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ORAL ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Ancestry-Specific Genetic Determinants of Clonal Haematopoiesis: A Comparative Analysis of 136,401 Admixed Americans and 419,228 Europeans

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Introduction:
Somatic mutations in blood stem cells can drive clonal expansion and result in clonal haematopoiesis (CH). CH is a precursor to myeloid malignancies, and is increasingly also recognised as a risk factor for non-malignant diseases. CH has been investigated in Europeans, but remains understudied in non-European populations. Here, we investigate the causes and consequences of CH in two large prospective cohort studies, specifically the Mexico City Prospective Study (MCPS) and UK Biobank (UKB). MCPS represents the largest CH study in a non-European population to date.

Methods:
Admixed Americans were identified from MCPS (n=136,401) while Europeans were identified from the UKB (n=419,228) participants. Somatic variant calling was performed using Mutect2 on whole exome sequencing (WES) data across a selected panel of genes to identify putative CH driver mutations. WES was performed at an average depth of 55x, and CH was defined using a variant allele frequency of ≥3%. Genome-wide association studies (GWAS) for CH were performed using imputed array data, and exome-wide association studies (ExWAS) and gene-level association analyses using WES data. Global/Continental-level ancestry was assigned based on peddy score ≥95% while local ancestry was inferred using RFMix (Ziyatdinov *et al.*, 2022).

Results:
The most recurrently mutated genes in MCPS and UKB were *DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *TP53*, *SF3B1* and *SRSF2*. The prevalence of CH increased progressively with age to approximately 8/22 (36%) detected as carriers at age 100 and above. CH was 40% more prevalent in age-matched Europeans (4.96%) compared to Admixed Americans (3.10%). Inter-population comparison revealed overall CH, *DNMT3A*-, *TET2*-, *ASXL1*-, *PPM1D*-, *TP53*-, *JAK2*-, and *SRSF2*-mutant CH to be more prevalent in UKB relative to MCPS (Figure A). Intra-population analysis of the Admixed American cohort further revealed that individuals with a higher fraction of European ancestry were at higher risk of overall CH, *DNMT3A*-, *ASXL1*-, and *SRSF2*-mutant CH, but not *TET2*-, *PPM1D*-, *TP53*-, and *JAK2*-mutant CH. These suggest differences in relative contribution of genetic, lifestyle or environment factors to specific CH genes.

CH GWAS performed in Admixed Americans recapitulated previously reported variants in Europeans, and also identified novel, ancestry-specific variants associated with CH risk, including SNPs upstream of *TCL1B* (rs968294563: OR=1.79, P=2.01x10^{-9}; rs187319135: OR=1.85, P=2.69x10^{-9}). Notably, *TCL1B* variants were associated with an increased risk of *TET2*- and *ASXL1*-mutant CH (rs968294563: OR=3.17, P=3.82x10^{-16} for *TET2*; OR=2.36, P=2.40x10^{-3} for *ASXL1*), but a decreased risk of *DNMT3A*-mutantCH (rs968294563: OR=0.51, P=6.32x10^{-4}) (Figure B). The minor allele frequency (MAF) of the most common *TCL1B* variant in Admixed Americans was 1.23% but was virtually absent in Europeans.

CH ExWAS can identify rare causal variants not captured by genotyping or imputation, and these variants may be in linkage disequilibrium with common variants detectable via GWAS. Indeed, ExWAS in Admixed Americans identified one rare SNP on the *TCL1B* promoter (rs774615666: OR=2.24, P=1.94x10^{-8}) that was associated with an increased risk of *TET2*-mutantCH (OR=4.19, P=2.77x10^{-10}) and a decreased risk of *DNMT3A*-mutantCH (OR=0.13, P=1.65x10^{-4}), mirroring our GWAS findings. The rs774615666 risk allele was >200-fold more common in Admixed Americans (MAF: 0.33%) compared to Europeans (MAF: 0.0011%) and was not in linkage disequilibrium with the previously reported *TCL1A* promoter CH risk SNP in Europeans (Weinstock *et al.*, 2023).

Meta-analyses were performed using 555,629 individuals, from both MCPS Admixed American CH GWAS and UKB European CH GWAS. Of the 11 loci reported for overall CH, one was novel, namely *GACAT3/ CYRIA*.

Lastly, we investigated the phenotypic associations of CH in Admixed Americans. Gene-specific CH was associated with increased risk of death from haematological malignancies (*TET2*, *TP53*, *SF3B1*, and *SRSF2*), other cancer types (*ASXL1*, *DNMT3A*, and *SRSF2*) and cardiovascular diseases(*DNMT3A*, *TP53*).

Conclusions:

The substantial difference in CH prevalence between populations and the ancestry-specific genetic associations, demonstrate how the analysis of non-European cohorts can generate novel insights and highlights the importance of such analyses in advancing health equality amongst different human populations.

Disclosures Wen: *AstraZeneca:* Current Employment. **Hu:** *AstraZeneca:* Current Employment. **Nag:** *AstraZeneca:* Current Employment. **Tachmazidou:** *AstraZeneca:* Current Employment, Current holder of *stock options* in a privately-held company. **Deevi:** *AstraZeneca:* Current Employment. **Taiy:** *AstraZeneca:* Current Employment. **Smith:** *AstraZeneca:* Current Employment. **Carss:** *AstraZeneca:* Current Employment. **Wasilewski:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Wang:** *AstraZeneca:* Current Employment. **Petrovski:** *AstraZeneca:* Current Employment. **Fabre:** *AstraZeneca:* Current Employment. **Harper:** *AstraZeneca:* Current Employment. **Vassiliou:** *STRM.BIO:* Consultancy; *AstraZeneca:* Other: Educational Grant. **Mitchell:** *AstraZeneca:* Current Employment.

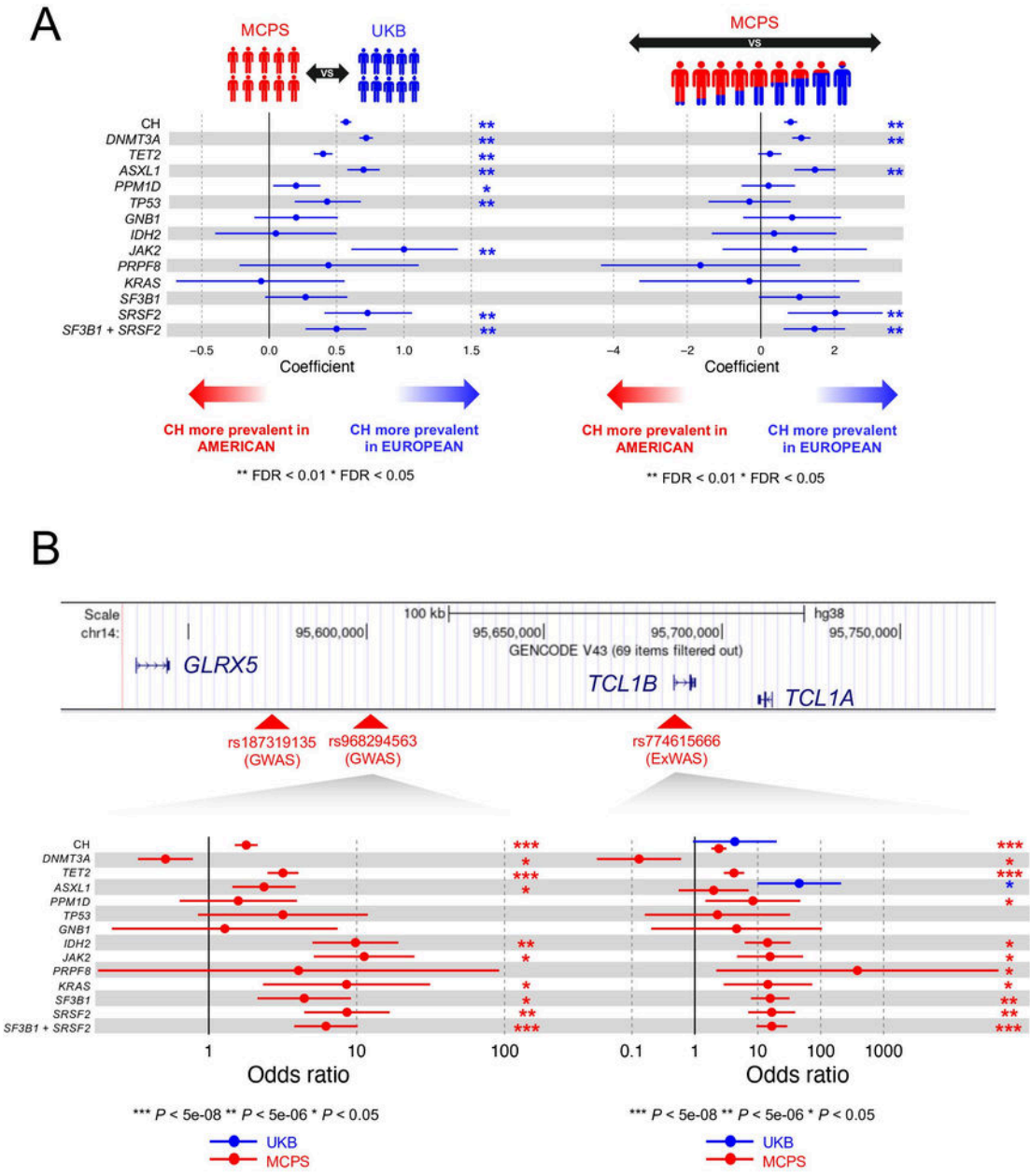

Figure captions

(A, left) Inter-population comparison of CH and gene-specific CH prevalence between UKB and MCPS. (A, right) Intra-population comparison of CH and gene-specific CH prevalence across MCPS participants with differing proportions of European and American genetic ancestry. (B, left) Odds ratio of *TCL1B* upstream variant rs968294563, identified from GWAS, for overall CH and across gene-specific CH. (B, right) Odds ratio of *TCL1B* promoter variant rs774615666, identified from ExWAS, for overall CH and across gene-specific CH.

Figure 1

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