blood advances

TO THE EDITOR:

Clonal hematopoiesis in autoimmune hemolytic anemia

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Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disorder characterized by the immune-mediated destruction of red blood cells.[1] AIHA incidence tends to increase with age.[2] The underlying mechanisms leading to AIHA remain only partially understood[3]; it can develop secondary to hematologic malignancies or systemic lupus erythematosus (SLE) or, more rarely, occur because of inherited errors of immunity. However, when no underlying cause is identified, as is the case in most patients, a diagnosis of primary AIHA is considered. Recently, clonal hematopoiesis (CH) has been identified as an increasing risk factor for immune thrombocytopenia (ITP),[4] a type of immune cytopenia. CH is the age-related expansion of a somatic variant, conferring a selective advantage to the hematopoietic stem or progenitor cell in which it occurs.[5] The role of CH as a potential risk factor in AIHA and whether the characteristics of CH are similar to those occurring in ITP have not yet been studied. The existence of CH as a risk factor for AIHA and its magnitude cannot be extrapolated from ITP data for several reasons: (1) ITP has a higher incidence compared to AIHA.[1,6] (2) AIHA and ITP have distinct pathophysiologies.[1,6,7] (3) The increased risk conferred by a disease can differ between AIHA and ITP (eg, several inherited errors of immunity have been reported to only be associated with AIHA or with ITP).[8]

Here, we leveraged the large UK Biobank cohort to assess the effect of CH on the incidence of AIHA. We used the published pipeline and results of CH curation available in the UK Biobank.[9] This data set includes high-confidence CH identification originating from the whole-exome sequencing performed on the DNA obtained at inclusion for 450 679 individuals, allowing the identification of 15 613 patients with CH (3.2%).

From the 251 patients with AIHA, we first analyzed only those with a newly diagnosed primary AIHA and excluded those with an AIHA diagnosis made before inclusion because we could not assess whether CH was present before AIHA occurrence. We also excluded patients with both AIHA and ITP (ie, Evans syndrome), and those with hematologic malignancy or SLE diagnosed before AIHA to avoid confounding factors in CH occurence because of underlying causes or treatment. Of the 132 patients with incident primary AIHA, we identified 15 CH clones in 12 patients (9.1%). The CH-carrying genes were *DNMT3A* (n = 7), *TET2* (n = 3), *SRFS2* (n = 2), *ASXL1* (n = 1), *IDH2* (n = 1), and *PPM1D* (n = 1; Figure 1A-B). A CH clone was identified in 9 of the 69 (13.0%) patients with an AIHA diagnosed at age $\geq$70 years and in 3 of the 67 (4.5%) patients with an AIHA diagnosed at age <70 years. The mean (± standard deviation) age at AIHA diagnosis appeared higher in patients with CH than in those without, but this finding was not statistically significant (72.5 ± 6.3 vs 69.0 ± 7.2 years; $P = .09$; Figure 1C).

To analyze the association between CH and the risk of developing AIHA, we fitted a multivariable Cox regression model to analyze the cumulative incidence of AIHA. We adjusted for age, sex, and the first 10 principal components to mitigate bias related to genetic ancestry-based population stratification. We identified that CH was associated with a higher risk of AIHA (adjusted hazard ratio [aHR], 2.39; 95% confidence interval [CI], 1.31-4.35; $P = .004$; Figure 2A).

We then sought to investigate whether the magnitude of risk between AIHA and CH compared to that of ITP and CH was similar. We investigated the 568 patients with incident primary ITP using the same

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The UK Biobank data can be accessed upon application at https://www.ukbiobank.ac.uk/.

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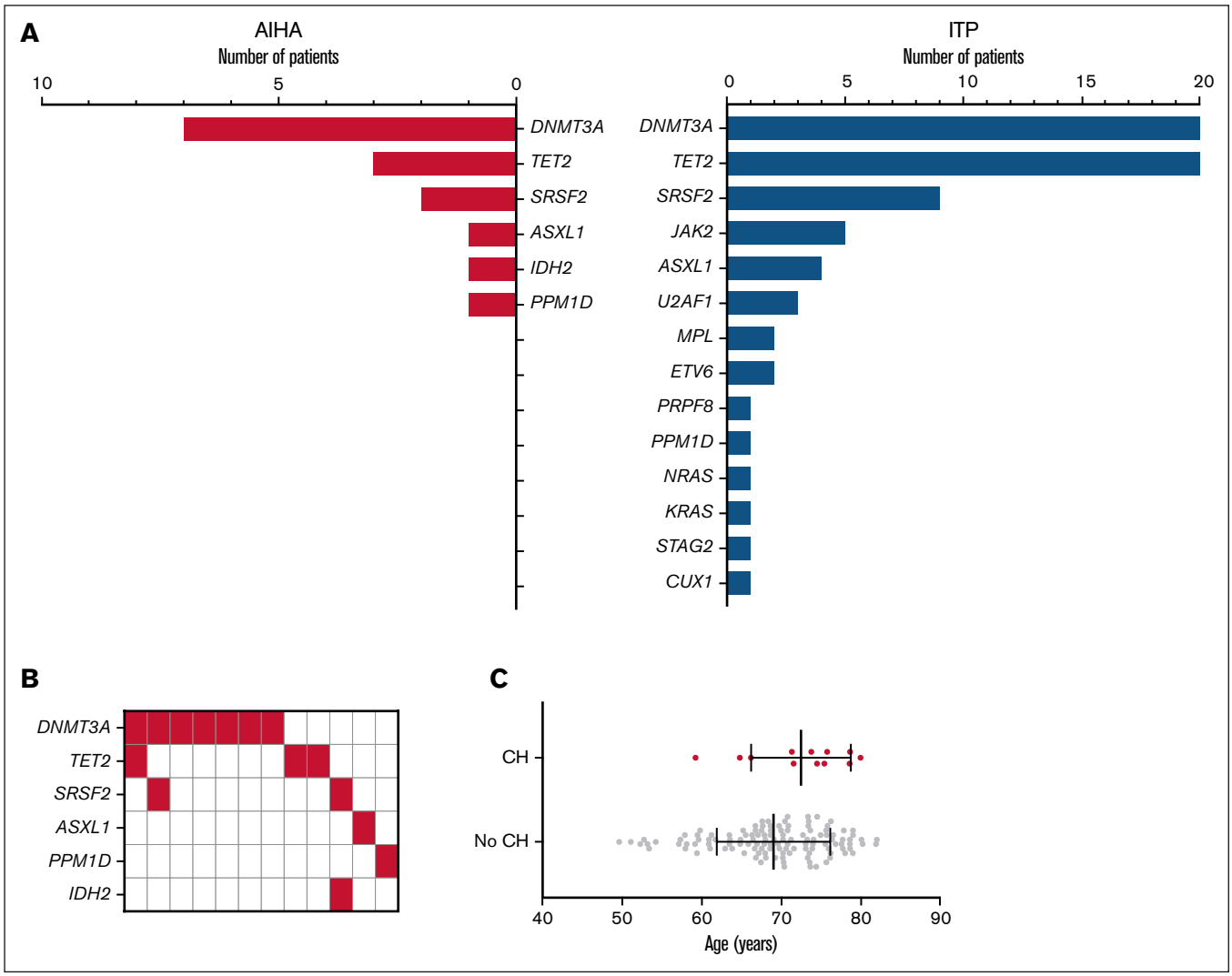


Figure 1. Characteristics of CH in AIHA. (A) Distribution of the genes carrying CH in patients with AIHA and ITP. (B) Heat map of the co-occurrence of CH variants in patients with AIHA. (C) Age distribution at AIHA diagnosis in patients with and without CH. We show the mean and standard deviation for each group.

criteria as AIHA. We found 71 CH clones in 53 patients (9.3%; Figure 1A). The risk of ITP associated with CH was similar to that of AIHA, with overlapping CIs (aHR, 2.61; 95% CI, 1.97-3.48; $P = 4.2 \times 10^{-11}$).

Cumulative incidence curves showed that the increased risk of AIHA associated with CH was present for at least 15 years after CH detection (Figure 2B). Ten years after inclusion, 4.5% of patients with CH and 1.7% of those without CH had developed AIHA, respectively. Patients with CH had a higher cumulative incidence of ITP than AIHA, in accordance with the higher incidence of this immune cytopenia in the general population. Patients with CH had a comparable risk of AIHA to the risk of ITP in those without CH.

Finally, we performed a sensitivity analysis considering all patients with AIHA or ITP (ie, prevalent cases), including those with disease before inclusion and those with prior diagnoses of ITP, hematological malignancy, or SLE. Among the 251 patients with AIHA, 20 had CH (8.0%). AIHA was diagnosed at a slightly older age in patients with CH than in those without (69.9 ± 7.6 vs 66.0 ± 9.5 years; $P = .046$). Among the 937 patients with ITP, 80 had CH (8.5%). Using multivariable logistic regression, we found associations between CH and AIHA and ITP, which were similar to those of incident primary diseases (Figure 2C). We found consistent results after excluding patients with both ITP and AIHA (ie, Evans syndrome).

In summary, we found that CH was associated with a twofold increased risk of AIHA. This risk of AIHA associated with CH seems to be of roughly the same magnitude as the one with ITP. However, our sample size does not allow us to determine whether the slightly higher aHR for ITP is real or because of sampling fluctuations. The risk of ITP associated with CH found in this study is comparable to the findings reported in the only other study on this disease, which was also conducted with the UK Biobank (aHR, ~2.3).[4] The slight difference in estimates is likely because of methodological differences. Notably, we used published, expert-curated CH identification, whereas the study by Liu et al[4]

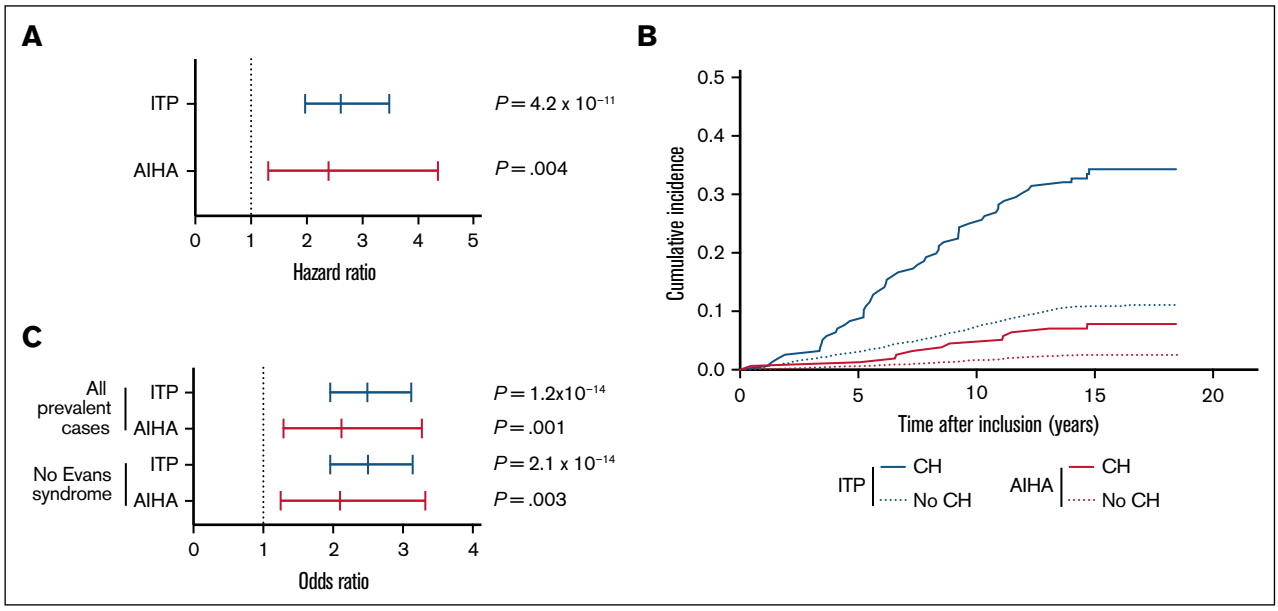


Figure 2. CH increases the risk of AIHA. (A) aHR and 95% CI for the risk of incident primary AIHA (n = 132) and ITP (n = 568) from a multivariable Cox regression model adjusted for age, sex, and the first 10 principal components considering genetic ancestry. (B) Cumulative incidence of primary AIHA and ITP according to the presence of CH. (C) Adjusted odds ratio and 95% CI for the risk of AIHA (n = 251) and ITP (n = 937) considering all cases (ie, prevalent cases) from a multivariable logistic regression model adjusted for age, sex, and the first 10 principal components. We also performed a sensitivity analysis by excluding 24 patients with both ITP and AIHA (ie, Evans syndrome).

performed its own CH calling. Additionally, as each research team must perform censoring date estimates in the UK Biobank, we may have obtained slight differences.

As expected, the proportion of patients with AIHA carrying CH clone increased with age. The proportion of patients with CH was similar in both immune cytopenias and was lower than that found in one previous report of ITP.[10] This is likely because of differences in technology used for CH identification and the varying population characteristics in terms of age and underlying disease. CH in the UK Biobank has been analyzed based on exome sequencing and restricted to clones with a variant allele frequency of $\geq$2%.[9] Nevertheless, smaller CH clones may be present and have a biological effect.[11,12]

DNMT3A and *TET2* were the most frequent genes carrying CH in both AIHA and ITP, as in the general population.[4,5] Nevertheless, some differences may exist between the risk of these 2 immune cytopenias associated with CH. In a previous study in the UK Biobank,[4] the higher risk of ITP was conferred by *JAK2* variants, which were absent in our patients with AIHA. Thus, some variants may specifically drive the risk of ITP and could contribute to the slightly higher risk of ITP compared to AIHA that may be associated with CH.

In addition to the pathophysiological insights, our results could be clinically relevant. Drug targeting of CH is an active field of study, and several approaches are under investigation, including epigenetic modulators, anti-inflammatory therapies, metabolic inhibitors, and signaling pathway inhibitors.[13] Such treatments could represent a new approach for patients with AIHA and a contributing CH.

Our study has limitations. Although the UK Biobank is one of the largest biobanks,[14] the rarity of AIHA limits the number of patients studied and prevented us from studying the gene-specific aHR. Because of the lack of sufficient clinical data, it was not possible to determine whether CH is associated with a particular subtype of AIHA (ie, warm or cold) or with its clinical course. Because no diagnostic code is available for autoimmune neutropenia, we could not consider this immune cytopenia in our analysis considering Evans syndrome. Finally, the mechanisms by which CH increases AIHA and ITP risk remain unclear. CH has also been associated with other autoimmune diseases.[15] Current knowledge suggests that CH leads to chronic inflammation and changes in immune function, which could promote autoimmunity.[16] The impact of these alterations in AIHA pathogenesis will require further investigation.

The CHU Sainte-Justine Research Ethics Board approved the project. This study was conducted in accordance with the Declaration of Helsinki.

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