New genetic loci associated with the risk of clonal hematopoiesis

Genetic and phenotypic analyses of data from over 400,000 participants in the UK Biobank identified 10 new loci associated with the development of clonal hematopoiesis and implicated DNA damage, oncogene signaling, telomere maintenance and blood cell homing in its pathogenesis. These findings can help to decipher the pathogenesis of clonal hematopoiesis and develop therapeutic approaches.

This is a summary of:
Kar, S. P. et al. Genome-wide analyses of 200,453 individuals yield new insights into the causes and consequences of clonal hematopoiesis. *Nat. Genet*. https://doi.org/10.1038/s41588-022-01121-z (2022).

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The question

Hematopoietic stem cells (HSCs) steadily acquire somatic mutations with advancing age. A small, well-defined subset of these mutations, most commonly affecting genes involved in epigenetic regulation (*DNMT3A*, *TET2* and *ASXL1*), splicing (*SF3B1* and *SRSF2*) and the DNA-damage response (*TP53* and *PPM1D*), can impart HSCs with a fitness advantage. This results in the common phenomenon of clonal hematopoiesis (CH) — the preferential proliferation of an HSC and its progeny driven by such mutations. However, the molecular basis of the fitness advantage remains poorly understood. Also, individuals with CH are at increased risk of blood cancers and some non-hematological diseases, such as ischemic cardiovascular disease and stroke[1], but data on the correlation between different CH subtypes and specific blood cancer types are lacking, and reports on the associations with non-hematological diseases diverge.

To investigate the molecular pathways involved in the development of CH and its causes and consequences, we analyzed linked genetic and phenotypic information from over 400,000 participants in the UK Biobank. In our study, the largest of its kind so far, we were able to both study CH collectively and investigate its major subtypes, including those driven by mutations in *DNMT3A* and *TET2*.

The solution

We leveraged exome sequence data to identify individuals with CH in the UK Biobank and used matched germline genotype data to perform genome-wide association studies (GWAS) for inherited susceptibility to CH, trans-ancestry analyses to demonstrate similar effects of the identified loci associated with overall CH across ancestry groups, and replication analyses to robustly validate such associations. We applied a range of post-GWAS methods including estimations of heritability and genetic correlation, gene-level and transcriptome-wide association testing, network analysis, fine-mapping, functional annotation and gene prioritization, and Mendelian randomization. We coupled these genetic studies to observational analyses, including a detailed investigation of the risks of specific blood cancer types associated with CH, harnessing the deep phenotyping of participants in the UK Biobank.

We identified 10 new genetic loci associated with CH risk (including several that were specific to CH subtypes such as *DNMT3A*-associated CH; Fig. 1), tripling the number of known genome-wide associations of significance across overall and subtype-specific CH[2]. Mendelian randomization analyses showed that smoking and longer leukocyte telomere length are causal risk factors for CH, similar to associations between these risk factors and other proliferative disorders such as cancer. Mendelian randomization also demonstrated that genetic predisposition to CH increases the risk of myeloproliferative neoplasia, several types of non-hematological cancer, atrial fibrillation, and epigenetic aging in white blood cells. Notably, two of the newly identified germline loci, *TCL1A* and *CD164*, showed inverse associations with the CH subtypes driven by somatic mutations in *DNMT3A* and *TET2*. That is, alleles at these germline loci were protective for *DNMT3A*-associated CH while increasing the risk of *TET2*-associated CH. This finding makes *TCL1A* and *CD164* prime candidates for roles in CH pathogenesis and mirrors recently described differences in the lifelong evolution of CH associated with *DNMT3A* and *TET2* mutations[3].

The implications

In-depth knowledge of the mutations that drive CH has not translated into an understanding of its mechanistic basis. The discovery of 10 new loci linked to the development of CH provides important clues into the cellular mechanisms involved in CH emergence, and enabled us to devise a CH genetic risk score, which was associated with the development of several solid cancer types in Mendelian randomization analyses. The biological basis of these observations alludes to shared mechanisms of clonal progression among different tissues or stem cells.

Our work also reveals that mutations in the main CH driver genes, *DNMT3A* and *TET2*, result in very different risks of progression to different myeloid malignancies, with some of the highest hazard ratios observed for the risk of developing myelodysplastic syndromes with CH driven by mutations in genes that encode components of the spliceosome.

The identification of the germline modifiers of somatic selection in CH proposes putative mechanisms underlying the phenomenon. Investigation of the identified genes and pathways has the potential to decipher the basis of somatic clonal evolution and its links to aging, malignancy and other diseases. In turn, such insights can catalyze therapeutic advances to avert, delay or modify the clinical sequelae of CH and equivalent somatic clonal phenomena in other tissues[4,5].

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EXPERT OPINION

"This is a well-designed and highly powered genetic study that comprehensively assesses the genetic backgrounds of clonal hematopoiesis". **Yukinori Okada, Osaka University, Suita, Japan.**

FIGURE

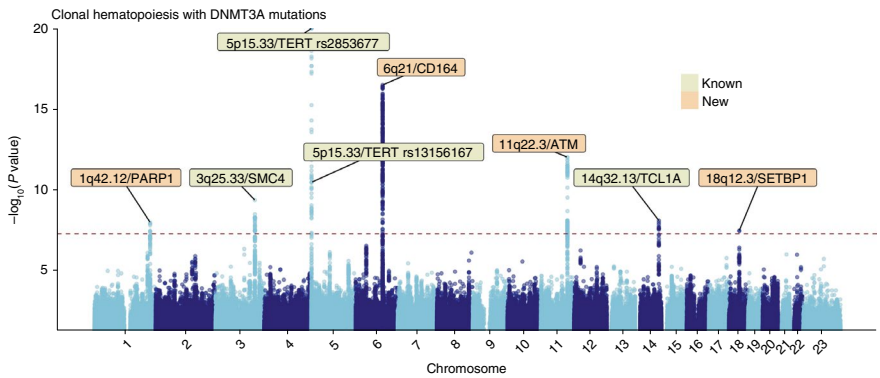

Fig. 1 | Manhattan plot of genome-wide associations between common germline variants and CH associated with *DNMT3A* mutations. The *y* axis indicates the strength of the associations; the *x* axis depicts the position on each chromosome. The dotted line indicates the genome-wide significance threshold of $P = 5 \times 10^{-8}$. Known (previously reported) and new loci are indicated by chromosomal location and potential target gene.

BEHIND THE PAPER

This paper began as a collaboration in the midst of the COVID-19 pandemic in the second half of 2020, and in many respects reflects our academic lives as scientists during the pandemic, when the virtual world replaced the physical one and meetings, even with members of our own groups, were held remotely. One of the authors (S.P.K.) has not yet met the other co-first author, Pedro M. Quiros, nor the last author (G.S.V.), in person. Our research collaboration — and indeed friendship — developed entirely over countless emails and video conferences. We look forward to celebrating the publication of this paper by finally meeting in person at a pub in Cambridge or Bristol! **G.S.V. and S.P.K.**

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FROM THE EDITOR

"Clonal hematopoiesis (CH) remains underexplored, so we were pleased to see a study that addressed its genetic and phenotypic associations so comprehensively. Moreover, the subtype-specific analysis could refine the way CH is stratified, thereby refining the way we approach it". **Safia Danovi, Senior Editor, *Nature Genetics*.**