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The number and type of mutations in cancer-linked genes is associated with outcome of systemic mastocytosis

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Background: The *KIT* D816V somatic mutation is present in nearly all adult systemic mastocytosis (SM) patients at similar frequencies in indolent and advanced cases. Thus, while this *KIT* mutation might represent the genetic driver of SM, on its own, it cannot explain malignant transformation of the disease.

Objective: To identify common genetic variants, other than *KIT* D816V mutation, in cancer-linked genes of patients with advanced forms of SM and their potential impact on disease outcome.

Methods: Here we investigated the presence and frequency of genetic variants in 410 cancer-linked genes in purified bone marrow (BM) cells from 20 SM patients -12 mild and 8 advanced SM- with multilineal *KIT* D816V mutation, followed by whole-genome-sequencing in 4 cases.

Results: Targeted next-generation-sequencing identified 52 non-synonymous genetic variants involving 39 different genes, of which 10 were mutated in ?2 patients. Twenty-six genetic variants (50%) were somatic (mostly multilineage) mutations, while the other half were germline variants. Despite no common mutation was identified in patients undergoing malignant transformation, presence of ?1 multilineage somatic mutation involving genes other than *KIT* D816V, ?2 germline variants or ?1 mutation in the *SRSF2*, *ASXL1*, *RUNX1* and/or *EZH2* genes, were associated with a poorer patient outcome.

Conclusion: These findings suggest that despite multilineage *KIT* mutation is the only genetic alteration associated with the onset of SM, it also seems to be a trigger for advanced disease under a multi-mutated genetic background and/or in combination with other (frequently preexisting) somatic mutations that usually involve multiple hematopoietic BM cell lineages.