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GATA2 coming of age: 15 years from discovery to symptoms

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MAIN TEXT

At 14 (actually, 15) years of age, GATA2 deficiency is definitely into its adolescence: stubborn, unpredictable and resistant to rules. Much like a teenager testing the limits of a curfew, it presents a constant challenge to clinical predictions. While one GATA2 carrier remains perfectly healthy well into their 50s, another with a similar variant must face life-threatening immunodeficiency or myelodysplastic syndrome (MDS). The latest longitudinal study by Hsu et al., analyzing a comprehensively characterized cohort of 232 GATA2-deficient individuals across 122 pedigrees, provides the next puzzle piece to these “rebellious” patterns.[1] Yet it also confirms that GATA2 deficiency still has plenty of surprises for us.

The earliest clinical description of what is now recognized as GATA2 deficiency dates back to 1972, when Kaur et al. reported familial AML, warts and group C aneuploidy in an Icelandic family.[2] However, the true journey of discovery began in 2010, when it was described as a constellation of infections, cytopenia, and pulmonary issues.[3] In the next year, 5 independent groups named germline variants in the master hematopoietic regulator GATA2 as the culprit, and extended the GATA2 phenotype to immunodeficiency (loss of B-/NK- and dendritic cells, monocytopenia, mycobacterial infections), familial MDS, and lymphedema.[4-8] Additional phenotypic constellations, including pediatric MDS,[9] chronic neutropenia,[10] and G2BMID (GATA2 deficiency related bone marrow and immunodeficiency disorder)[11], emerged to define GATA2 deficiency as a multisystem transcriptopathy. Along the way, the NIH group has charted several key milestones from the identification of GATA2 in human disease[4] to comprehensive phenotypic[4,12] and somatic characterization.[13]

How do these phenotype sequelae link to specific GATA2 genotypes? A comprehensive review of all published cases in 2021 concluded that no conclusive genotype-phenotype correlations could be established across variant types.[14] Smaller cohort studies have, however, linked truncating/null variants to lymphedema and earlier onset of myeloid neoplasms.[10] Nonetheless, the most common variants, including substitutions in the zinc finger 2 (ZF2) domain, continue to defy clear genotype-phenotype correlations. The work of Hsu et al. brings some much-needed clarity and confirms that truncating and null variants, along with ZF2 variants, are associated with earlier onset and increased hazard risk when compared to intron 4 enhancer variants. When further stratifying recurrent ZF2 variants, they also found that substitutions at R396 and T354 residues, but not R398, present with onset and hazard risk comparable to truncating and null variants.

Despite all we have learned over the past 15 years, predicting which carriers will go on to develop symptoms is still challenging. GATA2 deficiency, just like many other early-onset diseases, exhibits near-complete penetrance at the population level (based on the virtual absence of pathogenic/likely pathogenic variants in gnomAD population database). However, this is neither accurate nor helpful for individual families, where some carrier members may remain seemingly healthy while others with the same variant develop severe disease. The Hsu study proposes to navigate this challenge by sorting GATA2 variants into ‘early’ (truncating, null, R396, T354) and ‘late’ (other ZF2, C-terminal, enhancer) onset groups. Although arbitrary, this classification reveals a difference in penetrance. Early variants are associated with a 95.5-100% penetrance, usually presenting in late teens. On the other hand, late variants act more like “late

bloomers": their onset is delayed until early to late adulthood and they have incomplete penetrance ranging from 54-81.7%. This is the first time we see such strong correlation between onset and penetrance across all variant groups: the earlier the disease presents, the more certain it is to eventually show up in every carrier.

Timing is not the only thing that separates the early and late onset groups. Through a systematic analysis of clinical data generated during years of specialized care at the NIH, Hsu et al. reports an increased prevalence of cytopenia, infections, thromboembolism and hearing loss in patients with early onset variants. Against this background, it comes as a surprise to see no difference in rates of malignancies between the groups, suggesting that tumor development is a genotype-independent, universal feature of GATA2 deficiency. In fact, when compared to NCI's SEER database, the incidence of both leukemia and non-hematological malignancies among GATA2 patients was at least 100-fold higher than in the general population. Showing this increase is particularly meaningful for HPV-driven neoplasms and breast cancer: for the first time, we have population-wide data confirming the long-held suspicion that GATA2 deficiency carries a substantially increased risk for these tumors.

Alongside these much-anticipated results that bring statistical power to anecdotal observations, a new player enters the scene: biological sex. GATA2 deficiency has a fairly balanced M:F ratio of 1:1.09 across all published cases in the St. Jude GATA2 database (https://www.stjude.org/gata2) and sex bias in clinical presentations has not been reported to date. However, Hsu et al. identified male sex to be associated with some infectious presentations and cytogenetics. Based on their data, men were 3-fold more likely to present with nontuberculous mycobacterial (NTM) infections and had a preference for monosomy 7. On the other hand, women were more likely to present with HPV and had more trisomy 8. While male sex is a known risk factor for chromosome 7 loss in childhood MDS independent of underlying GATA2, the association with NTM as initial presentation is somewhat enigmatic. It is plausible that biological sex plays a role in NTM-directed immune responses in GATA2 patients. However, given that the overall frequency of NTM was similar between sexes with no differences in immune cell subsets, and that girls reportedly underwent closer HPV surveillance, this association may actually reflect different diagnostic pathways in this cohort rather than inherent susceptibility.

Whether we should consider biological sex in clinical predictions remains to be seen, but taken together, Hsu et al. offers an important update to the roadmap to risk assessment and patient management in GATA2 deficiency. By synthetizing and completing genotype-phenotype patterns, this study moves us closer to understanding symptom development. It seems like at 15 years old, GATA2 deficiency is still just a teenager – but at least we are beginning to speak its language.

These findings carry direct clinical implications. For example, clinicians should maintain a heightened index of suspicion for GATA2 deficiency in patients presenting with MDS/AML with monosomy 7 or patients presenting with typical immunological/infectious phenotypes. Recognizing the underlying germline diagnosis in this context is urgent: these patients require prompt referral for hematopoietic stem cell transplantation, and any delay substantially increases the risk of infectious mortality. Favorable transplant outcomes are achievable with

timely diagnosis and expert multidisciplinary care. The NIH team's experience speaks for itself, and so does the story of one of their patients, who documented their journey in the personal blog "A Mutant Among Us" (https://amutantamongus.wordpress.com). This also serves as a powerful reminder of why getting transplant early saves lives.

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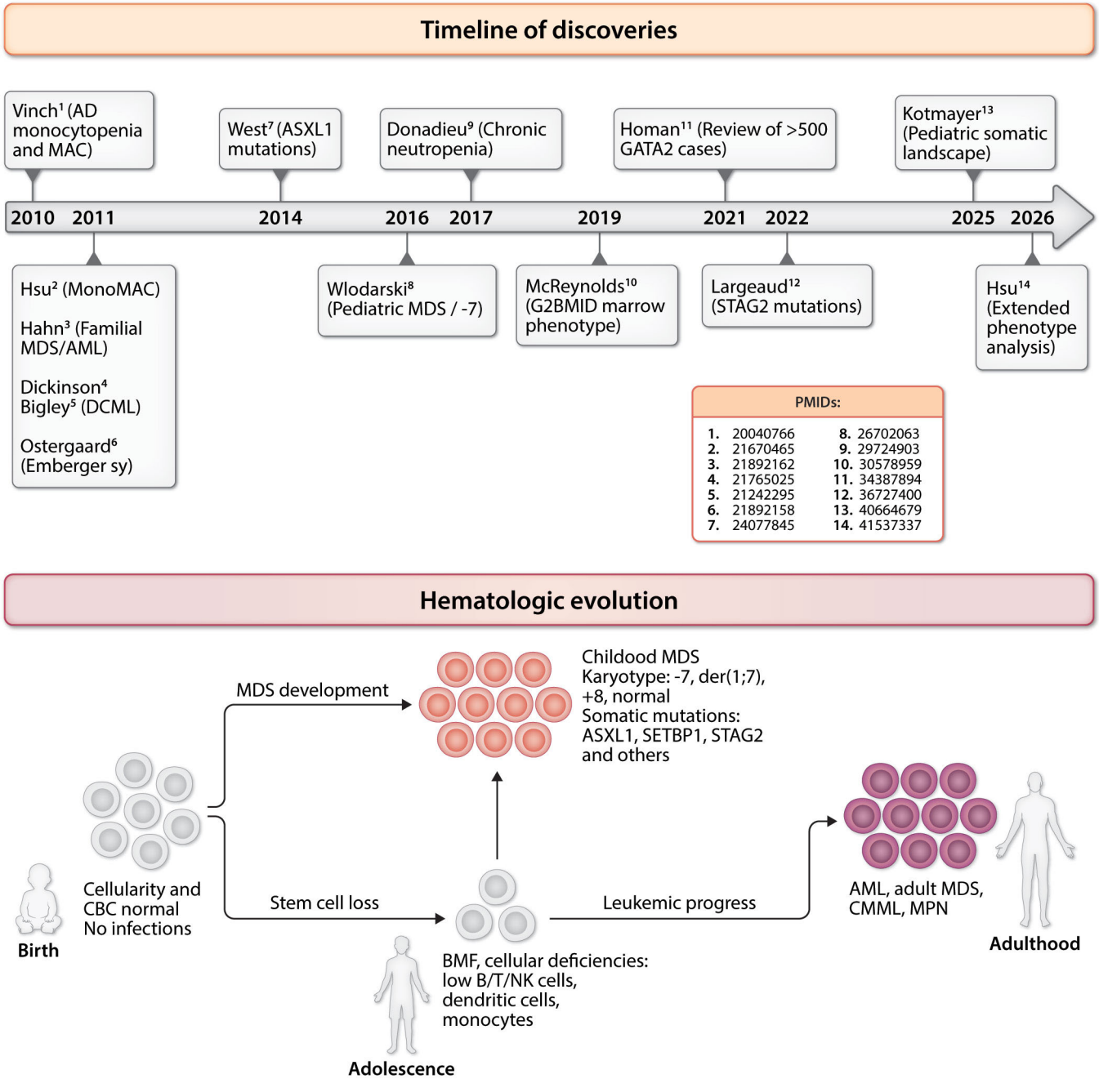
Figure 1. Timeline of key discoveries and hematologic evolution in GATA2 deficiency. (Top) Timeline of landmark publications (2010–2026) that shaped the understanding of GATA2 deficiency, with corresponding PubMed identifiers (PMIDs). (Bottom) Natural evolution from birth to adulthood, illustrating progressive stem cell loss leading to bone marrow failure and/or childhood MDS, with potential leukemic progression to AML, adult MDS, CMML, or MPN later in life. Abbreviations: +8: trisomy 8; −7: monosomy 7; AD: autosomal dominant; AML: acute myeloid leukemia; BMF: bone marrow failure; CBC: complete blood count; CMML: chronic myelomonocytic leukemia; DCML: dendritic cell, monocyte, B cell, and natural killer cell deficiency; G2BMID: GATA2 deficiency–related bone marrow and immunodeficiency disorder; MAC: Mycobacterium avium complex infection; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm.


Timeline of discoveries
Vinch[1] (AD monocytopenia and MAC)
West[7] (ASXL1 mutations)
Donadieu[9] (Chronic neutropenia)
Homan[11] (Review of >500 GATA2 cases)
Kotmayer[13] (Pediatric somatic landscape)
2010
2011
2014
2016
2017
2019
2021
2022
2025
2026
Hsu[2] (MonoMAC)
Hahn[3] (Familial MDS/AML)
Dickinson[4]
Bigley[5] (DCML)
Ostergaard[6] (Emberger sy)
Wlodarski[8] (Pediatric MDS / -7)
McReynolds[10] (G2BMID marrow phenotype)
Largeaud[12] (STAG2 mutations)
Hsu[14] (Extended phenotype analysis)
PMIDs:
1. 20040766
2. 21670465
3. 21892162
4. 21765025
5. 21242295
6. 21892158
7. 24077845
8. 26702063
9. 29724903
10. 30578959
11. 34387894
12. 36727400
13. 40664679
14. 41537337
Hematologic evolution
MDS development
Childood MDS
Karyotype: -7, der(1;7), +8, normal
Somatic mutations: ASXL1, SETBP1, STAG2 and others
Cellularity and CBC normal
No infections
Birth
Stem cell loss
BMF, cellular deficiencies: low B/T/NK cells, dendritic cells, monocytes
Adolescence
Leukemic progress
AML, adult MDS, CMML, MPN
Adulthood