusted immunologist, geneticist or genetic counselor can help to determine whether it is appropriate in a patient's case and which method would be most likely to yield a helpful result. ■

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