BMC Medicine

RESEARCH

Open Access

Clonal hematopoiesis of indeterminate potential and risk of autoimmune thyroid disease

Xue Zhang[1,2†], Yuqing Wang[3,4†], Huiwen Xue[3,4†], Yingsuo Zhao[3,4], Mingcheng Liu[1,2], Hui Wei[1,2*] and Qianwei Liu[3,4*]

Abstract

Background Autoimmune thyroid disease (AITD) is the most common organ-specific autoimmune disease, often remaining asymptomatic until the thyroid is significantly affected. Clonal hematopoiesis of indeterminate potential (CHIP) has been reported to drive many inflammatory diseases and autoimmune diseases. The association between CHIP and AITD is scarcely reported. This study aims to investigate whether CHIP is associated with the risk of AITD.

Methods We conducted a prospective community-based cohort study at the UK Biobank. CHIP, defined as the exposure, was identified using whole-exome sequencing (WES) data. AITD was sourced from the inpatient hospitalization register, the death register, and the primary healthcare register. Cox regression models were utilized to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between CHIP and AITD. Next, we conducted a subgroup analysis to investigate the role of specific gene mutations (*DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *SRSF2*, and *JAK2*) in the investigated association. Finally, we assessed the association across small CHIP clones (variant allele frequency, VAF: 2–10%) and large CHIP clones (VAF ≥ 10%). All models were adjusted for sex, age, ethnicity, education, Townsend deprivation index, body mass index, smoking status, and drinking status.

Results A total of 454,618 individuals were included in the final analysis. We identified 14,059 (3.1%) participants with CHIP. Compared with individuals without CHIP, those with CHIP were generally older and more likely to be smokers. Over a median follow-up of 12.7 years (interquartile range, IQR: 11.9–13.5), 21,708 cases with AITD were diagnosed. CHIP was associated with an increased risk of AITD (HR 1.11, 95% CI 1.03–1.19). Specifically, individuals with *TET2*-mutant CHIP (HR 1.23, 95% CI 1.07–1.41) had an elevated risk of AITD. A large CHIP clone (HR 1.17, 95% CI 1.08–1.27) was associated with an increased risk of AITD. Focusing on large CHIP clone, we also observed an association between *TET2*-mutant (HR 1.27, 95% CI 1.10–1.47) and *ASXL1*-mutant (HR 1.33, 95% CI 1.02–1.73) CHIP and risk of AITD.

Conclusions Individuals with CHIP were associated with a modestly increased risk of AITD, especially *TET2*-mutant CHIP. Future studies are needed to verify current findings and elaborate potential mechanisms.

Keywords Autoimmune thyroid disease, Clonal hematopoiesis of indeterminate potential, Risk factor

†Xue Zhang, Yuqing Wang and Huiwen Xue contributed equally to this work.

*Correspondence:
Hui Wei
weihui@ihcams.ac.cn
Qianwei Liu
qianweiliu@smu.edu.cn
Full list of author information is available at the end of the article

Background

Autoimmune thyroid disease (AITD) is the most common organ-specific autoimmune disease, is characterized by a strong genetic predisposition, accounts for approximately 90% of all thyroid diseases, and affects 2–5% of the general population [1–5]. AITD is caused by a complex interplay of genetic susceptibility and environmental exposures, with the breakdown of the immune tolerance and overexpression of the autoimmune antibodies leading to a spectrum of phenotypes, such as thyroid hormone excess (hyperthyroidism) or deficiency (hypothyroidism) [2, 6, 7]. Most cases of AITD remain asymptomatic until the thyroid is significantly affected [8]. There is an unmet need for early diagnosis of AITD. Therefore, additional risk factors must be identified for early intervention and potential targeted treatment.

Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the presence of a somatic leukemia-associated mutation in the peripheral blood or bone marrow with a variant allele frequency (VAF) ≥ 2% in otherwise healthy people [9, 10]. It is a common, age-related state affecting more than 10% of people over 70 years old [9–11]. Individuals with CHIP showed an increased risk of hematologic malignancy, cardiovascular disease, and all-cause mortality [9]. It is well documented that CHIP might evoke pro-inflammatory effects and alter the immune effector cells' function [12–17]. Thus, CHIP has been reported to be the cause of many inflammatory diseases, including chronic liver disease, chronic kidney disease, and chronic obstructive pulmonary disease [18–20]. CHIP also demonstrated an increased risk in some autoimmune diseases, like inflammatory bowel disease [21]. Therefore, we hypothesized that the inflammatory and immune changes in CHIP might be involved in the process of AITD. However, the association between CHIP and AITD is scarcely reported. This study aims to investigate whether CHIP is associated with the risk of AITD.

Methods

Study population

Our study adopted data from the UK Biobank (https://www.ukbiobank.ac.uk/), a large prospective cohort with over 500,000 participants aged 40–69 across 22 centers located in England, Scotland, and Wales between 2006 and 2010 [22]. It is continuing to collect phenotypic and genotypic details about its participants, including data from questionnaires, physical measures, sample assays, accelerometry, multimodal imaging, and genome-wide genotyping [23]. By linking to the national health records, it can conduct a continuous follow-up for a wide range of health-related outcomes [24].

We found 469,877 individuals with whole-exome sequencing (WES) information and excluded 355 participants for informed consent withdrawal or with missing information on blood sampling. Then, we excluded 3296 participants with a diagnosis of any prevalent hematologic malignancy to preclude secondary CHIP. Those with a diagnosis of AITD were further excluded ($N = 12{,}058$), leaving 454,168 individuals in the final analysis (Additional file 2: Fig. S1). To minimize the impact of reverse causation, we conducted the follow-up from 1 year after initial blood sampling until a diagnosis of AITD, death, or December 2022, whichever occurred first.

Definition of exposure

CHIP was ascertained as recently described [25]. CRAM files from the UK Biobank were aligned to the GRCh38 reference genome and filtered against the Genome Aggregation Database (gnomAD) to exclude germline variants [26]. Briefly, we first used 74 genes associated with myeloid malignancy to identify CHIP [27]. Somatic mutations were identified using Mutect2 (Genome Analysis Toolkit v. 4.2.4.0) in "tumor-only" mode, focusing on the exons in 73 of the 74 genes in relation to myeloid malignancy (except for *U2AF1*) [27, 28]. Raw Mutect2 outputs were filtered via FilterMutectCalls, utilizing probabilities derived from LearnReadOrientationModel [28, 29]. We ran the Rust-HTSLIB binary (https://github.com/weinstockj/pileup_region) to identify *U2AF1* variant reads [27]. Gene annotation was performed on ANNOVAR [30]. Variants were removed if: a total read depth of ≤ 20, minimum read depth for the alternate allele < 5, and VAF < 2%, or no evidence on both forward and reverse sequencing reads. Variants not associated with either age or telomerase reverse transcriptase promoter were removed to minimize potential artifacts [27]. In addition, genes that were not observed in myeloid malignancy in one previous study were further removed [27]. After filtering and excluding the above gene variants, there were 55 genes in the final list (Additional file 1: Table S1).

Potential clonal cytopenia of undetermined significance (CCUS) was defined as the presence of CHIP and cytopenia, specifically anemia (hemoglobin < 12 g/dL in females and < 13 g/dL in males), neutropenia (absolute neutrophil count $< 1.8 \times 10^9$/L), and/or thrombocytopenia (platelet count $< 150 \times 10^9$/L), in the absence of an alternative explanation [31–33].

Any CHIP was identified as the aforementioned CHIP somatic mutations with a VAF of 2% or greater, and the large CHIP had a VAF of 10% or greater. We separately examined gene-specific CHIP subtypes in the common driver genes *DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *SRSF2*,

and the prior reported autoimmune diseases associated with mutation *JAK2* [34, 35].

Definition of outcome

The study outcome was the incident diagnosis of AITD, ascertained by the 10th edition of the International Classification of Diseases (ICD-10) from the inpatient records and death register (Additional file 1: Table S2) [36]. We also identified AITD using read codes from the primary healthcare register.

Covariates

We collected data on demographic factors, including sex (male and female), ethnicity (white, other, and unknown), and education (college/university degree, other degree, and unknown) at recruitment. Age was calculated according to dates of birth and time of baseline assessment. Height and body weight were measured by trained nurses at enrollment [22]. Body mass index (BMI) was calculated as (weight/height^2) and classified into four categories using WHO criteria: underweight ($\leq$18.5), normal weight (18.5–25), overweight (25–30), and obese ($\geq$30). Townsend deprivation index (TDI) was obtained from the postcode of residence by the integration of unemployment, car and home ownership, and household overcrowding [37]. Lifestyle factors, smoking, and drinking statuses were collected at recruitment and categorized into never, previous, current, and unknown. We used the ICD-10 codes to identify myeloid malignancy (i.e., acute myeloid leukemia, AML; myelodysplastic syndromes, MDS; myeloproliferative neoplasms, MPN) in both the Cancer Register and Inpatient Register (Additional file 1: Table S3).

Statistics analysis

Cox proportional hazard models were used to investigate the association between CHIP and the risk of AITD. The analysis was adjusted for sex, ethnicity, education, TDI, smoking, and drinking. Age and BMI were fitted as a natural cubic spline in Cox regression models to reduce potential residual confounding. Stratified analyses were conducted by sex, age (<60 years, $\geq$60 years), BMI, ethnicity, education level, TDI categories, smoking, and drinking. We also performed subgroup analyses in several common mutations of CHIP (*DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *SRSF2*, and *JAK2*). The association of small CHIP and large CHIP with incident AITD was also evaluated.

To evaluate the robustness of our findings, we conducted a series of sensitivity analyses using multiple approaches. First, we implemented lag-time analyses with 3-year and 5-year intervals between CHIP and AITD onset to account for potential reverse causality. Second, we replicated our primary analyses using propensity score matching (PSM) to address potential confounding. Propensity scores for CHIP were calculated using logistic regression, in which exposure status was regressed on age, sex, BMI, ethnicity, education, TDI, smoking, and alcohol drinking. For each individual with CHIP, one matched individual without CHIP was randomly selected based on their propensity scores. In addition, we also perform a sensitivity analysis using inverse probability weighting (IPW). IPW was conducted using the propensity scores obtained from the PSM procedure, weighting CHIP carriers by the inverse of their propensity score and non-carriers by the inverse of 1 minus their propensity score. Third, we performed an additional analysis by excluding participants with rheumatoid arthritis to minimize potential confounding from autoimmune comorbidities. Fourth, we further explore the dose–response association of VAF of any CHIP mutation and specific CHIP mutations with risk of AITD. Fifth, to investigate the different effects between CHIP and CCUS, we performed a sensitivity analysis by dividing exposed individuals into two groups: (1) CHIP without CCUS and (2) CCUS. Sixth, to relieve potential concern of the effect of myeloid malignancy in the association between *TET2*-CHIP and AITD, we performed a sensitivity analysis by excluding individuals with a diagnosis of myeloid malignancy from the exposed group, regardless of the diagnostic time of myeloid malignancy.

The analyses were performed in SAS 9.4 and R version 4.1.3. UK Biobank has approval from the Northwest Multi-centre Research Ethics Committee, with all participants given written informed consent (reference 21/NW/0157). This work was approved by the Ethical Review Board in Nanfang Hospital, Southern Medical University in China (NFEC-2023–559).

Results

Among the 454,168 individuals in the final analysis, 14,059 (3.1%) individuals had any CHIP. The median age of participants with or without CHIP was 58 and 53, respectively. Individuals with CHIP exhibited a higher percentage of being elderly (67.9 to 44.2%) and smoking (51.4 to 44.7%) than those without CHIP. Sex, BMI, education, TDI, and drinking status were comparable between participants with and without CHIP (Table 1).

Over a median follow-up of 12.7 years (IQR 11.9–13.5), we identified 817 (5.8%) incident cases of AITD with CHIP and 20,891 (4.7%) without CHIP, with an incident rate of 497.8 and 391.5 per 100,000 person-years, respectively (Table 2). Individuals with CHIP carried a statistically significantly increased risk of AITD (HR 1.11, 95% CI 1.03–1.19). The association did not change largely by sex, age, BMI, race, education, TDI, smoking status, and

Table 1 Characteristics of the individuals included

Characteristic	Individuals with CHIP *N* (%)	Individuals without CHIP *N* (%)
Number of individuals	14,059 (100.0)	440,109 (100.0)
Sex		
Male	6830 (48.6)	204,297 (46.4)
Female	7229 (51.4)	235,812 (53.6)
Age		
< 60	4508 (32.1)	245,425 (55.8)
≥ 60	9551 (67.9)	194,684 (44.2)
BMI		
≤ 18.5	139 (1.0)	3898 (0.9)
18.5–25	4306 (30.6)	143,710 (32.7)
25–30	6153 (43.8)	186,939 (42.5)
> 30	3461 (24.6)	105,562 (24.0)
Ethnicity		
White	13,339 (94.9)	414,188 (94.1)
Other	670 (4.8)	24,337 (5.5)
Unknown	50 (0.4)	1584 (0.4)
Education		
College/university degree	4086 (29.1)	143,743 (32.7)
Other degree	6575 (46.8)	217,756 (49.5)
Unknown	3398 (24.2)	78,610 (17.9)
TDI		
First quartile	3516 (25.0)	111,463 (25.3)
Second quartile	3551 (25.3)	110,272 (25.1)
Third quartile	3466 (24.7)	109,929 (25.0)
Fourth quartile	3526 (25.1)	108,445 (24.6)
Smoking statuses		
Never smoked	6732 (47.9)	241,019 (54.8)
Previous smoked	5525 (39.3)	150,729 (34.2)
Current smoked	1700 (12.1)	46,172 (10.5)
Unknown	102 (0.7)	2189 (0.5)
Drinking statuses		
Never drank	601 (4.3)	18,959 (4.3)
Previous drank	530 (3.8)	15,357 (3.5)
Current drank	12,892 (91.7)	404,695 (92.0)
Unknown	36 (0.3)	1098 (0.2)

N number of participants, *CHIP* clonal hematopoiesis of indeterminate potential, *BMI* body mass index, *TDI* Townsend area deprivation index

drinking status (Table 2). The robustness of this association was further supported by multiple sensitivity analyses. Lag-time analyses with 3-year (HR 1.11, 95% CI 1.02–1.19) and 5-year (HR 1.10, 95% CI 1.01–1.20) intervals between CHIP and AITD diagnosis yielded consistent results. Furthermore, the association persisted after PSM (HR 1.08, 95% CI 1.01–1.16) and IPW (HR 1.09, 95% CI 1.01–1.18) analyses. Additionally, exclusion of participants with rheumatoid arthritis did not substantially alter the observed association (HR 1.10, 95% CI 1.03–1.18). Individuals with CCUS had a higher risk increase of AITD (HR 1.47, 95% CI 1.18–1.83) than individuals with CHIP but without CCUS (HR 1.08, 95% CI 1.01–1.17) (*P* for difference: 0.001).

In the analysis by gene-specific CHIP mutations, *TET2*-mutant CHIP was found to be associated with risk of AITD (HR 1.23, 95% CI 1.07–1.41) at any VAF level. Other CHIP mutations, such as *DNMT3A* (HR 1.04, 95% CI 0.95–1.15), *ASXL1* (HR 1.22, 95% CI 0.98–1.53), *PPMID* (HR 1.12, 95% CI 0.72–1.74), *SRSF2* (HR 1.55, 95% CI 0.93–2.57), and *JAK2* (HR 1.40, 95% CI 0.67–2.94), did not associate with risk of AITD

Table 2 HRs with 95% CI of AITD among individuals with CHIP, compared to individuals without CHIP[a]

Characteristic	Individuals without CHIP		Individuals with CHIP		Adjusted HR (95% CI)
	N	IR	*N*	IR	
Overall	20,891	391.5	817	497.8	1.11 (1.03–1.19)
Sex					
Male	5004	201.2	214	270.4	1.08 (0.94–1.24)
Female	15,887	557.6	603	709.6	1.12 (1.03–1.21)
Age					
< 60	9416	309	190	344.7	1.02 (0.88–1.17)
≥ 60	11,475	501.2	627	575.3	1.14 (1.05–1.23)
BMI					
≤ 18.5	201	453.5	7	466.3	1.10 (0.44–2.73)
18.5–25	5758	326.9	230	451.4	1.17 (1.02–1.33)
25–30	8417	370.0	344	476.7	1.11 (0.99–1.23)
> 30	6515	518.5	236	597.6	1.05 (0.92–1.20)
Ethnicity					
White	19,723	392.3	768	493.4	1.09 (1.02–1.17)
Other	1096	376.9	48	608.2	1.48 (1.11–1.99)
Unknown	72	385.7	1	179.6	0.44 (0.06–3.20)
TDI					
First quartile	4876	356.1	192	458.8	1.11 (0.96–1.28)
Second quartile	5194	386.3	198	472	1.05 (0.91–1.21)
Third quartile	5249	394.4	215	536.3	1.19 (1.04–1.36)
Fourth quartile	5572	431.2	212	527.1	1.08 (0.95–1.25)
Education					
College/university degree	5476	309.7	169	345.4	0.96 (0.82–1.12)
Other degree	10,536	398.4	392	508.9	1.11 (1.01–1.23)
Unknown	4879	528	256	671.2	1.21 (1.07–1.37)
Smoking statuses					
Never smoked	10,915	369.1	398	494.7	1.14 (1.03–1.26)
Previous smoked	7697	425.4	331	520.0	1.10 (0.99–1.23)
Current smoked	2157	395.8	80	423.3	0.97 (0.78–1.22)
Unknown	122	477.9	8	804.3	1.69 (0.81–3.51)
Drinking statuses					
Never drank	1357	605.4	51	743.4	1.12 (0.84–1.48)
Previous drank	1025	577.5	46	797.7	1.22 (0.91–1.64)
Current drank	18,447	374.8	718	475.2	1.10 (1.02–1.18)
Unknown	62	485.7	2	719.3	1.45 (0.34–6.23)

N number of incident AITD, *IR* incident rate of AITD, *HR* hazards ratio, *CI* confidence interval, *AITD* autoimmune thyroid disease, *CHIP* clonal hematopoiesis of indeterminate potential, *BMI* body mass index, *TDI* Townsend area deprivation index

[a] Cox regression adjusted for sex (female or male), age (as natural cubic spline), BMI (as natural cubic spline), ethnicity, education, TDI, smoking, and drinking

(Fig. 1). We observed a linear association of VAF of any CHIP, *DNMT3A*-mutant CHIP, *ASXL1*-mutant CHIP, or *JAK2*-mutant CHIP with risk of AITD (Additional file 2: Fig. S2). The association was also noted for CHIP with VAF > 0.1 (HR 1.17, 95% CI 1.08–1.27) with AITD, but not for small CHIP clone (HR 0.98, 95% CI 0.85–1.11) with incident AITD (Table 3). Focusing on large CHIP clone, we also observed an association between *TET2*-mutant (HR 1.27, 95% CI 1.10–1.47) and *ASXL1*-mutant (HR 1.33, 95% CI 1.02–1.73) CHIP and risk of AITD. We further evaluated the results after excluding CHIP individuals who were diagnosed with MDS, MPN, or AML. The analysis revealed that *TET2*-mutant CHIP carriers continued to exhibit a significantly elevated risk of AITD incidence (HR 1.22, 95% CI 1.06–1.40).

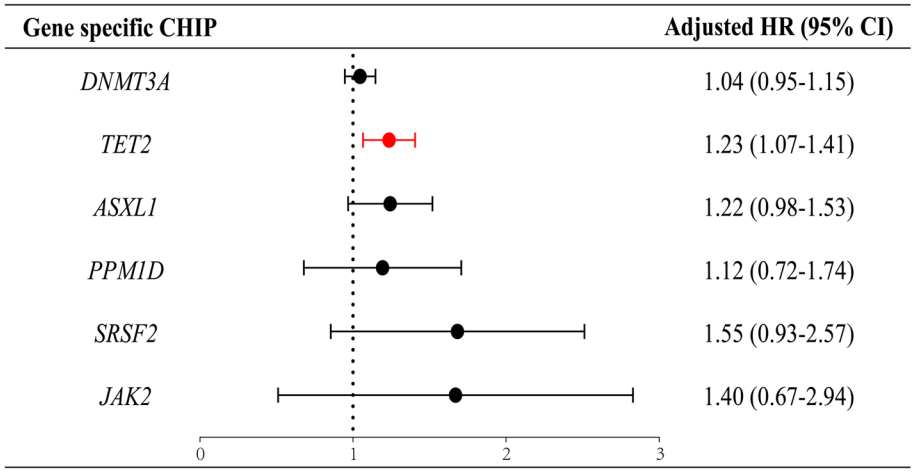

Fig. 1 HRs with 95% CI of AITD incidence among individuals with gene-specific CHIP, compared to individuals without CHIP*

HR, hazards ratio; CI, confidence interval; AITD, autoimmune thyroid disease; CHIP, clonal hematopoiesis of indeterminate potential. *Cox regression adjusted for sex (female or male), age (as natural cubic spline), BMI (as natural cubic spline), ethnicity, education, TDI, smoking statuses, and drinking statuses

Table 3 HRs with 95% CI of AITD among individuals with large CHIP and small CHIP, compared to individuals without CHIP[a]

	Small CHIP Adjusted HR (95% CI)	Large CHIP Adjusted HR (95% CI)
Overall	0.98 (0.85–1.11)	1.17 (1.08–1.27)
Gene specific CHIP		
DNMT3A	0.97 (0.83–1.14)	1.09 (0.96–1.22)
TET2	1.02 (0.71–1.45)	1.27 (1.10–1.47)
ASXL1	1.01 (0.65–1.56)	1.33 (1.02–1.73)
PPM1D	0.86 (0.39–1.92)	1.29 (0.76–2.18)
SRSF2	1.60 (0.51–4.95)	1.54 (0.87–2.71)
JAK2	NA	1.40 (0.67–2.94)

HR hazards ratio, *CI* confidence interval, *AITD* autoimmune thyroid disease, *CHIP* clonal hematopoiesis of indeterminate potential, *BMI* body mass index, *TDI* Townsend area deprivation index

[a] Cox regression adjusted for sex (female or male), age (as natural cubic spline), BMI (as natural cubic spline), ethnicity, education, TDI, smoking statuses, and drinking statuses

Discussion

In this study, we revealed an association between CHIP and risk of AITD. CHIP carriers demonstrated a modestly increased risk of AITD. This association showed minimal heterogeneity when stratified by sex, age, BMI, race, education, TDI, smoking status, and drinking status. In gene-specific analyses, the association was observed for *TET2*-mutant CHIP. The association was particularly obvious in individuals with a higher VAF (>10%), with pronounced association observed for *TET2*- and *ASXL1*-mutant CHIP in large CHIP clones.

Inflammation and immunity play a significant role in AITD provoking [1, 38–43]. What might be the underlying mechanisms behind CHIP and increased AITD risk? The recognition of somatic mosaicism as a cause of autoinflammatory diseases has been increasingly acknowledged recently. Somatic mutations in *TET2* and *UBA1* have been reported in adult-onset autoinflammatory disease [44, 45]. CHIP is a cause of inflammation [46]. Loss of *TET2* results in elevated levels of pro-inflammatory cytokines release to the inflammation initiation, such as IL-1β, IL-6, and TNF-α [12, 47, 48]. *TET2* is essential to suppress IL-6 and IL-1β expression during the resolution stage of inflammation via the HDAC-introduced histone deacetylation in innate myeloid cells and macrophages, respectively [49, 50]. Growing reports have identified *TET2* mutation in thyroid diseases, including thyroid cancers and mucosa-associated lymphoid tissue lymphoma, although the specific reasons for these associations are not yet fully understood [51, 52]. Besides, CHIP mutation causes immune dysregulation. Evidence from in vivo and in vitro experiments in mice has revealed that *TET*-family enzymes suppress regulatory T-cell functions, alter T-cell polarization, and attenuate the inhibitory effects on pro-inflammatory Th17 activity [13–16, 53]. AITD, known as a "T cell-mediated organ-specific autoimmune disorder," is characterized by a significant lymphocytic infiltration of the thyroid follicles, including both T cells and B cells [2, 49]. Studies have indicated that immune effector cells derived from hematopoietic stem cells, such as Th1 and Th17 cells, can modulate both adaptive and innate immune responses through the activation of inflammasomes (e.g., NLRP3) and the release of inflammatory

cytokines (e.g., IL-1β) [1, 17, 42, 50–52]. These mechanisms may underlie the increased risk of AITD among individuals with CHIP. Future studies are needed to verify current findings and elaborate potential mechanisms.

Strengths of this study are the large sample size and prospective follow-up of the UK Biobank study. We included a thorough assessment of confounders, including sociodemographics, socioeconomic status, BMI, smoking, and alcohol consumption. Since we did adjust for multiple covariates in the individual gene analyses, there may be less associations with AITD due to confounding. Our study also has some limitations that should be acknowledged. Firstly, we only conducted this analysis in the UK Biobank, predominantly comprised of European ancestry individuals, impeding the broadening of the participant's race into others. Secondly, exposure misclassification bias might exist in this study for unexposed participants at the beginning might have developed to have CHIP during the follow-up period. For the same reason, we also could inevitably misjudge the clone size. Thirdly, although the statistical power is enough for the main analysis, subgroup analyses suffered from the issue of insufficient power. Due to such issue, we did not further investigate the association by the subgroup of AITD. Fourthly, although important known confounders were adjusted in the study, there was still possible residual confounding. Fifthly, the UK Biobank dataset did not encompass data on the severity of AITD, precluding an investigation into the association between CHIP and AITD severity. Finally, we cannot fully exclude reverse causality between CHIP and AITD, though similar results were noted when excluding the first 3-year or 5-year follow-up.

Conclusions

In summary, individuals with CHIP were at a modestly increased risk of AITD, especially *TET2*-mutant CHIP. These data add to our growing understanding of AITD pathogenesis and provoke timely screening of AITD in CHIP populations. This study also highlights the importance of CHIP screening in AITD patients. Future studies are needed to verify current findings and elaborate potential mechanisms.

Abbreviations

AITD	Autoimmune thyroid disease
AML	Acute myeloid leukemia
BMI	Body mass index
CCUS	Clonal cytopenia of undetermined significance
CHIP	Clonal hematopoiesis of indeterminate potential
CI	Confidence interval
HR	Hazard ratio
ICD- 10	10Th version of the International Classification of Diseases
IPW	Inverse probability weighting
IQR	Interquartile range
MDS	Myelodysplastic syndromes
MPN	Myeloproliferative neoplasms
PSM	Propensity score matching
TDI	Townsend deprivation index
VAF	Variant allele frequency
WES	Whole-exome sequencing

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04077-z.

Additional file 1. Table S1 Gene list of definition of CHIP. Table S2 The 10th version International Classification of Diseases (ICD) codes and the number of patients for AITD. Table S3 The 10th version International Classification of Diseases (ICD) codes for myeloid malignancy.

Additional file 2. Fig. S1 Flowchart of the study cohort. Fig. S2 Dose–response association between VAF of CHIP and risk of AITD.

Acknowledgements

We appreciate the endocrinologist Dr. Shuang Wan for AITD consultation. This research has been conducted using the UK Biobank Resource under Application Number [106912].

Authors' contributions

Xue Zhang and Yuqing Wang drafted the manuscript. Qianwei Liu and Hui Wei designed the study. Qianwei Liu and Huiwen Xue analyzed the data. Xue Zhang, Yuqing Wang, Yingsuo Zhao, Mingcheng Liu, Hui Wei and Qianwei Liu interpreted the data and revised this manuscript. Xue Zhang, Yuqing Wang, and Huiwen Xue contributed equally to the manuscript. All authors read and approved the final manuscript.

Authors' information

Authors and affiliations

State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, China; Tianjin Institutes of Health Science. Xue Zhang, Mingcheng Liu, and Hui Wei. Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, China; Clinical Medical Research Center of Hematological Diseases of Guangdong Province, Guangzhou, China. Yuqing Wang, Huiwen Xue, Yingsuo Zhao, and Qianwei Liu

Funding

Initial Founding for High Level Talented Scholars in Nanfang Hospital, Southern Medical University (2023G001); National Natural Science Foundation of China (82370183); Tian Jin Natural Science Foundation (23 JCZXJC00310); Haihe Laboratory of Cell Ecosystem Innovation Fund (HH22 KYZX0039).

Data availability

This study utilized the UK Biobank Resource, under Application Number 106912. Researchers can request access data from the UK Biobank at www.ukbiobank.ac.uk.

Declarations

Ethics approval and consent to participate

Data for this study were obtained from the UK Biobank. UK Biobank has approval from the Northwest Multi-centre Research Ethics Committee, with all participants given written informed consent (reference 21/NW/0157). This research has been conducted using the UK Biobank Resource under application number [106912]. This work was approved by the Ethical Review Board in Nanfang Hospital, Southern Medical University in China (NFEC-2023–559).

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form.

Competing interests

The authors declare no competing interests.

Author details
[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No. 288 Nanjing Road, Tianjin 300020, China. [2]Tianjin Institutes of Health Science, Tianjin, China. [3]Department of Hematology, Nanfang Hospital, Southern Medical University, No. 1838, North Guangzhou Avenue, Guangzhou 510515, China. [4]Clinical Medical Research Center of Hematological Diseases of Guangdong Province, Guangzhou, China.

Received: 4 September 2024 Accepted: 11 April 2025
Published online: 23 April 2025

References

1. Simmonds MJ. GWAS in autoimmune thyroid disease: redefining our understanding of pathogenesis. Nat Rev Endocrinol. 2013;9(5):277–87.
2. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14(2):174–80.
3. Moroncini G, Calogera G, Benfaremo D, Gabrielli A. Biologics in inflammatory immune-mediated systemic diseases. Curr Pharm Biotechnol. 2017;18(12):1008–16.
4. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. Endocrine. 2012;42(2):252–65.
5. Eber O, Langsteger W. Clinical aspects of autoimmune thyroid diseases. Acta Med Austriaca. 1994;21(1):1–7.
6. Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun. 2009;32(3–4):231–9.
7. Prummel MF, Strieder T, Wiersinga WM. The environment and autoimmune thyroid diseases. Eur J Endocrinol. 2004;150(5):605–18.
8. Vargas-Uricoechea H. Molecular mechanisms in autoimmune thyroid disease. Cells. 2023;12(6):918.
9. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–98.
10. Genovese G, Kahler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477–87.
11. Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20(12):1472–8.
12. Cook EK, Izukawa T, Young S, Rosen G, Jamali M, Zhang L, et al. Comorbid and inflammatory characteristics of genetic subtypes of clonal hematopoiesis. Blood Adv. 2019;3(16):2482–6.
13. Yue X, Lio CJ, Samaniego-Castruita D, Li X, Rao A. Loss of TET2 and TET3 in regulatory T cells unleashes effector function. Nat Commun. 2019;10(1):2011.
14. Yang R, Qu C, Zhou Y, Konkel JE, Shi S, Liu Y, et al. Hydrogen sulfide promotes Tet1- and Tet2-mediated Foxp3 demethylation to drive regulatory T cell differentiation and maintain immune homeostasis. Immunity. 2015;43(2):251–63.
15. Gamper CJ, Agoston AT, Nelson WG, Powell JD. Identification of DNA methyltransferase 3a as a T cell receptor-induced regulator of Th1 and Th2 differentiation. J Immunol. 2009;183(4):2267–76.
16. Ichiyama K, Chen T, Wang X, Yan X, Kim BS, Tanaka S, et al. The methylcytosine dioxygenase Tet2 promotes DNA demethylation and activation of cytokine gene expression in T cells. Immunity. 2015;42(4):613–26.
17. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. Science. 2019;366(6465):eaan4673.
18. Wong WJ, Emdin C, Bick AG, Zekavat SM, Niroula A, Pirruccello JP, et al. Clonal haematopoiesis and risk of chronic liver disease. Nature. 2023;616(7958):747–54.
19. Kestenbaum B, Bick AG, Vlasschaert C, Rauh MJ, Lanktree MB, Franceschini N, et al. Clonal hematopoiesis of indeterminate potential and kidney function decline in the general population. Am J Kidney Dis. 2023;81(3):329–35.
20. Miller PG, Qiao D, Rojas-Quintero J, Honigberg MC, Sperling AS, Gibson CJ, et al. Association of clonal hematopoiesis with chronic obstructive pulmonary disease. Blood. 2022;139(3):357–68.
21. Zhang CRC, Nix D, Gregory M, Ciorba MA, Ostrander EL, Newberry RD, et al. Inflammatory cytokines promote clonal hematopoiesis with specific mutations in ulcerative colitis patients. Exp Hematol. 2019;80:36-41.e3.
22. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3): e1001779.
23. Ho FK, Gray SR, Welsh P, Petermann-Rocha F, Foster H, Waddell H, et al. Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants. BMJ. 2020;368: m688.
24. Harshfield EL, Pennells L, Schwartz JE, Willeit P, Kaptoge S, Bell S, et al. Association between depressive symptoms and incident cardiovascular diseases. JAMA. 2020;324(23):2396–405.
25. Liu X, Xue H, Wirdefeldt K, Song H, Smedby K, Fang F, Liu Q. Clonal hematopoiesis of indeterminate potential and risk of neurodegenerative diseases. J Intern Med. 2024;296(4):327–35.
26. Van Hout CV, Tachmazidou I, Backman JD, Hoffman JD, Liu D, Pandey AK, et al. Exome sequencing and characterization of 49,960 individuals in the UK Biobank. Nature. 2020;586(7831):749–56.
27. Vlasschaert C, Mack T, Heimlich JB, Niroula A, Uddin MM, Weinstock J, et al. A practical approach to curate clonal hematopoiesis of indeterminate potential in human genetic data sets. Blood. 2023;141(18):2214–23.
28. Benjamin D, Sato T, Cibulskis K, Getz G, Stewart C, Lichtenstein L. Calling somatic SNVs and indels with Mutect2. bioRxiv. 2019:861054.
29. Gu M, Kovilakam SC, Dunn WG, Marando L, Barcena C, Mohorianu I, et al. Multiparameter prediction of myeloid neoplasia risk. Nat Genet. 2023;55(9):1523–30.
30. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010;38(16): e164.
31. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-19.31. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-19.
32. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200–28.
33. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Cytopenia levels for aiding establishment of the diagnosis of myelodysplastic syndromes. Blood. 2016;128(16):2096–7.
34. Huang H, Fang M, Jostins L, Umićević Mirkov M, Boucher G, Anderson CA, et al. Fine-mapping inflammatory bowel disease loci to single-variant resolution. Nature. 2017;547(7662):173–8.
35. Lu Y, Ma Q, Yu L, Huang H, Liu X, Chen P, et al. JAK2 inhibitor ameliorates the progression of experimental autoimmune myasthenia gravis and balances Th17/Treg cells via regulating the JAK2/STAT3-AKT/mTOR signaling pathway. Int Immunopharmacol. 2023;115: 109693.
36. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, et al. Association of stress-related disorders with subsequent autoimmune disease. Jama. 2018;319(23):2388–400.
37. Phillimore P, Beattie A, Townsend P. Widening inequality of health in northern England, 1981–91. BMJ. 1994;308(6937):1125–8.
38. Ferrari SM, Paparo SR, Ragusa F, Elia G, Mazzi V, Patrizio A, et al. Chemokines in thyroid autoimmunity. Best Pract Res Clin Endocrinol Metab. 2023;37(2): 101773.
39. Xiaoheng C, Yizhou M, Bei H, Huilong L, Xin W, Rui H, et al. General and specific genetic polymorphism of cytokines-related gene in AITD. Mediators Inflamm. 2017;2017:3916395.
40. Guo Q, Wu Y, Hou Y, Liu Y, Liu T, Zhang H, et al. Cytokine secretion and pyroptosis of thyroid follicular cells mediated by enhanced NLRP3, NLRP1, NLRC4, and AIM2 inflammasomes are associated with autoimmune thyroiditis. Front Immunol. 2018;9:1197.
41. Liu C, Papewalis C, Domberg J, Scherbaum WA, Schott M. Chemokines and autoimmune thyroid diseases. Horm Metab Res. 2008;40(6):361–8.

42. Tunbridge WM, Brewis M, French JM, Appleton D, Bird T, Clark F, et al. Natural history of autoimmune thyroiditis. Br Med J (Clin Res Ed). 1981;282(6260):258–62.
43. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003;348(26):2646–55.
44. De Langhe E, Van Loo S, Malengier-Devlies B, Metzemaekers M, Staels F, Vandenhaute J, et al. TET2-driver and NLRC4-passenger variants in adult-onset autoinflammation. N Engl J Med. 2023;388(17):1626–9.
45. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2020;383(27):2628–38.
46. Florez MA, Tran BT, Wathan TK, DeGregori J, Pietras EM, King KY. Clonal hematopoiesis: mutation-specific adaptation to environmental change. Cell Stem Cell. 2022;29(6):882–904.
47. Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, Chakraborty R, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842–7.
48. Cook EK, Luo M, Rauh MJ. Clonal hematopoiesis and inflammation: partners in leukemogenesis and comorbidity. Exp Hematol. 2020;83:85–94.
49. Zhang Q, Zhao K, Shen Q, Han Y, Gu Y, Li X, et al. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature. 2015;525(7569):389–93.
50. Cull AH, Snetsinger B, Buckstein R, Wells RA, Rauh MJ. Tet2 restrains inflammatory gene expression in macrophages. Exp Hematol. 2017;55:56-70.e13.
51. Pitt SC, Hernandez RA, Nehs MA, Gawande AA, Moore FD Jr, Ruan DT, Cho NL. Identification of novel oncogenic mutations in thyroid cancer. J Am Coll Surg. 2016;222(6):1036-43.e2.
52. Wu F, Watanabe N, Tzioni MM, Akarca A, Zhang C, Li Y, et al. Thyroid MALT lymphoma: self-harm to gain potential T-cell help. Leukemia. 2021;35(12):3497–508.
53. Wiersinga WM. Hashimoto's thyroiditis. In: Vitti P, Hegedüs L, editors. Thyroid diseases: pathogenesis, diagnosis, and treatment. Cham: Springer International Publishing; 2018. p. 205–47.

Publisher's Note