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CHOP introduces HLA typing by next-generation sequencing to its clinical services

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Immunogenetics experts at The Children's Hospital of Philadelphia (CHOP) have developed a unique laboratory test to characterize the genes that encode HLA molecules. The test relies on faster, more comprehensive gene sequencing technology to type human leukocyte antigens (HLAs)—complex, highly variable proteins on cell surfaces that are essential to immune function.

The new test may improve transplantation outcomes through a more refined assessment of donor compatibility, and will expedite the donor selection process from bone marrow registries. It also provides an advanced tool for research in immunological diseases, infectious diseases, and pharmacogenomics—the field that studies the influence of genetic variations on drug efficacy and toxicity.

"This new test addresses a sixty-year-old problem," said Dimitri Monos, Ph.D., director of the Immunogenetics Laboratory in the Division of Genomic Diagnostics at The Children's Hospital of Philadelphia. "Since the discovery of HLAs in the early 1950s, it has been a challenge to accurately and thoroughly characterize HLA gene sequences. We have now used next-generation sequencing tools to significantly advance HLA typing."

CHOP is the first hospital anywhere to offer this new comprehensive HLA-typing test, based on extensive research by Monos and colleagues. "This is a new, disruptive technology, with the potential to transform research and clinical practice, in transplantation and other fields," said

Robert Doms, M.D., Ph.D., pathologist-in-chief at CHOP.

HLA genes are the most complex gene family known in the entire human genome. Gene sequences for HLAs are extremely polymorphic—highly variable, to a degree not adequately captured by conventional typing tests. Current tests often provide ambiguous and limited results, by sequencing only segments of HLA genes and failing to distinguish among different alleles suggested by a given sequence. In addition, preliminary testing often must be followed by a second level of reflexive testing, adding expense and time to the HLA typing process.

The new test, says Monos, replaces preliminary and reflexive tests with a single test, providing the highest resolution possible by covering the full HLA genomic region. It can currently distinguish among 10,500 different alleles of all known HLA types and can fully characterize new alleles yet to be discovered. Next-generation sequencing is expected to dramatically increase the list of HLA alleles.

Monos and colleagues developed a new protocol for HLA genotyping using an Illumina® sequencing platform, the MiSeq. The scientists validated the test by comparing its results against previously sequenced data from a collection of over 300 samples characterized at five different genes. The agreement between the two methodologies was 100 percent.

CHOP will be offering the HLA typing test for patient testing as a service to medical and academic centers. The test is faster, more precise, and costs less than existing testing procedures.

The new test's most significant short-range impact may be in typing donors in bone marrow/stem cell registries. Because of the high cost of performing high-resolution HLA typing under current methods, most potential donors are typed at low- or intermediate-resolution, with a

repeat, high-resolution test needed to assess compatibility when a patient needs a transplant. The new method will save time and expense by initially typing donors at the allele level. Therefore, no additional typing will be necessary to assess compatibility.

"This faster, more thorough technology allows us to better account for subtle genetic differences between individuals," said Monos. "We expect this knowledge to yield clinical benefits, by facilitating more precise matches between transplant donors and recipients, and assessing the significance of mismatches in genomic regions of the HLAs that were previously uncharacterized. Additionally, by focusing on fine details of immune responses, this technology can advance our understanding of how specific individuals respond to infectious diseases, to vaccinations, and to particular drugs. This test represents a potentially powerful tool in personalized medicine."

Provided by Children's Hospital of Philadelphia