Multi-omic characterization of gastrointestinal stromal tumor (GIST) in a large real-world patient cohort

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Background

Molecular knowledge of GIST is limited due to its rarity, few genes have been identified as relevant determinants of outcomes, tumor evolution and therapeutic targets. Therefore, we aimed to dissect the GIST molecular landscape in the largest series of real-world patients reported to date.

Methods

491 GIST patient samples

Next-gen sequencing

- DNA (whole genome, N = 492; whole exome, N = 448)
- RNA (whole transcriptome, N = 592)

Gene expression signatures

- Prognostic (Christe et al., 2021)
- Cell cycle activation (DEGFC, Chilton, 2010)
- Inflammation (1-cell inflamed, Ayers, 2017)

Tumor microenvironment

- Cell population abundance was estimated using MCP-counter (Becht, 2016)
- Statistical significance tested by \( \chi^2 \)• Fisher’s exact, or Mann-Whitney U as appropriate.

Results

GIST molecular landscape

- Study cohort was comprised of 8% (N = 392)KITmut, 5% (N = 80)PDGFRAmut, and 10% (N = 48)KIT/PDGFRA wild-type (wt), with 14.6% (N = 140) samples harboring a secondary KIT variant suggestive of TKI resistance.
- KIT-primary mutation in exon 9 (11), 11 (14), or 13 (46/25)
- KIT secondary mutation in exon 13 (631-655), 14, 17, or 18
- PDGFRAmut primary mutation in exon 12, 14, or 18
- Overall median TMB was 2 mutations/MB (range 0-13)
- Variants were identified with mutations in KIT (33.5%), DNA repair genes (15.7%), PDGFRA (5.2%), BAP1 (6.8%), and PTEN (1.9%), along with NFIK2 (3.1%), JMD/KIT/PDGFRAfusions (0.8%), JMD/KIT/PDGFRAfusions (0.8%), KIT/PDGFRAfusions (0.8%), and ARK1, or CNV/SI co-mutations (1.5% each)
- Overall population (all cases)

Cohort demographics

<table>
<thead>
<tr>
<th>Sample type</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>491</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>64 (11-90)</td>
</tr>
<tr>
<td>Male</td>
<td>488 (99.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Race</td>
<td>White (83.3%), Black (53.9%), Hispanic (33.9%), Other (33.9%), Asian (0.0%), Unknown (0.0%)</td>
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</tbody>
</table>

GIST tumor microenvironment

- Compared to KITmut and KIT/PDGFRAfus had increased abundance of several immune cell populations (range 1.2-3.7-fold, p < 0.05), along with enhanced inflammation signatures (1.1- and 1.2-folds, p < 0.05)

Conclusions

- This series provides unprecedented resolution of KIT/PDGFRAfus GIST with features of clinical aggressiveness associated with KIT exon 11 indels and resistance mutations, illustrating a specific cytogenetic genotype with more aggressive growth and malignant behavior.
- Identification of less common molecular alterations that drive kinase activation and impaired DNA damage repair warrant further investigation.

References


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