Clinical genetics

CHIPping away at the genetic aetiology of clonal haematopoiesis

Reporting in *Nature*, Kessler et al. describe the use of exome sequencing to identify individuals with clonal haematopoiesis of indeterminate potential (CHIP), coupled with genetic association studies to discover new germline variants associated with particular CHIP subtypes and their links to particular health outcomes.

Clonal haematopoiesis — the age-related expansion of particular blood cell lineages — results from somatic mutations that confer a selective advantage to haematopoietic stem cells. In the absence of a haematological malignancy, this is referred to as CHIP. CHIP has previously been associated with increased risk of cardiovascular disease (CVD), infection and all-cause mortality, in addition to haematological malignancies. Thus, it is important to understand how germline variation might predispose to CHIP as a basis for understanding the biological mechanisms of CHIP and determining potential therapeutic targets.

Focusing on 23 well-defined, CHIP-associated genes, the authors used exome-sequencing data from 454,803 individuals from the UK Biobank (UKB) and 173,585 individuals from the Geisinger MyCode Community Health Initiative (GHS) to identify 27,331 and 12,877 individuals, respectively, with CHIP mutation carrier status (having single or multiple CHIP gene-specific somatic mutations).

Genetic association analyses were then performed to identify germline loci associated with CHIP carrier status. In total, 57 common variants in 24 loci (21 of which were previously unknown) were identified as having significant association with CHIP. In addition, the authors identified a rare frameshift variant of *CHEK2* that was significantly associated with CHIP. The cancer-associated genes *ATM* and *CHEK2*, as well as the telomere maintenance gene *CTC1*, were also associated with an increased risk of CHIP via rare variant gene burden testing.

Next, the authors separately analysed individuals with somatic mutations in one of eight of the most commonly mutated CHIP genes (but no other CHIP gene mutations) and identified genomic loci associated with particular CHIP subtypes, including some that were not significant in the overall CHIP association study. CHIP with somatic mutation of *DNMT3A* (*DNMT3A* CHIP) had the largest number of significantly associated genomic loci, most of which had variants that increased CHIP risk. Exceptions to this were *PARP1* and *LY75* variants, which decreased CHIP risk. Some genomic loci were associated with several CHIP subtypes, sometimes in an opposing manner; for example, *TCL1A* variants increased the risk of *DNMT3A* CHIP but decreased the risk of *TET2* CHIP or *ASXL1* CHIP. Together, the results show that different genomic loci can have shared, unique or opposing effects on CHIP subtypes.

Cross-sectional analysis of 5,041 health traits from the UKB showed, as previously reported, that CHIP carrier status is associated with cardiovascular, haematological, neoplastic, infectious, renal and/or smoking-related phenotypes. *ASXL1* CHIP was associated with the largest number of health traits. *DNMT3A* CHIP and *TET2* CHIP had opposing associations with haematopoietic phenotypes such as white blood cell count. Unexpectedly, body mass index and fat percentage were associated with CHIP carrier status — negatively with *DNMT3A* CHIP but positively with *TET2* CHIP and *ASXL1* CHIP. *PPM1D* CHIP was associated with an increased risk of severe COVID-19.

These results were complemented by longitudinal analysis of subsequent disease phenotypes in individuals with CHIP carrier status at the time of biobank enrolment and by Mendelian randomization. *TET2* CHIP carriers in the UKB had a significantly increased subsequent risk of CVD, although the risk estimate was lower than in a previous analysis of a smaller number of individuals and the risk of CVD was not replicated in the GHS cohort or by Mendelian randomization. Furthermore, an earlier finding of a cardioprotective effect of *IL6R* mutation in CHIP carriers was not replicated in the UKB or GHS cohorts.

Looking at cancer phenotypes, and excluding individuals with a previous cancer diagnosis, CHIP carriers had a significantly increased risk of developing blood cancer, particularly myeloproliferative neoplasms. CHIP carriers also had an increased risk of developing lung cancer, prostate cancer and non-melanoma skin cancer in the UKB, but only the lung cancer risk was replicated in the GHS cohort. The lung cancer risk was driven, in particular, by *DNMT3A* CHIP and *ASXL1* CHIP carriers and was independent of smoking status in both the UKB and GHS cohorts. Finally, all-cause mortality was significantly increased across *DNMT3A*, *TET2* and *ASXL1* CHIP subtypes.

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In summary, the large size of this study and the use of exome sequencing have enabled the identification of new genomic variants associated with CHIP and show the importance of considering CHIP subtypes separately. Although the study did not look at mechanisms directly, the loci identified offer some clues for further investigation. For example, *PARP1* variants that reduce PARP1 expression (which has a role in DNA repair) decrease the risk of *DNMT3A* CHIP; thus, PARP1-inhibitory drugs that have already been developed might limit the expansion of *DNMT3A* CHIP clones.

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Related article: Silver, A. J., Bick, A. G. & Savona, M. R. Germline risk of clonal haematopoiesis. *Nat. Rev. Genet.* **22**, 603–617 (2021)