From Specific to General, and Back Again

March 16, 2015

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Understanding the underlying mechanisms behind specific cancer types and other hereditary diseases is valuable not only for preventing and treating particular syndromes of interest, but also for adding general knowledge about cancer-promoting mutations overall. Considerable effort has been spent on sequencing the human genome to study how the order of nucleotides (As, Cs, Gs, and Ts) in our DNA code influences the likelihood of developing such inherited syndromes, but even if seemingly important individual mutations can be identified it is not always clear what part they play. Thus, combining specific case studies with general sequencing approaches informs our understanding of mutations that drive the malignant transformation. This premise was confirmed through a joint research effort undertaken by Fred Hutch scientists and external collaborators, led by the Clinical Research Division's Dr. Akiko Shimamura. The team studied a new hereditary syndrome featuring low blood platelet counts (thrombocytopenia) and a predisposition for various hematologic malignancies in multiple individuals from three families, with the aim of identifying common mutations. First-authored by a graduate student in the MD PhD program, Michael Zhang from the Shimamura Lab, their enlightening results were recently published in *Nature Genetics*.

Through exome sequencing studies of a family of German and Native American ancestry with genetically undefined familial thrombocytopenia and cancer predisposition, the investigators identified a heterozygous hereditary variant in the *ETV6* gene. "Heterozygous" signifies that only one of the two gene copies, coming from either the mother or the father, in a particular individual is mutated, as opposed to homozygous mutations which affect both gene copies. Targeted sequencing of individuals displaying similar disease characteristics (thrombocytopenia and hematologic malignancies) identified two additional families with germline heterozygous *ETV6* mutations. These two families, of Scottish and African-American ancestry, respectively, each had a different hereditary *ETV6* variant.

These familial genetic studies suggest a vital role for the gene *ETV6* in the formation, development and differentiation of blood cells, as well as in the promotion of malignancy. *ETV6* encodes a protein that regulates expression of other genes, and the Shimamura lab demonstrated that this *ETV6* function is impaired by mutations. The pinpointed gene was not an unknown player; large-scale cancer genome sequencing efforts had previously demonstrated recurrent evidence for a

potential role of somatic *ETV6*mutations in cancer, but whether *ETV6* played an active role in malignant transformation had not previously been demonstrated.

Dr. Shimamura elegantly summed up the new findings in three succinct sentences: "Acquired mutations in *ETV6* were previously observed in cancers arising in the general population. Our study demonstrates that *ETV6* mutations function to initiate or drive cancer development. Thus, the study of rare cancer predisposition syndromes advances our understanding of molecular pathways promoting cancer development in the general population."

Besides increasing the fundamental understanding of driving forces behind cancer progression, identifying hereditary mutations improves diagnosis and medical care of individuals at risk. "The elucidation of genes driving malignancy is critical to our ongoing efforts to develop personalized approaches to the diagnosis and treatment of cancer in individual patients. Identification of genetic causes of cancer predisposition allows appropriate medical monitoring to initiate treatments early when therapies are most effective," said Dr. Shimamura, who also emphasized that genetic testing is helpful for making informed therapy choices and guiding donor selection for bone marrow transplants.

Thus, the circle is closed; from defining a rare familial syndrome to understanding disease progression in the general population, and then back to personalized treatments for affected individuals. It's all in the code.

Zhang MY, Churpek JE, Keel SB, Walsh T, Lee MK, Loeb KR, Gulsuner S, Pritchard CC, Sanchez-Bonilla M, Delrow JJ, Basom RS, Forouhar M, Gyurkocza B, Schwartz BS, Neistadt B, Marquez R, Mariani CJ, Coats SA, Hofmann I, Lindsley RC, Williams DA, Abkowitz JL, Horwitz MS, King M-C, Godley LA, Shimamura A. 2015. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet*. 47(2):180-5.

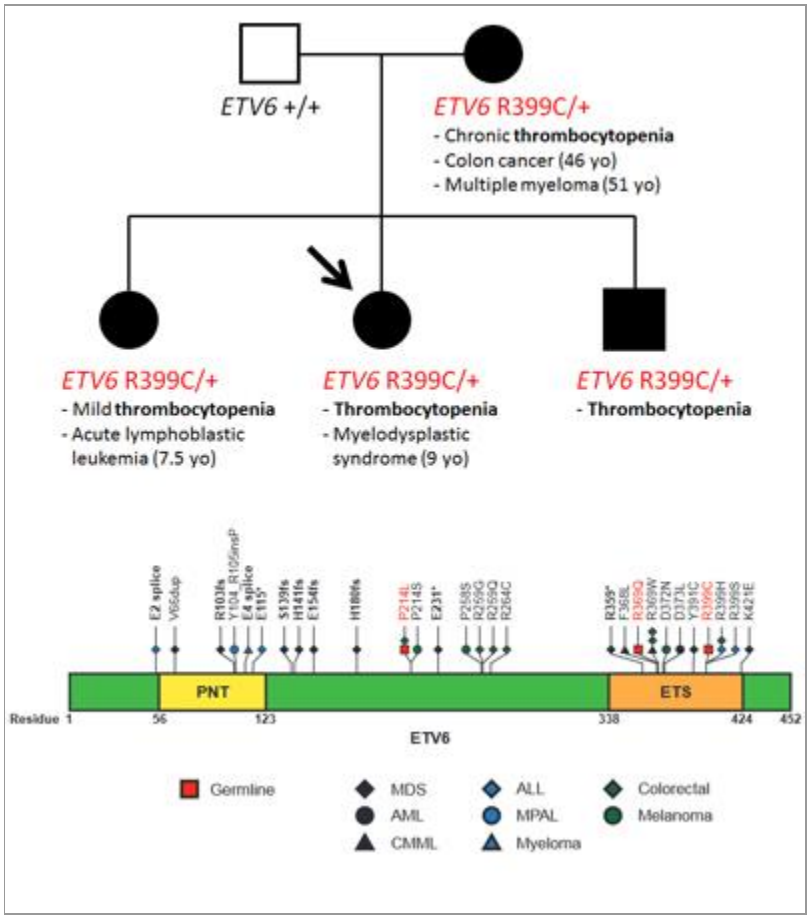

Image provided by Dr. Akiko Shimamura

Top: pedigree of a family with thrombocytopenia and cancer predisposition. Bottom: positions of germline and somatic mutations in ETV6, relative to the PNT oligomerization and ETS DNA-binding domains. Red highlights indicate germline alterations reported in this study. Somatic mutations described in the literature include alterations associated with a range of malignancies, as indicated.