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## **Genetic Characterization of a Very Low-Risk Gastro-Intestinal Stromal Tumor (GIST)**

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Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract. Thus far, a number of somatic and germ line mutations have been identified as molecular diagnostic markers of GIST tumors. The majority of the GISTs harbor either KIT or PDGFRA tyrosine kinase mutations within their genomes that make them good candidates for the treatment by tyrosine kinase inhibitors. Although GISTs respond well to tyrosine kinase inhibitors therapy, however, most tumors develop primary or secondary resistance to the treatment. Moreover, it remains unclear why many of GISTs despite identical mutations demonstrate various clinical behaviors from small not clinically detectable micro GISTs to the aggressive metastatic tumors. Additional alterations may explain these differences. To determine the minimal set of genetic abnormalities required for the development of a clinically symptomatic GIST, we sequenced the genome of a very low-risk GIST using Illumina whole genome sequencing technology. Furthermore, we performed a comparative genomic hybridization array analysis as well as a DNA-methylation profiling of the same tumor sample. Besides the typical loss of chromosome 14 and a KIT mutation, we identified eight genes that were potentially mutated, including ZNF407, a Zinc finger protein probably involved in the negative control of transcription, and RNF146, an E3 ubiquitin-protein ligase, qualified as possibly important in the acquisition of the malignant phenotype. To estimate the frequency of mutated genes, direct conventional sequencing of candidate genes was performed on 52 fresh frozen GISTs. In total, 117 single nucleotide variations (SNVs) including 1 novel amino acid substitution in ZNF407 (n=52, 2%), and a novel frame

shift deletion of RNF146 (n=21, 4.7%), in addition to 2 single nucleotide polymorphisms (SNPs) in this gene, were identified. The epigenetic profile of the tumor demonstrated no significant difference between the methylation pattern of the examined GIST sample and non- neoplastic neuronal and gastric tissues. The results indicate that the identified mutations in three genes beside the loss of the long arm of chromosome 14 are the so far minimal set of genetic abnormalities sufficient for the development of a very low-risk gastric GIST. Two of the three missense mutations found within the Zinc finger domains were germ line mutations. One of the mutations was not found in the general population before. This suggests that these SNVs might be rare variants that are preferentially found in GISTs and hence may predispose individuals to developing clinically symptomatic tumors. Similar studies in some other solid tumors using whole genome sequencing have reported frequent mutations in ZNF407. This suggests that mutations in this gene might be important in a subset of very common tumors in addition to GISTs. Further functional studies are required to investigate their impact on cancer development.

**Keywords:** GIST, whole genome sequencing, ZNF407