Molecular pathology selected abstracts

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Common and rare variants in clonal hematopoiesis phenotypes

April 2023—Clonal hematopoiesis of indeterminate potential refers to the clonal expansion of hematopoietic stem cells that harbor a somatic mutation in people who do not exhibit hematological symptoms. This phenomenon is common in the elderly and associated with an increased risk of hematological malignancies, cardiovascular disease, infection, and all-cause mortality. Several somatic alterations are frequently detected in clonal hematopoiesis of indeterminate potential (CHIP), but the medical community's understanding of the underlying genetic predisposition to CHIP is limited. The authors conducted a large-scale exome-sequencing study involving more than 600,000 people to characterize CHIP status and discover rare somatic variants and possible predisposing germline alterations. The prevalence of CHIP was 15 percent by 75 years of age, and the affected individuals were more likely to be heavy smokers, in agreement with previous studies. The association with age and smoking status was stronger among CHIP carriers who had mutations of higher variant allele frequency (VAF; 10 percent or more). The most commonly mutated genes were *DNMT3A, TET2, ASXL1, PPM1D*, and *TP53*. Somatic mutations in *IDH2* and *SRSF2* co-occurred more frequently than expected, and *JAK2* mutations had the highest VAF. Rare germline variants in the *ATM, CHEK2*, and *CTC1* genes were significantly associated with increased risk of CHIP. Interestingly, several loci had unique effects based on CHIP subtype (the somatic alteration causing CHIP). For example, the *PARP1* locus on chromosome one and the variant P1247L in *LY75* (rs78446341) on chromosome two were associated with reduced risk of *DNMT3A* CHIP. Some loci were associated with multiple CHIP subtypes, occasionally in opposing directions. For instance, the *TCL1A* locus was associated with increased risk of *DNMT3A* CHIP but decreased risk of *TET2* and *ASXL1* CHIP. This study also examined how various CHIP subtypes differ in their phenotypic associations. For example, *SUZ12* CHIP showed a distinct association with endocrine and ophthalmologic diseases; *ASXL1* CHIP showed a wide range of traits, many of which were correlated with smoking; and *JAK2* CHIP was significantly associated with gout. In addition, CHIP carriers with a VAF of 10 percent or more and, in particular, *PPM1D* CHIP carriers were more likely to have severe COVID-19 requiring hospitalization. CHIP carriers were also at higher risk of developing hematologic and solid tumors. Carriers with a VAF of 10 percent or more had a significantly elevated risk of any type of blood cancer, and high-VAF carriers had a markedly increased risk of developing lung cancer, regardless of smoking status. These associations were mostly driven by *DNMT3A* and *ASXL1* CHIP carriers, as they showed elevated risks of lung and blood cancers. Furthermore, the risk of death from any cause was significantly higher among high-VAF carriers, and this risk was similar across *DNMT3A, ASXL1*, and *TET2* CHIP subtypes. The findings of this landmark study can greatly enhance the medical community's understanding of CHIP, a complex set of somatic mutation-driven subtypes with underlying genetic predispositions and germline risk profiles.

Kessler MD, Damask A, O'Keeffe S, et al. Common and rare variant associations with clonal hematopoiesis phenotypes. *Nature*. 2022;612:301–309.

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FGF14 GAA repeat expansion in late-onset cerebellar ataxia

Late-onset cerebellar ataxias are a group of heterogeneous neurodegenerative disorders characterized by

cerebellar syndrome, a constellation of symptoms that can include speech or visual problems, imbalance, vertigo, gait disorders, and other difficulties with coordination. They usually present after 30 years of age, and molecular testing is frequently negative. To examine potential molecular causes of these disorders, a group of researchers from McGill University, Montreal, Canada, first studied six patients from three large French-Canadian families (two members of each family) who had autosomal-dominant late-onset cerebellar ataxias (LOCAs). All of the patients in this discovery cohort had similar symptoms, and the underlying genetic cause was unknown. The six patients underwent whole genome sequencing with long-read sequencing, and the initial analysis did not reveal any rare pathogenic variants. The researchers further analyzed the sequencing data using the ExpansionHunter Denovo bioinformatics tool and discovered a putative heterozygous GAA repeat expansion in intron one of *FGF14* in all patients. Long-range polymerase chain reaction (PCR) confirmed this repeat expansion in all patients, and similar findings were seen in 15 affected relatives. The smallest expansion in any affected family member was 250 GAA repeats ($[GAA]_{250}$). The authors confirmed their findings using a validation cohort of 345 affected patients (66 French-Canadian, 228 German, 20 Australian, and 31 Indian) and a control cohort of 408 healthy people (209 French-Canadian and 199 German). Other known potential causes of patients' neurological symptoms were excluded and sequencing of the *FGF14* repeat locus was performed. In the validation cohort, the authors identified the $(GAA)_{\geq 250}$ expansion in 40 (61 percent) French-Canadian patients, 42 (18 percent) German patients, three (15 percent) Australian patients, and three (10 percent) Indian patients. In contrast, two-thirds of alleles in the healthy control cohort had 25 or fewer repeats, none had more than 300 repeats, and the allelic frequency of 250–300 GAA expansion was 0.98 percent. In the French-Canadian index cohort, the diagnostic yield of this repeat expansion was 75 percent (24 of 32) in those with early episodic symptoms, 93 percent (26 of 28) in those with downbeat nystagmus, and 94 percent (17 of 18) in those with a combination of the two. The overall findings suggest that $(GAA)_{250\text{-}300}$ expansions are likely pathogenic and, perhaps, have reduced penetrance, while $(GAA)_{>300}$ expansions are fully penetrant. The authors also performed functional analyses in two Spanish patients—one with a $(GAA)_{300}$ expansion and one with a $(GAA)_{350}$ expansion that were found during postmortem evaluation of their brains. They demonstrated that the patients' *FGF14* RNA transcript levels and FGF14 protein levels were significantly lower than in control patients. The authors concluded that a dominantly inherited deep intronic GAA repeat expansion in *FGF14* was associated with LOCA. This underscores the importance of identifying alterations in noncoding regions of the genome that might account for some unsolved heritable neurodegenerative disorders.

Pellerin D, Danzi MC, Wilke C, et al. Deep intronic *FGF14* GAA repeat expansion in late-onset cerebellar ataxia. *N Engl J Med*. 2023;388(2):128–141.

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