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# New Gene Fusions and Mutations Linked to Gastrointestinal Stromal Tumors

## Findings could lead to additional targeted treatments for more patients

In recent years, researchers have identified specific gene mutations linked to gastrointestinal stromal tumors (GIST), which primarily occur in the stomach or small intestine, with 5,000 to 6,000 new cases per year in the United States.

But 10 to 15 percent of adult GIST cases and most pediatric cases lack the documented tell-tale mutations, making identification and treatment more difficult. In their paper published online Dec. 14 in the *Journal of Translational Medicine*, researchers at University of California San Diego School of Medicine and Moores Cancer Center have identified new gene fusions and mutations associated with this subset of GIST patients.

“We are continuing to slice the GIST pie into thinner pieces based upon identifying new driver genes,” said Jason Sicklick, MD, associate professor of surgery at UC San Diego School of Medicine and surgical oncologist at Moores Cancer Center at UC San Diego Health. “This will allow for a more personalized approach to treating GIST patients.”

Sicklick and colleagues are leading efforts to diagnose and treat GIST, which originates in special cells that signal muscles to contract, moving food and liquid through the digestive system. Many current therapies for GIST are ineffective in patients whose tumors lack mutations in the classic oncogenic drivers of GIST. Ultimately, more than 95 percent of patients eventually succumb to drug-resistant GIST, highlighting the necessity for alternative therapeutic targets.

Treatment with imatinib (marketed as Gleevec) has proven effective in many GIST cases associated with *KIT* oncogene mutations, the most common driver of the disease. Building upon that success and approach, Sicklick’s team, which included collaborators in Oregon, Texas, Massachusetts, Pennsylvania, Florida and South Korea, used broad genomic sequencing of GIST patients without *KIT* or other documented mutations to identify alterations in at least

two new genes: *FGFR1* and *NTRK3*. “Broad genomic sequencing was critical to expand our search beyond the *KIT* mutations streetlight,” said Olivier Harismendy, PhD, head of the oncogenomics laboratory at Moores Cancer Center, referring to observational bias of previous studies.

“These findings provide novel insights into the biology of the disease and new potential genetic drivers,” Sicklick said. “With further studies, we can build an even more complete genetic profile of GIST, which in turn can lead to new individualized treatments and better outcomes for more GIST patients. For example, one patient in this study had an *ETV6-NTRK3* mutant GIST and responded to a matched therapy with Loxo-101, a highly selective TRK inhibitor, after progressing on several earlier lines of FDA-approved therapies for GIST.”

Co-authors of the study include Eileen Shi, Chih-Min Tang, Katherine E. Fero, James D. Murphy, Paul T. Fanta, Martina De Siena, Adam M. Burgoyne, Lisa Madlensky, Gregory M. Heestand, and Razelle Kurzrock, UC San Diego Moores Cancer Center; Juliann Chmielecki, Kai Wang, Siraj M. Ali, Deborah Morosini, and Jeffrey S. Ross, Foundation Medicine Inc.; Michael C. Heinrich, Portland VA Health Care System; Guhyun Kang, and Christopher L. Corless, Oregon Health Sciences University; David Hong, University of Texas MD Anderson Cancer Center; Sujana Movva, Fox Chase Cancer Center; and Jonathan C. Trent, University of Miami Sylvester Cancer Center.

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