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[1-3]
- 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[4,5]

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, D816F, D816H and D816I, as well as **co-mutation** 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 paraffin-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

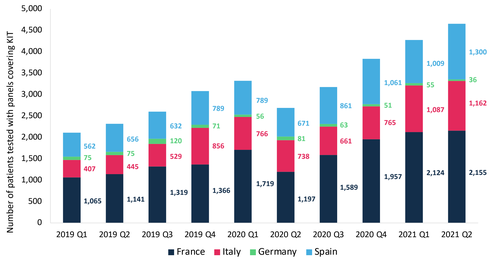

***Figure 1**. Number of individuals profiled with HemOnc panels covering KIT mutations, by country and quarter year*[1]

[1] Results are extracted from SOPHiA's community and thus data should be interpreted with caution as they might reflect only part of the general trend in those countries

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

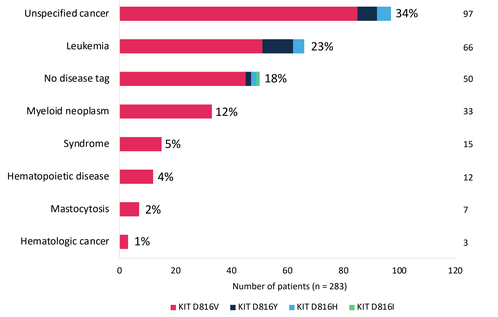

***Figure 2**. Disease tag associated with KIT D186 mutation-positive individuals, separated according to specific KIT variant (n = 283).*

KIT variant breakdown

- A total of **33,289 *KIT* gene variants** were identified amongst **12,840 *KIT* mutation-positive individuals**

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- ***KIT* D816 variants** represented **1.6-3.3%** of all *KIT* mutations (**Figure 3**)

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- ***KIT* D816V** represented **91%** of detected *KIT* D816 variants
- **Seven** *KIT* D816V mutation-positive cases **showed intratumoral heterogeneity for *KIT* D816 variants**, which could reflect a subclonal architecture of tumors

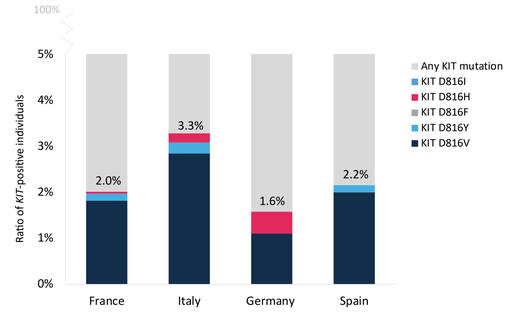


***Figure 3**. Frequency of specific KIT D816 mutations detected by HemOnc panels as a percentage of individuals positive for any KIT mutation, by country (normalized per number of KIT mutation-positive individuals per country) (total n = 12,840, n = 283 with KIT D816 variant).*

Oncogenic alterations co-occurring with *KIT* D816V

- The analysis of *KIT* drivers within *KIT* or other genes found that **48.8%** of *KIT* D816V 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***)

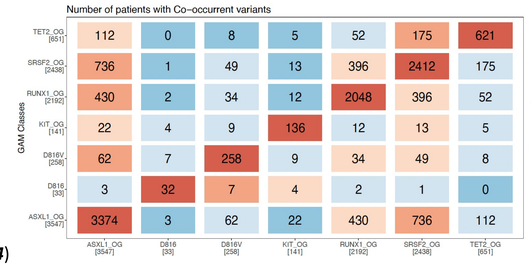
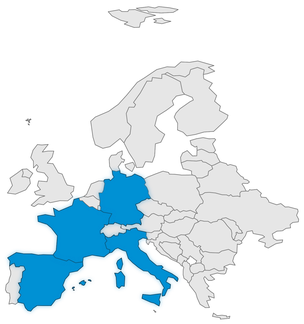


***Figure 4**. Number of cases with oncogenic variants co-occurring with KIT D816V.*

METHODS

- The **SOPHiA DDM™ Platform** (SOPHiA GENETICS SA, Switzerland) **proprietary algorithms** were used to analyze pseudo-anonymized real-world genomic profiles (Q1 2019 - Q2 2021) across 59 Institutions
- Data were obtained from testing with 34 SOPHiA GENETICS somatic onco-hematological (HemOnc) NGS panels capable of detecting *KIT* alterations from RNA or DNA



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 under-estimated 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

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