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Research reveals genetic variants linked to treatment-related complications in children with blood diseases

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Research to be presented today at the 57th American Society of Hematology (ASH) Annual Meeting and Exposition reveals genetic variants that are associated with disease severity and treatment-related complications in children with blood diseases.

Recent technological advances in genome sequencing have allowed researchers to discover small DNA alterations that are associated with particular clinical outcomes or characteristics of disease. As sensitive tools become more widely accessible, investigators are increasingly able to identify genomic variations that may lead to more personalized therapies aimed at correcting genetic mutations or preventing complications in specific high-risk populations. As treatments that target disease-specific molecular abnormalities have already drastically improved outcomes for some patients with blood diseases, researchers continue to uncover genetic clues that shed light on risk of relapse, potential treatment-related complications, and the likelihood of recovery.

Two studies present new insights on genetic mutations in children with acute lymphocytic leukemia (ALL) that indicate higher risk for debilitating chemotherapy-associated bone damage. Another study examines the potential of using real-time genetic analysis to personalize chemotherapy regimens for children with B-cell lymphocytic leukemia (B-ALL). Finally, researchers have discovered genetic variants that may be associated with the development of autoimmune bleeding disorders.

"We all have thousands of small variants in our genomes, some of which may predispose an individual to greater toxicity to a particular drug or alter the response to a specific treatment. Identification of these genetic variations using DNA sequencing provides a powerful and increasingly accessible tool to help predict which patients may be at risk for adverse treatment-related outcomes," said Wendy Stock, MD, Professor of Medicine in Hematology/Oncology and Director of the Leukemia Program at University of Chicago. "The exciting research presented today provides new information on specific genetic risk factors that could lead to more personalized therapeutic approaches to improve outcomes for children with devastating diseases."

This press conference will take place on Saturday, December 5, at 9:00 a.m. in Room W208AB of the Orange County Convention Center.

Researchers Identify Genetic Variants That Indicate Increased Risk of Osteonecrosis in Children Under 10 Years Old With Acute Lymphocytic Leukemia

Genetic Risk Factors for the Development of Osteonecrosis in Children Under Age 10 Treated for Acute Lymphoblastic Leukemia [250]

- Osteonecrosis, a disease caused by reduced blood flow to bones in the joints, is a significant side effect of chemotherapy in children with acute lymphocytic leukemia (ALL), especially in patients aged 10 to 20 years.
- As previous research has focused on patients older than 10, this study sought to evaluate whether genetic risk factors for osteonecrosis differ for younger children.
- Investigators performed a genome-wide association study in 1,186 children, including an initial discovery group of 82 with osteonecrosis and 287 patients who did not develop osteonecrosis, to identify genetic variants that are most common among those with the bone disease.
- Researchers observed that patients with osteonecrosis are eight to 15 times more likely to possess genetic variants near a gene important to bone development (*BMP7*) and between three to six times more likely to have variants near a gene important to fat levels in the blood (*PROX1*).
- The findings suggest that these genes are associated with increased risk of osteonecrosis in children under 10 years old.
- This study increases understanding of the development of osteonecrosis which may lead to better treatments in the future.

Seth E. Karol, MD, St. Jude Children's Research Hospital, Memphis, Tenn., will present this study during an oral presentation on Sunday, December 6, at 12:45 p.m. in room W331, level 3 of the Orange County Convention

Center.

Study Identifies Genetic Variant That Signifies Higher Risk for Avascular Necrosis in Children with Acute Leukemia

Homozygosity for the 2R Tandem Repeat Polymorphism in the Thymidylate Synthase (TS) Promoter is Associated with Increased Risk for Bony Morbidity Among Children Treated for Acute Lymphoblastic Leukemia on DFCI Protocol 05-001 [251]

- Bone fractures and avascular necrosis (AVN), the death of bone tissue caused by a lack of blood supply, can frequently complicate therapy for children with acute lymphocytic leukemia (ALL), resulting in significant pain and physical disability. These treatment-related side effects have been seen most commonly in ALL patients diagnosed in their early teenage years but can occur in children of any age.
- The study sought to determine if any of 19 common genetic variants are associated with increased risk of bone damage in children with ALL.
- Investigators collected blood or bone marrow from 627 children in remission and sequenced their DNA. Then they observed the children for signs of bone damage during post-induction therapy.
- Researchers observed that 61 patients (9.7%) developed AVN and 138 (22%) suffered one or more fracture.
- Of the patients tested, 20.6 percent had a specific genetic variant (2R/2R) in a promoter of thymidylate synthase (TS), an enzyme that is often linked to treatment resistance.
- Compared to those with other TS variants, researchers estimate that patients 10 and younger with the 2R/2R genotype have a nearly three-fold higher risk of developing AVN. Among older children, this variant was associated with a two-fold increased risk of bony fractures.
- The results indicate that children under 10 years of age with ALL and the 2R/2R genetic variant should be monitored more closely for the development of AVN during therapy.

Peter D. Cole, MD, Albert Einstein College of Medicine, Bronx, N.Y., will present this study on behalf of the Dana Farber Cancer Institute ALL Consortium during an oral presentation on Sunday, December 6, at 1:00 p.m. in room W331, level 3 of the Orange County Convention Center.

Real-Time Classification System Based on Cytogenetics and Treatment Response Identifies Leukemia Patients With High Risk Clinical Features but Outstanding Outcomes

Genetic and Response-Based Risk Classification Identifies a Subgroup of NCI High Risk Childhood B-Lymphoblastic Leukemia (HR B-ALL) with Outstanding Outcomes: A Report from the Children's Oncology Group (COG) [807]

- Adjusting the intensity of treatment based on the patient's likelihood of relapse has emerged as a promising strategy for treating children with acute lymphocytic leukemia (ALL).
- This is the first Children's Oncology Group (COG) study to systematically assess minimal residual disease at the end of induction therapy and use this, in concert with clinical and biological data, for risk stratification and treatment assignment.
- Newly diagnosed B-cell lymphocytic leukemia patients between one and 30 years of age received either standard or high-risk initial chemotherapy regimens based on the National Cancer Institute's (NCI) definitions of these risks.
- Patients underwent standardized testing to detect cytogenetic abnormalities associated with favorable and unfavorable outcomes.
- Investigators classified 5,104 NCI standard risk (SR) and 2,791 NCI high risk (HR) patients into low, standard, high, or very high risk groups at the end of induction therapy based on the presence of favorable and unfavorable cytogenetic findings and early treatment response.
- The investigators determined that the five-year event-free survival varies according to genetic subset, ranging from 70 percent for those with unfavorable cytogenetics to 95 percent for those with favorable cytogenetic abnormalities.
- Notably, patients with either standard or high-risk disease and favorable cytogenetic findings, who accounted for almost half of all patients, had a 98 percent likelihood of being alive five-years following diagnosis.
- Results demonstrate that this real-time classification identified a previously unrecognized subset of high-risk patients with excellent chances for cure without further intensification of treatment.

Elizabeth Raetz, MD, Huntsman Cancer Institute and Primary Children's Hospital, University of Utah, Salt Lake City, will present this study during an oral presentation on Monday, December 7, at 5:00 p.m. in room W331, level 3 of the Orange County Convention Center.

Whole Exome Sequencing Finds Genes Associated With Autoimmune Platelet Disorder in Children

Genes Influencing the Development and Severity of Chronic ITP Identified through Whole Exome Sequencing [73]

- Chronic immune thrombocytopenia (ITP) is a complex autoimmune disease characterized by low platelet count; this prevents the blood from properly clotting and increases risk of bleeding. The risk of developing chronic ITP may be affected by genetic factors.
- This study sought to identify genetic variants associated with susceptibility to chronic ITP and severity of ITP clinical condition.
- Investigators obtained DNA samples through the North American Chronic ITP Registry and the Platelet Disorders Center at the Weill-Cornell Medical Center. The majority of patients were younger than 19 years old at the time of diagnosis.
- Whole exome sequencing (WES) was performed at the Human Genome Sequencing Center at Baylor College of Medicine as part of a study initiated by the ITP Consortium of North America. Investigators used sophisticated analysis tools to identify genetic variants linked with chronic ITP.
- Results demonstrate that variants in genes associated with immune cell signaling (including *IFNA17* and *DGCR141*) are significantly more common in children with chronic ITP than in the healthy population.
- Of 172 ITP patients, more than 45 percent had a coding variant in *IFNA17*, a gene associated with immune cell activity. In contrast, investigators found *IFNA17* variants in fewer than 1 percent of 5,664 individuals without ITP.
- This study is the first of its kind in chronic ITP, and these findings may facilitate improved understanding of the development of this disease. Additionally, improved understanding of affected patients' genetic changes could lead to more personalized approaches to treatment of this disorder.

Jenny M. Despotovic, DO, Texas Children's Cancer and Hematology Centers, Houston, will present this study on behalf of the ITP Consortium of North America (ICON) during an oral presentation on Saturday, December 5, at 12:00 noon in room W315, level 3 of the Orange County Convention Center.

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