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SCIENCE SPOTLIGHT

Pediatric AML Prognosis with High WT1 Expression Depends On SNP Presence

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Acute myeloid leukemia (AML) is a complex blood cancer that includes multiple genetic and epigenetic aberrations that contribute to disease biology. The molecular characterization of both adult and pediatric AML has found informative chromosomal rearrangements, DNA mutations, and gene expression changes that stratify patients into low, standard and high-risk prognostic categories. De-regulated gene expression and gene mutations are typically considered as two different categories of molecular alterations in leukemia. A recent study from the laboratory of Dr. Soheil Meschinchì (Clinical Research Division) "suggests that the interplay between gene over-expression and genotype may have biologic and prognostic importance," according to lead author Dr. Phoenix Ho. The researchers found that high expression of a mutated Wilms' tumor suppressor 1 (*WT1*) gene has different prognostic significance than high expression of *WT1* with a single nucleotide polymorphism (SNP) in pediatric AML patients.

Previous work by Dr. Ho and colleagues from the Children's Oncology Group determined that inactivating mutations of *WT1* occur in 8% of pediatric AML patients. These mutations are associated with significantly worse survival outcomes (Ho *et al.*, 2010). Similarly, *WT1* mutations occur in 10% of adult AML patients. These DNA mutations are predicted to disrupt *WT1* function as they occur in the zinc finger DNA binding regions of the *WT1* protein, which functions as a transcription factor with both oncogenic and tumor suppressive roles. More commonly, 85% of pediatric AML patient blast cells have elevated *WT1* expression, both wild type and mutated. However, it has been unclear whether *WT1* expression has independent prognostic significance.

A previous study by Dr. Ho and colleagues (Ho *et al.*, 2011) determined the presence of a synonymous SNP in the *WT1* gene. SNPs occur throughout the genome and contribute to phenotypic diversity. Half of the SNPs identified result in a synonymous change in the DNA sequence that does not result in an amino acid change in the translated protein. SNP rs16754 is in *WT1* exon 7, where most inactivating mutations occur, and results in an A to G substitution in the third position of codon 352. This SNP occurs in around 29% of pediatric AML patients, and is more common in Asian and Hispanic patients than in white patients ($P < 0.001$). *WT1* SNP rs16754 was associated with improved outcome in pediatric AML patients (hazard ratio 0.76; $P = 0.031$), as well as in adult AML patients. Notably, SNP rs16754 was associated with higher *WT1* mRNA expression.

Taken together, these results indicate that this SNP has phenotypic consequences without altering WT1 protein sequence.

The current study extends these findings with 225 patient diagnostic samples obtained from a contemporary Children's Oncology Group clinical trial with uniformly treated pediatric AML patients. Importantly, when both SNP-positive and SNP-negative samples were analyzed together, overall survival was similar for high and low *WT1* expression levels. *WT1* expression varied widely, but was divided into four quartiles of increasing expression. When only SNP-negative patients were analyzed, those with the highest *WT1* expression had the poorest overall survival by univariate analysis (51% quartile 4 vs. 72% for quartiles 1-3, $P = 0.006$, see figure). No differences were significant in the SNP-positive patients even with high *WT1* expression. When other risk factors were included as covariates, high *WT1* expression did not retain significance as an independent prognostic marker. Ho *et al.* conclude that while measuring *WT1* expression does not appear to have clinical utility for pediatric AML patients, assessing *WT1* mutations and SNPs aid in prognosis.

The Meshinchi laboratory is currently pursuing exactly how this synonymous SNP contributes to both higher *WT1* expression and favorable survival outcomes. Synonymous SNPs may affect microRNA binding, protein folding, mRNA stability, splicing or expression. "We're investigating whether this SNP is inherited as part of a haplotype including SNPs in the promoter region of *WT1* which may regulate the gene's expression," according to Dr. Ho. Furthermore, this SNP may represent a genetic marker for an uncharacterized molecular change that influences response to chemotherapy.

[Ho PA, Alonzo TA, Gerbing RB, Kuhn J, Pollard JA, Hirsch B, Raimondi SC, Gamis AS, Meshinchi S.](#) 2013. The prognostic effect of high diagnostic *WT1* gene expression in pediatric AML depends on *WT1* SNP rs16754 status: Report from the Children's Oncology Group. *Pediatric Blood & Cancer*. Epub ahead of print; doi: 10.1002/pbc.24700.

Also see: [Ho PA, Kuhn J, Gerbing RB, Pollard JA, Zeng R, Miller KL, Heerema NA, Raimondi SC, Hirsch BA, Franklin JL, Lange B, Gamis AS, Alonzo TA, Meshinchi S.](#) 2011. *WT1* synonymous single nucleotide polymorphism rs16754 correlates with higher mRNA expression and predicts significantly improved outcome in favorable-risk pediatric acute myeloid leukemia: a report from the children's oncology group. *Journal of Clinical Oncology* 29:704-11.

[Ho PA, Zeng R, Alonzo TA, Gerbing RB, Miller KL, Pollard JA, Stirewalt DL, Heerema NA, Raimondi SC, Hirsch B, Franklin JL, Lange B, Meshinchi S.](#) 2010. Prevalence and prognostic implications of *WT1* mutations in pediatric acute myeloid leukemia (AML): a report from the Children's Oncology Group. *Blood* 116:702-710.

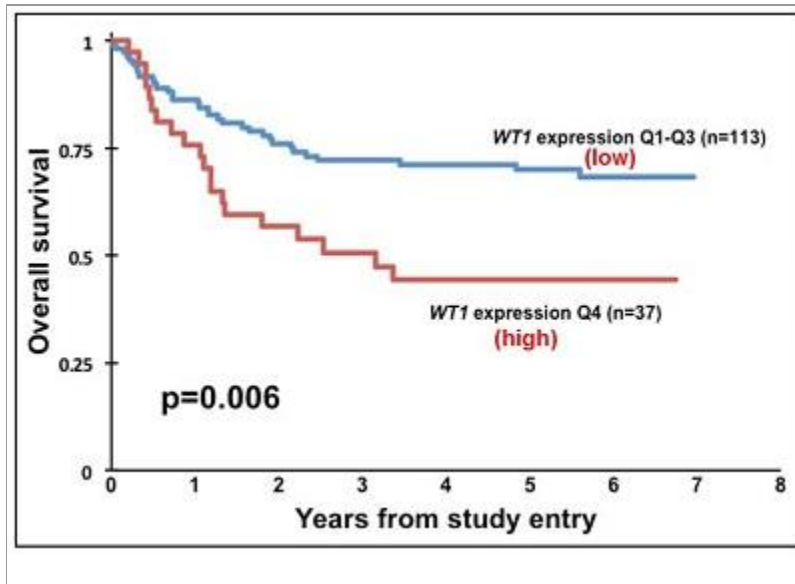


Image provided by Phoenix Ho

Survival outcomes for pediatric AML patients wild type for WT1 SNP rs16754, as estimated by the Kaplan-Meier method. SNP negative patients with diagnostic WT1 expression in the highest quartile had significantly decreased overall survival.