

Why Consider Genetic Testing to Detect a Primary Immunodeficiency?

What are primary immunodeficiencies?

Primary immunodeficiencies (PIDs) are a group of immune system disorders that result from single-gene defects. “Primary” refers to the fact that these disorders are genetic in nature, and therefore can be inherited, as opposed to secondary immunodeficiencies, which are acquired (eg, AIDS). At least 100 different forms of PID have been characterized, ranging widely in severity and symptoms. Despite the variability of PIDs, they all share the common feature of an unusual susceptibility to infection that can ultimately lead to severe complications – such as chronic lung damage, autoimmune disease, or an increased risk of certain types of cancer – or even death.¹⁻³

A brief overview of the immune system.

The immune system is designed to protect us from harmful agents. It uses three major “lines of defense,” humoral immunity, cellular immunity, and innate immunity, which function in collaboration to rid the body of infectious agents. Humoral immunity is mediated by antibodies, which are produced by specialized cells called B-cells. The role of antibodies is to coat foreign agents, and thereby neutralize them and target them for elimination. Cellular immunity is mediated by another set of specialized cells, the T-cells. T-cells recognize infected body cells and orchestrate an immune response against the infecting agent. T cells are responsible for both stimulating B-cells to produce antibodies as well as for targeting infected cells for destruction. Innate immunity is mediated in part by yet another type of specialized cells, the phagocytes. Phagocytes have the ability to “eat” and then destroy foreign agents or infected cells.

What type of genetic defect can lead to a PID?

PIDs can result from defects affecting humoral, cellular, or innate immunity. Sometimes, two or all three of these different types of immunity are impaired. The most commonly observed forms of PID include the following:

- Antibody deficiencies account for nearly half of all PID cases.⁴ Antibody deficiencies can occur when a patient has too few B-cells or B cells that don’t work properly.⁵ Antibody deficiency disorders include X-linked Agammaglobulinemia (XLA) and Common Variable Immunodeficiency (CVID).
- Combined B-cell and T-cell deficiencies comprise ~20% of all PIDs.⁴ Combined immunodeficiencies can arise when the body produces too few B cells and too few T cells or when the B cells and T cells that are produced don’t function correctly. Severe Combined Immunodeficiency (SCID) is the most common and serious type of combined immunodeficiency.
- Phagocyte defects represent ~18% of PIDs.⁴ Chronic Granulomatous Disease (CGD) is a prominent example of a phagocyte defect.

Early diagnosis and treatment are critical to assuring the best possible prognosis for patients with PIDs.

Effective therapies are available for most PIDs. Since these therapies are aimed at preventing infections, they are most effective if started before severe infections and the associated complications have occurred.⁶ However, some therapies (such as bone-marrow transplantation) are serious interventions that should not be undertaken unnecessarily. This highlights the importance of both early and accurate diagnosis.



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Diagnosing the specific type of PID can be difficult.

Unfortunately, recognizing a PID as the cause of infections is not always easy. In addition, different forms of PID can be difficult to distinguish. For example, the clinical symptoms of X-linked Agammaglobulinemia (XLA), Hyper IgM Syndrome (HIGM), Hyper IgE Syndrome (HIES), X linked Lymphoproliferative Disease (XLP), and Common Variable Immunodeficiency (CVID) can be very similar, but the prognosis and treatment for these disorders vary substantially.

Remember that each PID is caused by defects in a single gene. Already, the genes associated with >60 PIDs have been identified,^{6,7} allowing development of genetic tests for these disorders. Genetic tests can confirm the diagnosis of a PID by detecting PID-associated defects, or mutations, in a gene. Once a specific genetic defect has been identified in a patient, genetic testing readily allows identification of family members that carry the same defect. Family testing is recommended to detect carriers— individuals who are not affected by the disease, but harbor a disease-associated mutation that they can pass on to their children. Family testing can also help to identify PID directly after or even before birth in siblings of patients with PID.

► **Click here for more information on availability of genetic testing. If you believe genetic testing could be of benefit to you or your children, please consult your physician.**

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