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509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Maladaptive Somatic Rescue in FLT3 Mutations of Suspected Germline Nature

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Somatic genetic rescue (SGR) is a very rare process in which the occurrence of a somatic genetic event offsets the consequences of a germline (GL) mutation resulting in genetic mosaicism and, in some cases, in a milder disease phenotype [1]. Acquired somatic mutations may be adaptive by countering the negative effects of the primary mutation (*e.g.*, improving hematopoiesis) or maladaptive by overcorrecting the initial impairment causing a different, possibly opposite, disease phenotype (*e.g.*, leading to the development of a myeloid malignancy) [2]. Exemplary cases of the latter scenario are mainly represented by severe congenital neutropenia (SCN) cases developing AML as consequence of somatic *CSF3R* mutations [3] and, sporadically, by adaptive SGR in the context of germline *GATA2* and secondary acquisition of somatic *GATA2* mutation, counterbalancing the germline effect [4]. Although SGR has been functionally demonstrated in these two above mentioned cases, given the molecular heterogeneity of myeloid neoplasia (MN) and the rarity of such genetic events, one can suspect that, in various clinical contexts, any mutation in any gene could be the SG rescuer.

During our clinical experience, we encountered a case of a 57yo. woman with newly diagnosed aplastic anemia (AA) who was found to harbor a rare germline *FLT3* ^{R311W} mutation (VAF 50%; predicted to be a loss-of-function/hypomorphic alteration; Fig1) who subsequently evolved to MDS with monosomy 7. Coexisting somatic hits included non RUNT-homology domain, *RUNX1* ^{P398L} mutation (VAF 19%). Ultimately, the patient progressed to AML with emergence of a *FLT3* ^{D825V} (VAF 14%) and a *NRAS* ^{G13D} (24%) lesions. In this case carrying GL *FLT3* variant, biallelic somatic *FLT3* mutation may represent maladaptive SGR. Therefore, we reviewed NGS sequencing results of 5,308 patients with MN and found three other suspected cases harboring GL variants in *FLT3* gene, which inspired further investigations.

In total we identified 3 additional cases (total of 4/5308 screened patients and among 248 somatic *FLT3* mutations. Interestingly, the other case GL *FLT3* ^{A680T} occurred in a patient with AA (35yo.) who subsequently progressed to MDS and AML and acquired somatic *NPM1* ^{L258fs}, *PTPN*11 ^{A72V}, *WT*1 ^{A365fs} and most importantly, a somatic *CSF3R* ^{L619S} . The latter may represent an illustrative case of SGR, in analogy to AML developing in the context of SCN. In addition, 2 other cases with MDS or MDS/MPN were identified both presenting with cytopenia. A 53yo. woman diagnosed with MDS/MPN and GL *FLT3* ^{L262F} (gnomAD: 0.00000399) with a compound heterozygous somatic *JAK2* ^{V617F} mutation, again possibly serving as maladaptive clonal SGR event. Finally, we have identified a GL *FLT3*A291P mutation (VAF 60%, gnomAD frequency: 1.59×10-5) in a 58yo. man who eventually developed AML.

In sum, similar to other phosphotyrosine receptor kinases (PTRKs) such as *CSF3R*, somatic *FLT3* mutations may in rare biallelic cases correspond to SGR events of hypomorphic GL mutation or alternatively but not exclusively somatic mutations in other PTRK could evolve to reveal the GL *FLT3* deficiency. Indeed, in another abstract by our group (Abstract#187151) we show that somatic *FLT3* mutations can accompany GL variants in *CSF3R*, *CSF2RB*, and *CSF1R*.

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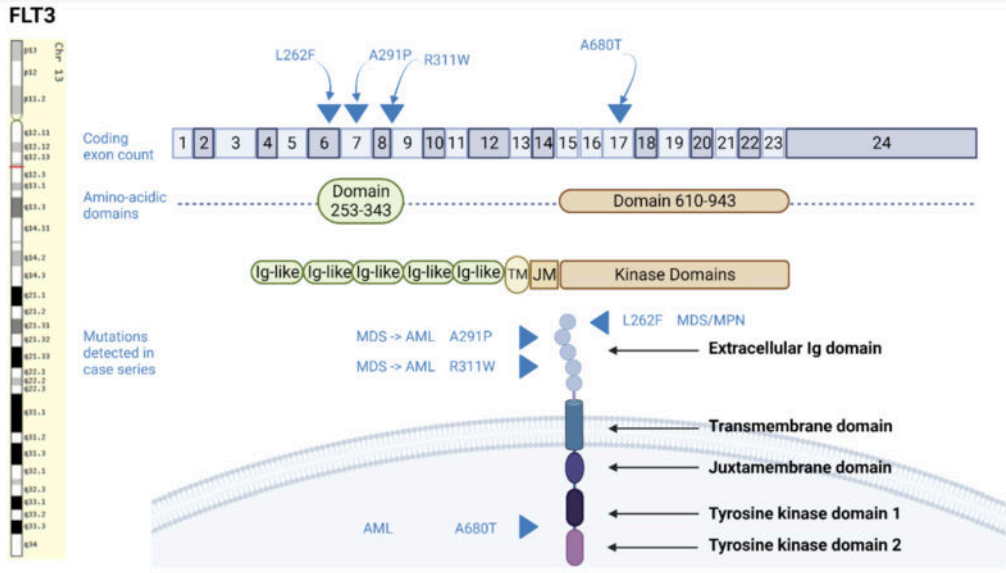

Figure 1. Localization of detected mutations in *FLT3* gene and protein. Chromosome structure was adapted from genecards.org (https://www.genecards.org/cgi-bin/carddisp.pl?gene+FLT3), while gene domains were designed according to uniprot.org (P36888). Part of the figure was created using BioRender.com

Figure 1

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