

Novel Clinically Relevant Genes in GIST—Letter

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Schoppmann and colleagues (1) have recently investigated 174 gastrointestinal stromal tumor (GIST) by DNA array, FISH, exome sequencing, and immunohistochemistry (IHC) and found that the majority of recurrent chromosomal imbalances were located in 12 regions of interest and that the loss of 1p and immunohistochemical expression of RAD54L2, SYNE2, KIT, and DIAPH1 were associated with survival.

In our opinion, some key points should be discussed in more detail. First of all, globally the number of patients with known KIT and PDGFRA kinase genotype was 113 of 145 (77.9%), in particular 92 patients (63.4%) presented KIT mutations and 21 patients (14.5%) PDGFRA mutations. It would be interesting to know the percentage of KIT/PDGFRA wild-type (WT) GIST among the remaining 32 cases for whom the kinase genotype status is not evaluated or not reported. Because KIT and PDGFRA mutations are mutually exclusive and the authors state that globally 53 patients did not present KIT mutations and, supposable, 21 patients of them presented PDGFRA mutations, it is possible that the remaining 32 cases would be considered as WT. As is well known, KIT/PDGFRA WT GIST have a molecular background completely different from KIT/PDGFRA-mutant GIST in gene copy number, gene expression profiling, and protein expression. Patients with KIT/PDGFRA WT GIST display few or none of the classical genomic imbalances (14q or 1p or 22q deletions; ref. 2). They have different genome profiles especially for neural-commitment transcription markers and for insulin-like

growth factor-I receptor (IGF-IR) expression that is more similar to precursor murine interstitial cells of Cajal (ICC) than to mature ICCs, suggesting a cell derivation from ICCs in a different step of differentiation or from a different cell (3). Moreover, approximately 13% of KIT/PDGFRA WT GIST present activating mutations in BRAF and approximately 20% to 25% show loss-of-function mutations of the mitochondrial complex 2 (succinate dehydrogenase, SDH) with a prevalence for the subunit A (SDHA; ref. 4). Therefore, KIT/PDGFRA WT GIST are definitely a set of different diseases from KIT/PDGFRA-mutant GIST sustained by specific molecular alterations. However, the mutational status of patients evaluated in each test in this study is not reported. In fact, in the exome sequencing study, gene variations were identified in KIT receptor for 6 patients and in PDGFRA for 3 patients (total 9 of 13 cases analyzed), so there are 4 patients without KIT and PDGFRA gene variations identified and the other gene variations found in them may be discussed more.

Moreover, also in the survival analyses, the details of mutations would be interesting because some specific mutations are known to have a relevant significance as prognostic and predictive factors to treatments efficacy such as the PDGFRA exon 18 D842V or KIT exon 11 deletions (5).

In conclusion, mature molecular data have been accumulating on the role of the KIT and PDGFRA kinase genotype status in GIST and for considering KIT/PDGFRA-mutant GIST and KIT/PDGFRA WT GIST as two completely separate families of disease in molecular background, treatments response, clinical behavior, and outcome. Details on KIT and PDGFRA kinase genotype status must be always considered and always reported in molecular studies on GIST, especially in those with high-throughput sequencing analyses.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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