NGS Testing Practices and Molecular Profile Landscape of the KIT Gene in Systemic Mastocytosis: Real-world Insights From Selected European Countries

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INTRODUCTION

• Globally, up to 95% of adult systemic mastocytosis (SM) cases are associated with somatic gain-of-function point mutations in the KIT gene, mainly KIT D816V mutations.
• Little is known about the molecular profile characterization of the KIT gene in Europe and whether clinicians are accurately diagnosing SM.
• Little is also known about the co-occurrence of somatic variants in other genes such as SRSF2, ASXL1, TET2, and RUNX1.
• Accurate diagnosis and understanding of co-mutations in SM can impact prognosis and treatment strategy.

AIMS

• We explored the landscape of next-generation sequencing (NGS) testing practices for KIT mutations in clinical practice in France, Italy, Germany, and Spain, to determine the potential number of individuals that could be impacted by KIT-targeted treatments for SM.
• To determine the molecular epidemiology of KIT point mutations such as D816V, D816Y, D816E, D816I, and D816L, as well as co-mutations of KIT with other genes such as TET2, SRSF2, ASXL1, and RUNX1 to investigate the molecular profiles of potential SM cases.

RESULTS

KIT testing landscape

• 32,052 individuals were tested with somatic HemOnc panels capable of detecting KIT alterations.
• For 76% of individuals, DNA/RNA was extracted from peripheral blood samples, and for 23% of individuals from formalin-fixed paraflin-embedded (FFPE) samples.
• The HemOnc somatic KIT testing footprint increased over time (Figure 1).
• Most cancer institutes used custom panels, while general hospitals (the majority of institutions) used more commercially available panels.

KIT D816 mutation disease associations

• KIT D816 mutations were associated with a myeloid/myeloproliferative malignancy in 85% of cases with a disease tag.
• Mastocytosis was the disease tag in 2% of individuals with a KIT D816 mutation detected by a HemOnc panel (Figure 2).
• It is important to note that the most common form of advanced SM is SM with associated hematologic neoplasm (SM-AHN), which could have been mistakenly classified under other tags such as myeloid neoplasm or leukemia.

KIT variant breakdown

• A total of 33,289 KIT gene variants were identified amongst 12,840 KIT mutation-positive individuals.
• KIT D816 variants represented 1.6-3.3% of all KIT mutations (Figure 3).
• KIT D816V represented 91% of detected KIT D816 variants.
• Seven KIT D816V mutation-positive cases showed intratumoral heterogeneity for KIT D816 mutations, which could reflect a subclonal architecture of tumors.

Oncogenic alterations co-occurring with KIT D816V

• The analysis of KIT drivers within KIT or other genes found that 48.8% of KIT mutation-positive cases had at least one co-occurring oncogenic alteration in KIT, SRSF2, ASXL1, TET2, or RUNX1.
• Co-occurring oncogenic alterations were most frequent in ASXL1 (Figure 4).

CONCLUSIONS

• The comprehensive characterization of the molecular epidemiology of KIT variants and co-mutations is crucial to better define SM prognosis and treatment strategies.
• This study provides new insights into the occurrence of KIT alterations and the concurrent presence of oncogenic co-mutations in potential SM cases, and how specific somatic NGS applications, namely HemOnc panels, are used across France, Italy, Germany, and Spain.
• Indeed, the reported frequency for KIT and co-occurring alterations is likely underestimated here, due to the availability of alternative genetic testing techniques and platforms (e.g. ddPCR, which can have a higher sensitivity than NGS).
• The low percentage of SM disease tags associated with KIT D816 cases highlights the difficulty in detecting and diagnosing individuals with SM and the potential number of individuals that could benefit from KIT-targeted treatment strategies.

REFERENCES


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