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ORAL ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Genetic Determinants of Clonal Hematopoiesis and Progression to Hematologic Malignancies in 479,117 Individuals

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Clonal hematopoiesis (CH), while common with aging, confers a high relative risk of hematologic malignancy (HM). Genome-wide association studies have identified multiple germline predisposition loci for CH but many have an unclear functional role. Here we characterized the contribution of pathogenic/likely pathogenic germline variants (PGVs) to CH and its progression to HM using the UK Biobank (UKBB) as a discovery cohort (N=454,859) with validation in Memorial Sloan Kettering IMPACT and The Cancer Genome Atlas (N=24,258). We profiled whole exome sequencing (WES) for PGVs in 240 cancer predisposition genes.We simultaneously analyzedWES for CH driven by single nucleotide variants/indels and SNP array data for mosaic chromosomal alterations.

Overall, 8.9% of individuals in the UKBB harbored PGVs in genes with a dominant inheritance mode (5.2% in HM-related genes). To identify germline CH predisposition genes, we performed multivariable logistic regression with adjustment for age, sex, race, smoking and prior cancer type. Our analyses focused on heterozygous PGVs in both dominant and recessive genes since the majority of participants carried one deleterious variant. We found PGVs in 15 genes (8 are novel) increased the risk of CH (FDR corrected p-value <0.05), including 3 recessive genes that haven't been shown to confer a phenotype in the heterozygous state (Figure 1). Prominently featured pathways include DNA damage repair/sensing, telomere maintenance, RAS, JAK/STAT signaling, and hematopoietic cell differentiation/development.

Through pairwise analysis, we identified 102 additional germline genes predisposing to CH in specific genes/genetic regions; Out of 61 germline genes with $\geq$1 carrier who developed CH in replication cohorts, we replicated 55 genes (30 were significant with $p<0.05$ and 25 were directionally consistent). Overrepresented pathways include immune regulation (*e.g. UNC13D, DOCK8* and *ADA*), homologous recombination deficiency (*e.g. FANCA RAD51D, BRIP1* and *BRCA1*) among others. We observed heterogeneity in CH patterns for different germline genes. We used a recently published method (*Watson et al., Science, 2020*) to quantify the fitness advantage of specific CH mutations among PGV carriers compared to non-carriers based on the distributions of variant allele frequency. We found that some associations between PGVs and CH appeared driven by selection including PGVs in *ATM, MPL*, and *TP53* and CH overlapping the same gene/genetic region and PGVs in *CHEK2* and *DNMT3A* CH. Other CH predisposition genes like *POT1* were associated with multiple CH events across the genome, suggesting that tolerance of genetic instability rather than selection accounts for their associations with CH.

During 14-years of follow-up, 4,596 UKBB participants developed HM. 18 CH predisposition genes were also associated with HM, including several genes not previously linked to HM in the heterozygous state (*e.g. CTC1, BLM, and WNR).* To characterize the interaction between PGVs and CH on HM risk, we performed stratified analyses by mutational status. We observed synergistic effect between PGVs and CH on HM risk whereby CH carriers with PGVs have a higher risk of developing HM (HR [95%CI]: 1.30 [1.14-1.48]) compared to those without PGVs. We looked into specific HM predisposition genes and found this synergistic effect was consistent across most genes (Figure 2). We further grouped PGV carriers into those acquired high risk CH (CH in specific gene/genetic region showing moderate/strong association with the mutated germline gene) and those acquired low risk CH (showing weak or no association). Compared to non-carriers, PGV carriers who developed high risk CH showed high risk of myeloid (24.2 [19.3-30.5]) and lymphoid malignancies (6.3 [5.2-7.7]), whereas the risk for myeloid (1.5 [1.3-1.8]) and lymphoid malignancies (2.5 [1.8-3.4]) were weaker among PGV carriers with low risk CH.
In summary, we identifyseveral novel genes/pathways predisposing to CH and its progression to HMs. The association between germline genetic background and CH is explained by a combination of selection for specific somatic events and increased mutational acquisition/tolerance. High risk CH mutations vary by germline genetic background emphasizing the need for patient specific models of CH risk. These findings highlight the importance of germline-CH interactions in determining the risk of CH progression to HMs.

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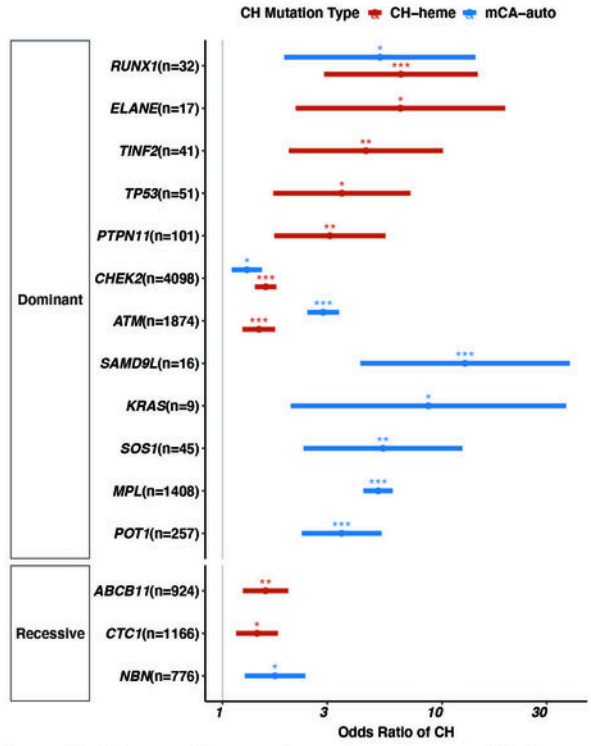

Figure 1. Significant germline mutated genes that predispose to CH in hematologic cancer relevant genes (CH-heme) or autosomal mCAs (mCA-auto). CH, Clonal hematopoiesis; mCA, mosaic chromosomal alteration * q<0.05; ** q<0.01; *** q<0.001.

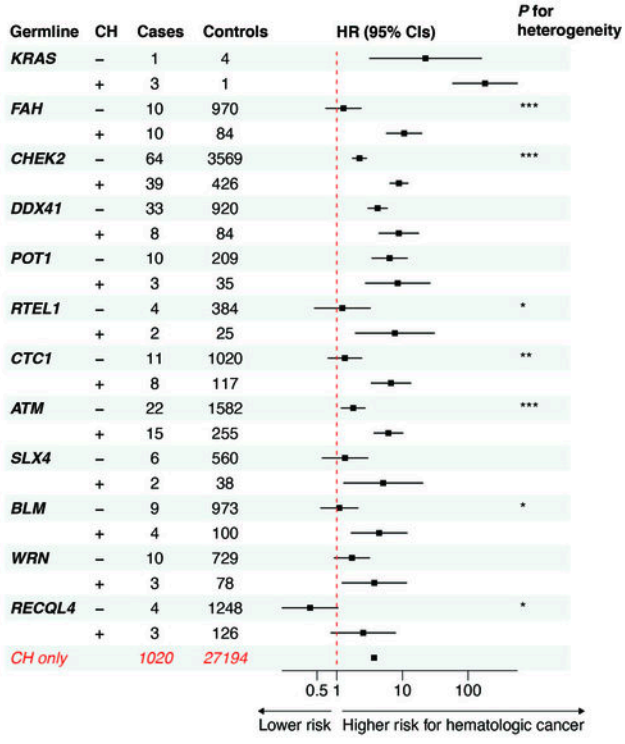

Figure 2. Risk of hematologic malignancies among germline mutation carriers with or without CH (+/-) by gene. CH, Clonal hematopoiesis; HR, hazard ratio; CI, confidence interval; * q<0.05; ** q<0.01; *** q<0.001.

Figure 1

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