Clonal haematopoiesis and risk of incident rheumatoid arthritis: results from the UK Biobank

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Abstract

Objective

Clonal haematopoiesis of indeterminate potential (CH), somatic genetic mutations conferring stem cells selective advantage, are associated with increased inflammatory cytokine production, cardiovascular disease (CVD), and malignancy. We investigated whether CH was related to risk of rheumatoid arthritis (RA), an inflammatory autoimmune disease.

Methods

Within the UK Biobank, we studied 186,577 unrelated individuals with baseline data collection, genome-wide genotyping, whole exome sequencing (WES) read for CHIP, and linked general practice (GP) data for identification of incident RA in follow-up. We excluded those with prevalent RA or taking RA medications at baseline. We tested for associations between variant allele fraction (VAF) >2% and >10% for the 8 most common CHIP mutations in the general population, and incident RA, identified by billing code algorithms. Cox regression models estimated hazard ratios (HR, 95% confidence interval) for incident RA.

Results

594 participants developed incident RA over median follow-up 7.1 years (IQR 6.4–8.0); median time to RA was 3.9 years (IQR 2.0–5.6). Incident RA cases were slightly older at enrolment, more likely to be female, have smoked, have higher body mass index (BMI), and have prevalent CVD, and hypercholesterolaemia at baseline. However, there was no difference in the presence of CHIP mutations at baseline; 6.3% vs. 6.4% of those who did and did not develop incident RA in follow-up had any CHIP mutation at >2% VAF.

Conclusion

Common CHIP mutations, including TET2, TP53, and SF3B1 mutations, were not associated with risk of incident RA when restricted to those with most complete general outpatient and hospital record follow-up in the UK Biobank.

Key words

clonal haematopoiesis, somatic mutation, rheumatoid arthritis, epidemiology, risk factor, inflammation, cohort

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Introduction

Rheumatoid arthritis (RA), a systemic autoimmune disease with chronic, destructive arthritis, is the most common autoimmune rheumatic disease, affecting ~1% of the population (1, 2). RA is two to three times more prevalent among women than men and has enormous personal, social, and economic impact, morbidity, and excess mortality (3, 4). RA pathogenesis is still incompletely understood, but involves a series of 'hits' in genetically-predisposed individuals, with upregulation of inflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor-α (5). Early diagnosis and aggressive treatment can improve outcomes, although disease modifying anti-rheumatic drugs are potentially toxic and long-term joint destruction and systemic comorbidities remain common (3, 6). As costs of treatment, disability, and lost productivity are high, early identification of those at high risk, and improved understanding of RA disease mechanisms to enable targeted and personalised therapies are urgent research goals (7, 8).

Clonal haematopoiesis (CH) is the clonal expansion of somatically mutated haematopoietic stem cells in people without haematologic malignancy. CH genetic mutations confer selective advantage to stem cells and have been associated with aging and increased production of inflammatory cytokines, as well as with increased risk of cardiovascular disease (CVD) and haematologic malignancies, especially myeloid neoplasia (9-11). CH is detectable in the peripheral blood using whole exome sequencing (WES) as mutated stem cells differentiate into circulating granulocytes, monocytes, and lymphocytes. When these mutations are detected at ≥2% variant allele frequency (VAF) in those without myeloid neoplasia, it is defined as clonal haematopoiesis of indeterminant potential (CHIP), reflecting the increased risk of malignancy (9, 10, 12). Rare in healthy people prior to age 40, CHIP increases with age as somatic mutations accumulate, reaching ~10% prevalence in those ≥70 years old (10, 11).

CHIP encompasses several distinct genes that are recurrently somatically mutated in both large healthy population cohorts and patients with myeloid neoplasia. Within many cohorts, the most commonly mutated genes are in epigenetic regulators, *e.g. DNMT3A*, *TET2*, and *ASXL1*; other mutations include cellular growth signalling (*JAK2*), DNA damage response (*TP53*, *PPM1D*), and splicing factors (*SF3B1, SRSF2)* (9, 10, 13-16). Clones with mutations in *TET2, DNMT3A, JAK2*, and other 'driver' genes in particular, expand, affecting myeloid cells, such as monocytes and macrophages, increasing levels of IL-1β, IL-6, and other inflammatory cytokines, and upregulating systemic inflammation (17, 18). In recent studies, CH has been associated with prevalent or incident rheumatic diseases, including VEXAS syndrome, giant cell arteritis, and gout (19-21). One past study reported high CH prevalence among 59 patients with prevalent RA treated with glucocorticoids and immunosuppressants at Helsinki University (22). Thus, we hypothesised that CHIP mutations might be associated with increased risk of RA, a systemic autoimmune disease that also increases with age characterised by high levels of systemic inflammation, even prior to clinical diagnosis. A relationship between CHIP and RA is potentially bidirectional, as systemic inflammation preceding RA diagnosis might contribute to the accumulation of CHIP, and/or CHIP-driven inflammation might contribute to the onset of RA.

Methods

Study population and incident RA outcome identification

We tested our hypothesis in the UK Biobank *Exomes* dataset. The UK Biobank prospective study consists of 502,629 adults aged 40-69 years recruited 2006–2010 from 22 United Kingdom medical centres (23, 24). All participants provided written informed and consent for linkage to medical records, blood collection, and genetic studies. Participant surveys were collected at baseline and included questions about lifestyle factors, smoking, alcohol intake, and body mass index (BMI). At the baseline visit, blood samples for DNA (45mL, EDTA tubes) were collected and immediately processed for freezing in aliquots per standard-

ised protocol (25). Details regarding this cohort have been described elsewhere in detail (23). De-identified data were obtained via a materials transfer agreement from the UK Biobank. All aspects of this study were approved by the Mass General Brigham Institutional Review Board.

For this analysis, baseline exclusions included any prevalent myeloid neoplasia, to identify CHIP by definition, and prevalent RA (self-reported at baseline, any RA ICD codes before or at baseline) (26). We also excluded those taking any of the conventional or biologic disease modifying biologic drugs identifiable in the UK Biobank data (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, cyclosporine, or adalimumab) to mitigate the possibility of associations being driven by these common RA medications. We identified cardiovascular disease (CVD, composite of myocardial infarction, coronary revascularisation, or stroke) type 2 diabetes, and hypercholesterolaemia from participant surveys and International Classification of Diseases-9th revision (ICD-9) and ICD-10 billing codes occurring in the baseline period. Serum C-reactive protein (CRP) and creatinine (mg/dl) were measured on collected blood at baseline.

Incident RA occurring after baseline was the study outcome. As RA is a chronic rheumatic disease that is diagnosed and managed in the outpatient setting, we restricted the sample population to the 45% of the sample who had linked general practice (GP) outpatient records to accurately identify the date of incident RA (27, 28). We identified new onset RA using ≥2 UK Biobank GP database codes for RA (online Supplementary file: Appendix A) on separate days, the first code belonging to a new onset category, rather than a follow-up or complication of disease code. Participants were followed in the GP outpatient records, and hospitalisation and death records through December 2018 for this analysis.

Whole exome sequencing and identification of CHIP

Exomes of UK Biobank participants were sequenced from blood-derived DNA at the Regeneron Genetics Center (29). Exomes were captured by Integrated Data Technologies' (IDT's) xGen probe library and sequenced on the Illumina NovaSeq platform. Sample-specific FASTQ files were aligned to the GRCh38 reference. The resultant binary alignment file (BAM) containing the genomic information was evaluated for duplicate reads using the Picard3 MarkDuplicates tool and then converted by SAMtools to CRAM files that, after going through quality controls, were submitted to the UK Biobank data repository for distribution. CHIP detection was conducted through using GATK Mutect2 software (https://software.broadinstitute.org/gatk). Participants were annotated as having putative CHIP if the output contained at least 1 of a prespecified list of putative CHIP variants in genes anticipated to cause myeloid malignancy at a VAF of >2% or >10%. Common sequencing artifacts and germline variants were excluded (30, 31).

We studied CHIP in the 8 most commonly mutated genes previously identified in population-based studies: *DNMT3A, TET2, ASXL1, JAK2, PPM1D, TP53, SF3B1,* and *SRSF2* (10, 11, 17, 32). We examined two VAFs in relation to risk of incident RA, >2% and >10%, reflecting carriers of large CHIP clones, which has been associated with higher risk of CVD, atherosclerosis, and myeloid neoplasia in prior studies (10).

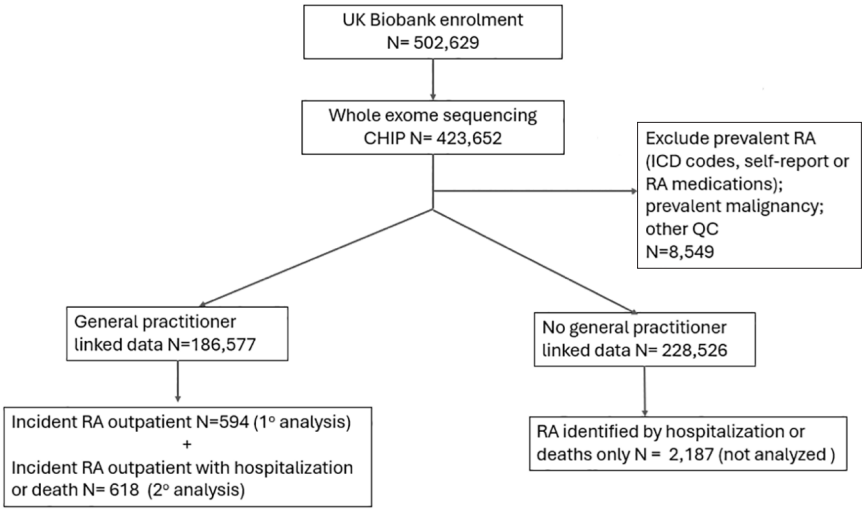

Fig. 1. Flow diagram demonstrating identification of participants with incident rheumatoid arthritis and CHIP data in the UK Biobank.

Statistical analyses

We employed bivariable tests of significance at baseline, t-tests and Chi-squared tests, to examine the characteristics of the populations with and without baseline CHIP mutations and to compare those who later did or did not develop RA, including unadjusted baseline prevalence of CH mutations in both groups. We then used Cox regression models to calculate hazard ratios (HR) (95% confidence intervals) for incident RA according to any CH mutations at 2% VAFs, adjusted for baseline age, sex, race and top 10 genetic principal components. Primary analysis included those identified as incident RA using only the outpatient GP linked data, as above and a secondary analysis included those who had at least one outpatient encounter for RA prior to a second encounter that was a hospitalisation or death with an RA ICD code. We constructed cumulative incidence curves to examine the accumulation of any of the CHIP mutation at VAF >2% over time in those who did *versus* did not develop RA. Sample sizes <5 were suppressed per UK Biobank privacy guidelines.

Results

After exclusions, we studied 186,577 people with baseline WES and genotyping data, surveys, and linked outpatient medical records in this analysis (Fig. 1). Median overall follow-up in the cohort was 7.1 (IQR 6.4–8.0) years. Any of the eight CHIP mutations at >2% VAF

was present in 11,731 participants at baseline. Table I displays the baseline cohort characteristics of this cohort and the presence of baseline CHIP mutation at the >2% VAF threshold. Mean age at enrolment was 3.56 years older in those with baseline CHIP (59.88 *vs*. 56.32 years). Also as expected, a higher proportion of those with CHIP mutations at baseline had ever smoked, had prevalent cardiovascular disease and hypercholesterolaemia, and their mean CRP was slightly higher.

For the primary analysis, we identified 594 participants (0.32%) who later developed incident RA in the outpatient GP data (Table II). The median (IQR) follow-up time in the cohort was 7.1 (6.4–8.0) years and median time to the onset of RA was 3.9 (2.0–5.6) years. Among the 594 participants identified as having incident RA using the outpatient linked data, 304 (51%) also had later codes for RA in hospitalisation or death data. Fewer of those who developed incident RA were male, while more had ever smoked, had higher mean BMIs, and were more likely to have hypercholesterolaemia at baseline. In unadjusted comparisons, any CHIP (at the 2% VAF 6.3% *vs*. 6.4% of those who later developed RA), and *DNMT3A, TET2* mutations at the 2% or 10% VAF threshold were not present in significantly higher proportions of the incident RA population at baseline. The *SF3B1* mutation was slightly more common in those who later developed RA at the 10% VAF (p=0.02), but not at the 2% VAF threshold (p=0.06), although with very low prevalence in both populations. Additionally, in Cox models neither the presence of CHIP at the > 2% threshold, HR 0.95 (95%CI 0.69–1.33), nor the >10% threshold, HR 1.23 (95%CI 0.80–1.88), were associated with risk of incident RA. Cumulative incidence curves are shown in Figure 2 and display that the risk of RA was low overall and no different among those with *versus* without CHIP at VAF >2% at baseline. In the secondary analyses, 24 more individuals were identified who had a hospitalisation or death ICD code for RA occurring after a first outpatient code for RA. Results of analyses including the total of 618 individuals were practically unchanged (results not shown).

Table I. Baseline characteristics of the UK Biobank study population with linked general practice follow-up, according to baseline CHIP mutation (n=189,844).

	None of the 8 CHIP mutations (n=174,846)	Any of the 8 CHIP mutations VAF >2% (n=11,731)	p*
Age in years, mean (SD)	56.32 (8.02)	59.88 (7.04)	<0.001
Male (%)	80460 (46.0)	5456 (46.5)	0.306
White British ancestry (%)	148782 (85.1)	10116 (86.2)	0.001
Ever smoked (%)	77364 (44.2)	5809 (49.5)	<0.001
Body Mass Index, kg/m^2, mean (SD)	27.48 (4.75)	27.58 (4.62)	0.036
Type 2 diabetes (%)	4002 (2.3)	320 (2.7)	0.002
Cardiovascular disease (%)	5970 (3.4)	583 (5.0)	<0.001
Hypercholesterolaemia (%)	36138 (20.7)	3013 (25.7)	<0.001
C-reactive protein, mg/L, mean (SD)	2.53 (4.20)	2.70 (4.37)	<0.001
Creatinine, mg/dL, mean (SD)	0.82 (0.21)	0.83 (0.27)	<0.001

CHIP mutations: *DNMT3A, TET2, ASXL1, JAK2, PPM1D, TP53, SF3B1*, and *SRSF2*.
* t-tests for continuous variables; Chi-square for categorical variable.s

Table II. Baseline characteristics of the UK Biobank study population with linked general practice follow-up, according to Baseline CHIP mutation and later incident rheumatoid arthritis (RA) (n=189,844).

	Incident RA (n=594)	No Incident RA (n=185,983)	p*
Age in years, mean (SD)	57.98 (7.56)	56.54 (8.01)	<0.001
Male (%)	196 (33.0)	85720 (46.1)	<0.001
White British ancestry (%)	488 (82.2)	158410 (85.2)	0.05
Ever smoked (%)	319 (53.7)	82854 (44.5)	<0.001
Body mass index, kg/m^2, mean, (SD)	28.19 (4.70)	27.48 (4.74)	<0.001
Type 2 diabetes (%)	14 (2.4)	4308 (2.3)	1
Cardiovascular disease (%)	22 (3.7)	6531 (3.5)	0.89
Hypercholesterolaemia (%)	162 (27.3)	38989 (21.0)	<0.001
C-reactive protein, mg/L, mean (SD)	4.09 (5.85)	2.54 (4.21)	<0.001
Creatinine, mg/dl, mean (SD)	0.78 (0.17)	0.82 (0.21)	<0.001
CH Mutations >2% VAF			
Any CH (%)	38 (6.4)	11693 (6.3)	0.98
DNMT3A	25 (4.2)	6414 (3.4)	0.37
TET2	7 (1.2)	2303 (1.2)	1
ASXL1	**	1131 (0.6)	0.27
JAK2	**	143 (0.1)	1
PPM1D	**	325 (0.2)	1
TP53	**	276 (0.1)	1
SF3B1	**	112 (0.1)	0.06
SRSF2	**	142 (0.1)	1
CH Mutations >10% VAF			
Any CH (%)	22 (3.7)	5331 (2.9)	0.27
DNMT3A	14 (2.4)	2674 (1.4)	0.09
TET2	5 (0.8)	1028 (0.6)	0.50
ASXL1	**	582 (0.3)	0.32
JAK2	**	140 (0.1)	1
PPM1D	**	122 (0.1)	1
TP53	**	106 (0.1)	0.78
SF3B1	**	80 (0.0)	0.02
SRSF2	**	93 (0.1)	1

* t-tests for continuous variables; Chi-square tests for categorical variables **cell sizes <5 suppressed per UK Biobank policy.

Discussion

In this UK Biobank-based study of CHIP mutations of individuals followed before the onset of RA, we investigated CHIP in eight commonly somatically mutated genes, in particular *TET2, TP53, and SF3B* mutations, in association with risk of incident RA. This may be due to a smaller sample size than we first anticipated, although the population was still large with

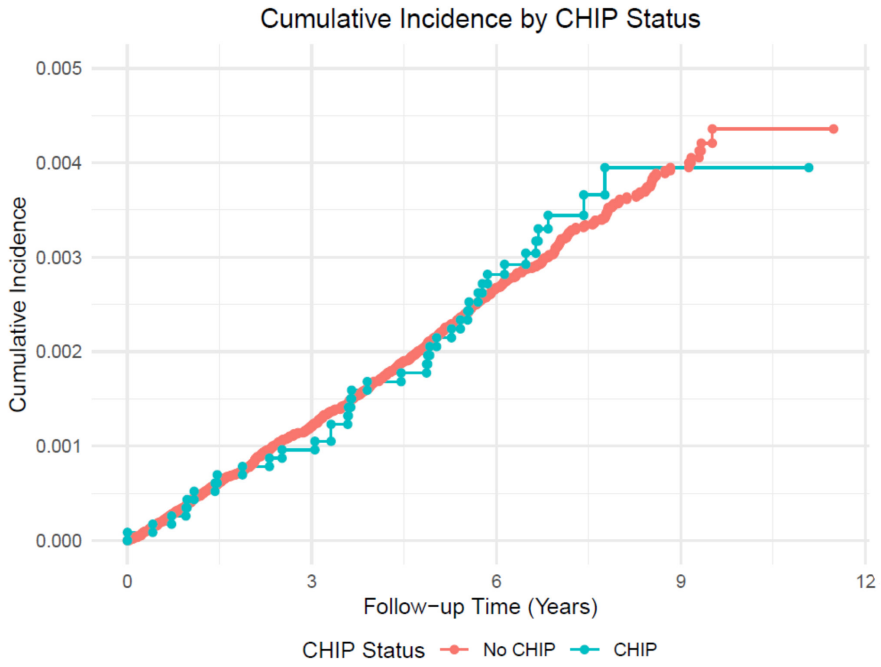

Fig. 2. Cumulative incidence of rheumatoid arthritis by baseline presence of any of eight most common CHIP mutations >2% variant allele fraction among 186,577 participants in the UK Biobank.

>186,577 individuals followed for a median of 7.1 years. Follow-up among participants in the UK Biobank has not been conducted through linkage of all medical records, and at this time only a segment of approximately 45% of the baseline enrollees are followed through their linked outpatient GP records (27). As RA is a predominantly outpatient diagnosis, we paid scrupulous attention to defining the date of incident disease as the first code for RA from outpatient (GP) or inpatient records among those with linked and available GP records, and without evidence of prevalent RA or RA medications at baseline. Unlike incident cardiovascular events, which are likely to be captured in inpatient records as patients are hospitalised, RA is a primarily outpatient disease and many patients are never hospitalised for it and it is a rare cause of death. We realised that defining the date of 'incident RA' as the first hospitalisation or death linked to RA among those without earlier outpatient records to establish the incident date would falsely induce a strong association with CHIP at baseline, as CHIP is already known to be strongly associated with morbidity and mortality from several causes (9, 13, 15, 17, 33).

There are few past studies of CH and RA and there was a strong biologic rationale for this study. Within the *Health and Anaemia* cohort (n=1,004), CH was associated with CVD, death, and 'rheumatological disease' and CH was reported in 4/17 (24%) subjects with prevalent RA (34). In a small study of 59 patients with prevalent RA (mean age 58 years), 17% had CH, but again no age-matched controls were included (22). CVD, haematologic and other malignancies, and all-cause mortality are elevated among those with RA (3). Elevated CVD risk is observed even prior to RA diagnosis, attributed to systemic inflammation via cytokine and chemokine upregulation (3, 35, 36). Systemic inflammation, driven by monocyte and macrophage overproduction of inflammatory cytokines and chemokines, is thought to link CHIP mechanistically to accelerated CVD (9, 37). Like CVD, RA is characterised by systemic inflammation, often at high levels. RA develops in a series of stages over time, with RA serologies and elevated systemic inflammatory cytokines and chemokines detectable years prior to diagnosis (38-41). However, in this initial study examining CHIP and risk of developing incident RA, employing a large population-based cohort study with rich data and DNA samples banked prior to the onset of RA and follow-up through linked GP and hospital records for many years, we did not find an increase in CHIP mutations prior to incident RA diagnoses compared to those who did not develop RA. The lack of strong relationship between CHIP and RA risk may be due to the effect of CHIP in upregulating the inflammatory functions of myeloid cells, *e.g.* macrophages and monocytes, whereas dysregulated adaptive immune responses, characterised by production of autoantibodies such as anticitrullinated protein antibodies (ACPA) and rheumatoid factor (RF), as well as T cell-mediated inflammation, may be more important in driving early in particular seropositive RA. However, this hypothesis deserves further investigation.

Limitations of the study include that it was performed in a UK-only, predominantly White British population and findings will need to be replicated in a more diverse population. The identification of incident RA using these codes has not been validated in the UK Biobank and we were very conservative in classifying RA and may have missed cases who were never received billing codes related to RA from their GPs, only specialist providers. However, past studies have shown acceptable performance of similar algorithms using two codes separated in time in other cohorts (42, 43). We performed a secondary analysis including RA-related hospitalisation or death ICD codes as well, again at least two separate RA-related codes, which increased the number of incident RA cases to 618, but did not alter the study findings. We limited our entire analysis to the subcohort of UK Biobank participants who had linked GP data and there is no reason to believe that the selection process into this sub-cohort was dependent on the exposure or the outcome in this study. We acknowledge that in doing so we not only limited the sample size and statistical power for the analyses, but also may have influenced the external generalisability of this smaller complete cohort to individuals worldwide who are at risk of developing RA. We examined RA without specifying seropositivity as ACPA and RF results were not available in follow-up and unfortu-

nately billing codes were not specific as to RA serostatus. The relatively short follow-up for the onset of RA limited the ability to examine CHIP in relationship to RA risk by stratified time period prior to onset or in different age windows. However, as we found no overall relationship of this irreversible genetic marker with RA risk in the period closest to disease onset, it is doubtful that its presence in earlier time periods would have been statistically related to the outcome.

While past studies in the UK Biobank have examined baseline factors and risk of 'incident' RA using the entire UK Biobank population, those studies may have reported associations that were actually between baseline factors and the risk of hospitalisation and death, rather than risk of incident RA (44-46). We thus restricted our analyses to the population that had more complete outpatient GP records, as well as linkage to hospitalisations and deaths. Overall, these analyses do not point to the presence of CHIP prior to the onset of RA or as a useful biomarker of the risk of RA, although given the confluence of risk factors for both RA and CHIP, it is likely that CHIP increases in prevalence after the onset of this systemic inflammatory disease.

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