GATA2 deficiency syndrome: A decade of discovery

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February 28, 2021

Abstract

GATA2 deficiency syndrome (G2DS) is a rare autosomal dominant genetic disease predisposing to a range of symptoms of which myeloid malignancy and immunodeficiency including recurrent infections are most common. In the last decade since it was first reported, there have been over 465 individuals identified carrying a pathogenic or likely pathogenic germline GATA2 variant with symptoms of G2DS, with 231 of these confirmed to be familial and 22 de novo. For those that develop myeloid malignancy (75% of all carriers with G2DS disease symptoms), the median age of onset is 17 years (range 0-78 years) and myelodysplastic syndrome (MDS) is the first diagnosis in 75% of these cases with acute myeloid leukemia (AML) in a further 9%. All variant types appear to predispose to myeloid malignancy and immunodeficiency. Apart from lymphedema in which haploinsufficiency seems necessary, the mutational requirements of the other less common G2DS phenotypes is still unclear. These predominantly loss-of-function variants impact GATA2 expression and function in numerous ways including perturbations to DNA binding, protein structure, protein:protein interactions, and gene transcription, splicing and expression. In this review, we provide the first expert curated ACMG/AMP classification with codes of published variants compatible for use in clinical or diagnostic settings.

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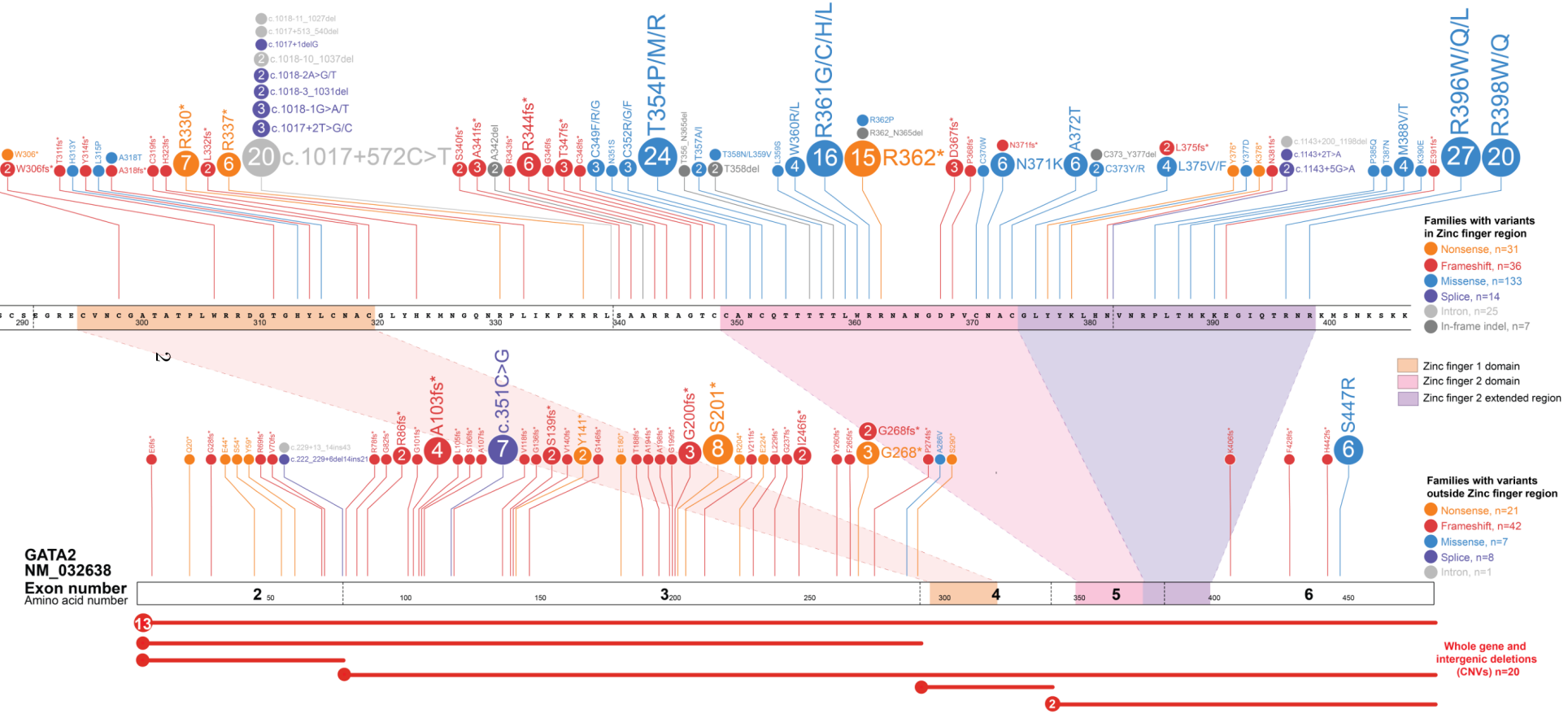

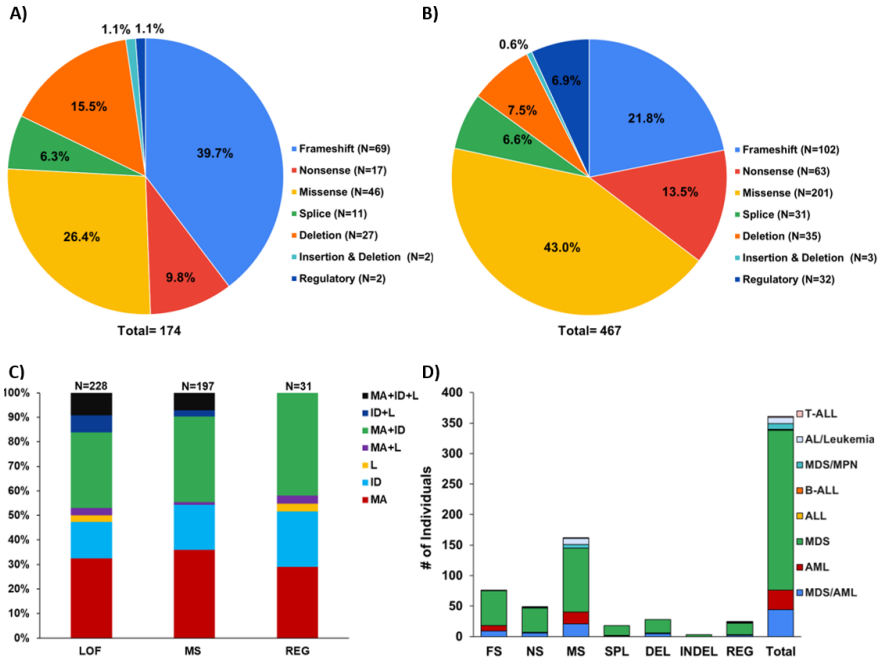

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