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Genetic Predisposition to Clonal Hematopoiesis

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Clonal hematopoiesis (CH), the clonal expansion of a hematopoietic stem cell (HSC) and its progeny driven by somatic mutations, is a common phenomenon that becomes progressively more prevalent with age to affect the majority of people aged 70 years or older.[1–4] CH is associated with increased risks of hematological cancers[1] and several nonhematological diseases,[5–11] such that an improved understanding of its pathobiology can help manage or prevent some of these consequences. However, despite a flourishing interest in CH, our understanding of how somatic mutations impart an HSC with enhanced fitness to drive clonal expansion remains very limited. Studies of the heritability of CH can help identify genetic pathways involved in the genesis of the phenomenon and, by extension, improve our understanding of its prognosis, natural history, disease associations, and potential therapeutic vulnerabilities.

Somatic mutations begin to accumulate in human cells from the time the zygote first divides and continue to do so throughout life, generating a genetic heterogeneity within tissues known as somatic mosaicism.[12] This progressive accumulation of somatic mutations is associated with an increased risk of cancer and other age-related diseases.[13] As a result, normal tissues accumulate hundreds to thousands of mutations per cell over an individual's lifetime. Most of these mutations have a neutral effect on cell growth, a few have a deleterious effect and fewer still impart the host cell with an increased fitness leading to clonal expansion (driver mutations). Such clonal expansions are ubiquitous in dividing tissues and can lead to cancer development, the likelihood of which is influenced by both genetic variation and environmental factors, and chance.[14,15]

The rate of acquisition of somatic mutations varies depending on the tissue and cell type.[16] HSCs acquired ≈17 somatic mutations per year after birth,[17] which is equivalent to ≈2–3 new coding mutations per decade.[18,19] When one of these mutations is capable of enhancing HSC fitness, a clonal expansion can ensue a phenomenon known as CH, which becomes increasingly common with age, rising in prevalence from 2% to 5% of people <30 years and to >30% of those over 70 years, depending on assay sensitivity.[20] Most CH carriers remain unaware of their status, but 1%–2% go on to develop a hematological malignancy such as a myeloproliferative neoplasm, myelodysplastic syndrome (MDS), or acute myeloid leukemia. The likelihood of progression escalates as the clonal size and mutation number increase, and is greater with mutations in high-risk genes such as *SRSF2*, *U2AF1*, *IDH1*, and *IDH2*.[21] In addition to myeloid neoplasms, CH has also been associated with an increased risk of all-cause mortality and with nonhematological illnesses such as cardiovascular diseases, liver disease, solid cancers, chronic obstructive pulmonary disease, and gout.[1,2,5–11] In some instances, the disease risk may be mediated by abnormal mature cell progeny (eg, macrophages) of the CH clone,[7] but in others the basis of the association is not clear.[5]

The somatic mutations responsible for CH affect a selected set of genes previously identified as drivers of myeloid malignancies, including those coding for epigenetic regulators DNMT3A and TET2; the chromatin regulator ASXL1; splicing factors such as SF3B1, SRSF2, and U2AF1; DNA damage response proteins such as TP53 and PPM1D; and regulators of growth signaling, such as JAK2, GNAS, CBL, and GNB1.[1–4] Collectively, these 12 genes account for the great majority of cases of CH, with the remaining cases driven by a long tail of >30 genes. Different forms of CH can be driven by structural somatic variants, such as mosaic chromosomal alterations[22] or mosaic loss of chromosome Y,[23] or arise in the absence of identifiable driver mutations, potentially through genetic drift[2,24] or unidentified rare/weak drivers.[17] Finally, although CH is mainly associated with the myeloid linage, it can also affect the lymphoid lineage and be driven by genes mutated in lymphoid malignancies.[25]

Notably, while CH becomes more common with advancing age, the relationship between CH prevalence and age differs between different driver mutations.[3,5,26] For example, the prevalence of *DNMT3A*-CH rises steadily up to the seventh decade, but then more slowly. By contrast, *TET2*-CH continues to rise steadily throughout life and as a result becomes more common than *DNMT3A*-CH in octogenarians. More strikingly, CH driven by splicing factor gene mutations is rare before the age of 50 years and rises rapidly after the seventh decade,[3,5,10] reflecting the rapid rise in MDS incidence beyond this age. These epidemiological trends in CH prevalence appear to be driven by changes in driver-specific clonal dynamics with advancing age.[26] For example, *DNMT3A*-mutant clones preferentially expand early in life and display slower growth in old age, while splicing gene mutations only appear able to drive clonal expansion later in life when they drive some of the fastest growing clones. On the contrary, *TET2*-mutant clones show minimal

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age-dependency.[26] These findings suggest that certain mutations may rely on age-associated changes to promote clonal growth, and that somatic mutations may not be the sole factor determining the development and progression of CH.

The mechanisms by which driver gene mutations impart a clonal advantage on HSCs and lead to CH remain poorly understood. However, it is evident that most CH mutations do not affect classical oncogenes, as is the case in established hematological cancers, and result in relatively subtle molecular consequences. Reflecting this, mutant HSCs are not significantly different to normal ones and expand only slowly over years/decades.[26] There is also clear evidence that noncell autonomous factors influence CH development. The best examples of this are as follows: (1) postchemotherapy CH, driven by mutations in proapoptotic genes such as *TP53* and *PPM1D*[27]; and (2) *PIGA*-driven CH in patients with autoimmune aplastic anemia, where loss of *PIGA* enables an HSC to evade immunological attack.[28] In addition, exposure to environmental factors, such as smoking, also increases the risk of CH,[5,29] although the mechanism for this remains unclear.

While somatic mutations and environmental factors are critical in CH development, it is becoming clear that inherited genetic variation also has a significant role to play, as it does for a range of human diseases. In this regard, the establishment and study of large-scale genetic studies based on cohorts of tens or hundreds of thousands of individuals has led to the identification of multiple genetic variants associated with an increased risk of CH (Figure 1). Focusing on CH driven by single-gene mutations (and indels), >25 different loci have been found to be associated with increased risk of CH[5,6,10,24,29] (Figure 1).

HERITABLE VARIATION AND CH

A genome-wide association study (GWAS) in a cohort of >10,000 Icelanders from deCODE genetics was the first one to describe a common germline deletion in the intron 3 of the telomerase reverse transcriptase (*TERT*) gene that increased the risk of CH.[24] Since then, multiple GWAS using large cohorts, such as NHLBI Trans-Omics for Precision Medicine (TOPMed), UK Biobank (UKB), and Geisinger Health System (GHS), have identified multiple germline variants in the *TERT* locus to be associated with increased risk of CH.[5,6,10,29] *TERT* encodes a catalytic (reverse transcriptase) subunit of telomerase, which is responsible for maintaining the length of telomeres. Telomerase is active during early human development, but is transcriptionally silenced in a tissue-specific manner between 12 and 18 weeks of gestation in all somatic tissues, although stem cells of proliferative tissues such as blood do retain some expression.[30] Also, *TERT* expression is reactivated in ≈85%–90% of cancers, where it is thought to be critical in enabling them to divide inexorably without suffering the normal telomere attrition experienced by nontransformed cells.[31]

The potent association of multiple genetic variants in the *TERT* locus with an increased CH risk revealed an important role of telomeres in facilitating clonal expansion of mutant HSCs. Yet, deCODE study participants with CH were found to have lower leukocyte telomere length than controls.[24] This finding was replicated using both TOPMed and UKB cohorts, although it varied by driver gene mutation.[32] Mendelian randomization analysis using >200 k UKB individuals proposed that longer telomere length is causal risk factor of CH,[5] and analysis combining both TOPMed and UKB cohorts revealed that this relationship displays a bidirectional regulation: longer telomeres cause CH, whereas CH leads to telomere shortening.[32] Based on the multiple associations of *TERT* with blood cancers and other age-related diseases, more studies are required to elucidate the precise mechanisms through which telomere biology contributes to the development of CH and determine its role in malignant progression.

Beyond *TERT*, GWAS analyses of the TOPMED, UKB, and GHS cohorts have identified multiple additional common germline variants associated with CH located at the *PARP1*, *SMC4*, *CD164*, *ATM*, and *TP53* gene loci, among others[5,6,10] (Figure 1). Although the specific mechanisms through which these variants affect the risk of CH remain unknown, fine-mapping and gene prioritization approaches have identified target genes associated with DNA damage repair, stem cell migration, and oncogene signaling.[5] Also, many of these variants are associated with altered expression levels of neighboring or distant genes (expression quantitative trait loci [eQTL]).

The ability to explore data from hundreds of thousands of individuals has also allowed researchers to investigate CH by driver gene mutation. As a result, many common and novel loci associated with the risk of CH driven by genes such as *DNMT3A*, *TET2*, and *ASXL1*[5,6] have been identified (Figure 1) and are discussed below.

DNMT3A-CH

CH driven by somatic *DNMT3A* mutations (DNMT3A-CH) had the largest number of significantly associated genomic loci, most of which have also been found to be associated with overall CH, which is unsurprising given that >60% of CH cases are caused by mutations in *DNMT3A*. DNMT3A-CH-specific variants include those at the *TCL1A*, *RABIF*, *ABCC5*, *MYB*, *OBFC1*, and *FLT3* loci (Figure 1). Also, some variants associated with the overall risk of CH seem mostly driven by *DNMT3A*, such as those in the loci of *PARP1*, *SETBP1*, *LY75-CD302*, and *BCL2L1*, among other genes. In general, the minor alleles (ie, the variants found in the minority of individuals) are associated with increased risk of CH; however, some minor alleles, such as those in the *PARP1* and *LY75* loci, are associated with decreased CH risk.[5,6]

Several variants in the *PARP1* locus have been found to be associated with reduced *PARP1* gene expression (eQTL),[33] including one that represents a missense germline mutation in the catalytic domain of PARP1, associated with reduced activity (rs1136410; p.V762A).[5,6] The PARP1 (poly-ADP-ribose polymerase 1) protein plays a key role in DNA damage repair, through its ability to add poly-ADP-ribose chains to DNA repair proteins and to itself, facilitating the recruitment of downstream DNA repair factors at DNA lesions.[34] PARP1 has also been found to be involved in other cellular processes, such as chromatin remodeling, transcriptional regulation, and cellular senescence, which contribute to tumor suppression or promotion depending on the context.[35] Due to the important role of PARP1 in DNA repair, PARP inhibitors (PARPi) have been approved for the treatment of certain types of ovarian, breast, and prostate cancers associated with defective homologous recombination pathways.[36] Notably, the rs1136410 variant has been identified as a prognostic factor and predictive biomarker for MDS.[37] These data suggest that PARPi may have the effect of reducing or reversing CH clonal expansion of clones driven by *DNMT3A* mutations.

Similarly, variants in the *LY75* locus have also been associated with reduced risk of DNMT3A-CH. LY75 (lymphocyte antigen 75) encodes an endocytic receptor, known as DEC-205, that participates in the innate immune response. Some variants associated with reduced risk of CH include a common missense variant (rs78446341-A; p.P1247L) located in the extracellular domain and a rare missense variant (rs147820690-T; p.G525E) located in the receptor ligand domain for a type C lectin, suggesting that blocking this interaction may curb the expansion of *DNMT3A*-CH. Interestingly, variants in both *PARP1* and *LY75* loci have been associated with multiple blood traits, including platelet counts.[38,39]

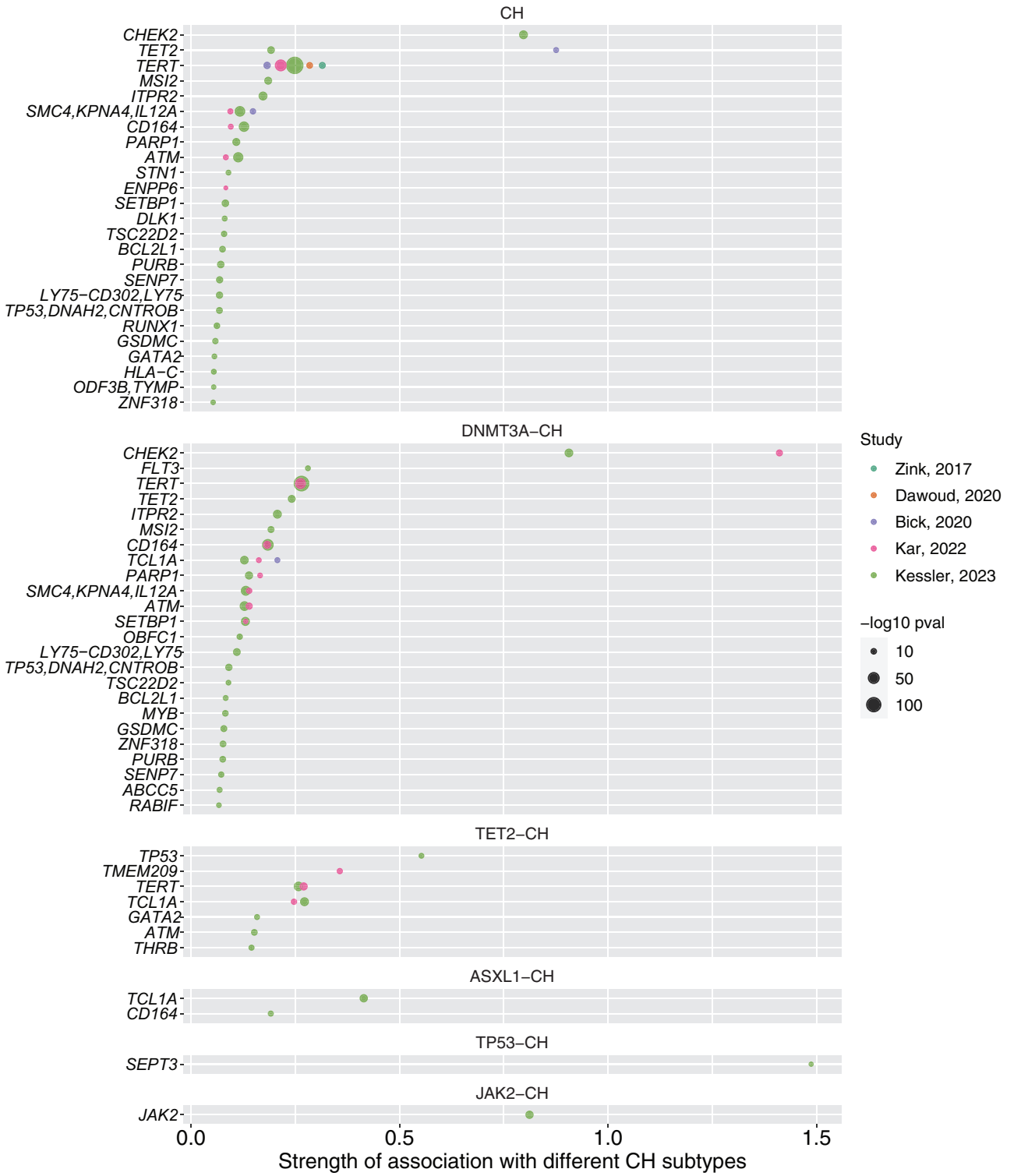

Figure 1. Germline variants associated with CH. List of variants associated with overall CH and driver-specific CH: DNMT3A-CH, TET2-CH, ASXL1-CH, TP53-CH, and JAK2-CH. Dots depicting the strength of association with genetic variants are colored according to the study in which they were described, and their size corresponds to the negative logarithm of the *P*-value obtained. For each subplot, genes are sorted by the absolute beta value, which reflects the effect size of the genetic association. CH = clonal hematopoiesis.

OTHER CH DRIVERS

Analysis of *TET2*-driven CH (TET2-CH) identified some variants shared with overall CH, such as those in the *TERT*, *ATM*, and *TP53* gene loci, and specific variants in *THBR*, *GATA2*, *TCL1A*, and *TMEM209* (Figure 1). For ASXL1-CH, only 2 significant loci were identified at *CD164* and *TCL1A* and *TP53*-CH only 1 locus, *SEPT3*. *JAK2*-CH was associated with polymorphisms in the *JAK2* locus itself (Figure 1). The small number of loci detected in these less common forms of CH is probably due to a lack of statistical power, given the smaller number of individuals with these mutations.

Among the many variants associated with different CH subtypes, those located at the *TCL1A* locus were only identified in *DNMT3A*-, *TET2*-, and *ASXL1*-CH, but not in the overall

CH analysis. This was because the same variants are associated with opposite effects in different CH subtypes, namely increased risk of *DNMT3A*-CH, but a reduced risk of *TET2*- and *ASXL1*-CH[5,6,10] (Figure 1). *TCL1A* (T-cell leukemia/lymphoma 1A) is primarily expressed in lymphoid tissues and has been implicated in the development of T-cell leukemia. Also, it has been reported that it can inhibit *DNMT3A* function in B-cell chronic lymphocytic leukaemia.[40] A recent study has showed that *TCL1A* activation is an important mediator of clonal expansion in CH driven by *TET2* and *ASXL1* mutations, with these mutations associated with promoter demethylation and increased *TCL1A* mRNA expression specifically in carriers if the inherited risk allele.[41] In addition, one of these variants is also associated with a reduced risk of LOY clonal mosaicism.[42]

Similarly, variants in the *CD164* locus are associated with an increased risk of *DNMT3A*- and *ASXL1*-CH, and a trend toward a decreased risk of *TET2*-CH[5,6] (Figure 1). *CD164* encodes a transmembrane sialomucin protein that regulates the adhesion and migration of HSCs,[43] suggesting important roles for these processes in the CH pathogenesis. The presence of loci with opposite associations with different CH subtypes mirrors differences in age-related prevalence and growth dynamics between CH subtypes.[26] Additional studies will be required to address the effect of these genes/variants and identify whether other factors collaborate with these variants in modulating the risk of each CH subtype.

RARE VARIANT GWAS

In addition to these common variants (present in ≥1% of the population), 2 GWAS analyses also identified a rare frameshift variant in the tumor suppressor and DNA repair gene *CHEK2*, to be significantly associated with overall CH and CH driven by *DNMT3A*[5,6] (Figure 1). Furthermore, *ATM* and *CTC1*, involved in DNA damage and telomere maintenance, respectively, have also been associated with increased risk of CH via rare variant gene burden testing.[6] Collectively, these findings re-emphasize the importance of genome stability and telomere biology in CH pathogenesis.

CH AND ANCESTRY

Finally, it is important to mention that almost all published studies of genetic variants associated with CH involve individuals of European ancestry, as a result of their overrepresentation in large cohorts with deep genetic and phenotypic information, such as TOPMed and UKB. Many of the CH risk loci identified in European ancestry cohorts have been validated in either combined non-European ancestry groups[5] or in specific ancestries[6]; however, the lack of large non-European ancestry cohorts is making it difficult to identify new non-European ancestry-specific loci. The study of different human populations does not only offer the opportunity to discover the impact of variants that are common in specific ancestries, but can also give fundamental insights into CH pathogenesis across populations. An example of this comes from the TOPMed cohort, where a variant at the TET2 locus was associated with an increased risk of CH in individuals of African descent[10]; however, this finding could not be replicated in the UKB/GHS cohort where the risk allele is very uncommon.[6]

FUTURE DIRECTIONS

Since the identification of CH less than a decade ago, the field has expanded and evolved rapidly. While those who first searched for the phenomenon may have been primarily looking for the precursor of myeloid malignancies, it has become clear that CH is associated with several nonhematological diseases, in some of which it plays a pathogenetic role.[5,7–9,11] Furthermore, the unexpectedly high frequency of CH and that of equivalent clonal expansions in other organs/tissues propose a re-evaluation of the relationship between CH, aging, and cancer. Overall, it appears more accurate to view CH as an inevitable accompaniment of aging driven by the relentless force of natural selection on mutation-bearing HSCs. It is in this light that genetic predisposition to CH needs to be interpreted.

The studies performed so far in this area have revealed some intuitive associations between CH and loci involved in telomere maintenance, DNA damage, hematopoiesis, and oncogenesis, but others are more intriguing. Both categories will need to be investigated mechanistically in order to both understand how they promote CH and also to derive insights into possible therapeutic interventions both in the area of myeloid cancer prevention and the alteration of risk of CH-associated nonhematological diseases. As discussed earlier, some of the GWAS hits proposed areas of potential therapeutic intervention such as the associations with druggable targets like *TERT*, *PARP1*,[5] or FLT3.[24]

It should also be remembered that despite their large size, studies so far have not been able to give us sufficient insights into the heritable determinants of the less common forms of CH namely CH driven by mutations in splicing factor genes or genes involved in the DNA damage response such as*TP53*, *PPM1D*, and *BRCC3*. Advances here will need to rely on the use of new larger cohorts, the integration of existing ones or the application of new statistical methodologies such as Mendelian Randomization to identify variants associated with these less common, but higher risk forms of CH. Additionally, it is critical to investigate the heritable genetic basis of CH in individuals of non-European ancestry, not only because this may identify ancestry-specific associations, but also because it would harness untapped genetic diversity to reveal associations that cannot be discovered in European-only studies.

Moving forward, it can be anticipated that the increasing availability or large genetic datasets and the advent of new methodologies for their investigation will provide novel mechanistic insights into CH and somatic mosaicism in other tissues. Such findings will likely be directly relevant to the understanding of aging and the pathogenesis, prevention, or treatment of common pathologies including cancer, cardiovascular disease, and others.

AUTHOR CONTRIBUTIONS

PMQ and GSV wrote the article.

DISCLOSURES

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