**Clonal hematopoiesis-an update on hematopoietic CH through genetics and genomic lenses**

**Abstract**

A prevalent biological condition in middle-aged and older people is clonal hematopoiesis (CH), which is defined as an excessive contribution to the formation of circulating blood cells by a single genetically modified hematopoietic clone in the absence of diagnostic evidence of a hematologic malignancy. CH is often caused by a hematopoietic stem or progenitor cell acquiring one or more somatic mutation repertoires. CH is quite frequent as people age, and it raises the chance of developing overt hematologic cancer as well as all-cause mortality and concomitant conditions including diabetes and cardiovascular disease. Genetic and concurrent non-genetic risk factors (such as high blood pressure or smoking cigarettes) determine the level of risk. Since it is currently unknown how to reduce these risks, the prospect of future clinical repercussions may add to anxiety and uncertainty even though the chance of clonal advancement or concomitant events in a single patient with clonal hematopoiesis may be minimal. Given this context, the goal of the current review is to examine the body of recent research in the field. Background information on somatic mosaicism, hematological disorders, and CH is included in the review to provide background literature. In-depth discussions of CH nosology, detection, and CH involvement in hematological and lymphoid disorders are described emphasizing novel findings with research and clinical medicine implications. The role of driver genes and non-involevement in somatic events vering a spectrum of topics. raises few questions. Using the lens of genetics and genomics the fitness, selection and multiplication of clones are discussed. Finally, prevalent methods for intervention and knowledge gaps are discussed thus co

**Keywords -** Variant allele frequencies (VAF), Clonal hematopoiesis of indeterminate potential (CHIP), bone marrow failure syndromes (IBMFSs), Multiplex ligation-dependent probe amplification (MLPA).

**1.0.Introduction**

The clonal proliferation of mutant hematopoietic stem cells (HSC) brought about by somatic mutation is known as clonal hematopoiesis (CH). According to Kusne et al. (2022), it describes a population of HSCs that may grow over time and in response to positive clonal selection pressures which possess one or more somatic mutations or copy number changes. CH is frequently diagnosed in the elderly and is linked to a number of non-malignant conditions in addition to myeloid cancers such as conditions like diabetes, atherosclerotic cardiovascular disease, etc.. Mutant immune effector cells including monocytes, granulocytes, and lymphocytes are also produced by the HSCs that acquire these somatic mutations. According to Luo et al. (2015), these effector cells may have an impact on various disease states that have a chronic inflammatory component. Because of additional collaborating mutations, CH is linked to a higher risk of blood malignancies, including acute myeloid leukemia. CH offers a framework for comprehending how alterations in tissue stem cell functions and composition due to aging affects human health (Ahmad et al., 2023). Based on Mary Lyon's theory of X-inactivation, the first reports of clonality in the hematopoietic system were made more than 60 years ago (Lyon, 1962). Fialkow et al., 1967 demonstrated the clonal origin of CML, which was a further advancement supported by recent studies (Rinaldi and Kevin Winston 2023). They further imply that the clones are likely begin and reside in long-lived hematopoietic stem and progenitor cells (HSPCs) because they are found in various hematopoietic lineages and persist for several decades. Although the discovery of such precancerous lesions in other tissues had long suggested the existence of a pre-malignant state in blood cancers, the development of sequencing studies enabled us to identify the mechanism by which healthy HSCs acquires these initiating mutations and subsequently develop into frank leukemia (Corces-Zimmerman et al., 2014; Shlush et al., 2014). Acute myeloid leukemia (AML) and other blood cancers are associated with CH due to cooperating mutations. It is also associated with an increased prevalence of non-cancerous diseases such as atherosclerotic cardiovascular disease, diabetes, etc. CH provides a paradigm for understanding the impact of aging-induced changes in tissue stem cell composition and function on human health (Liu and Jing 2022).

After acquiring somatic driver mutations, hematopoietic stem and progenitor cell (HSPC) clones and their offspring proliferate in the circulating blood cell population, a process known as clonal hematopoiesis (CH)(Fuster and Walsh 2018). Clonal hematopoiesis of indeterminate potential (CHIP) patients do not produce aberrant blood cell counts or any other signs of hematologic disease, but they do possess somatic mutations in hematological malignancy-associated driver genes in HSC with variant allele frequencies (VAF) of ≥ 2% (Marnell et al., 2022). Nonetheless, CHIP is linked to elevated risk factors, including genetic predisposition, history of cancer and cancer treatments, cigarette smoking, male sex, aging, and inflammation. Recent improvements in high-throughput sequencing experiment resolution indicate that CHIP is far more common than previously believed, especially in adults of age 60 years and older. CHIP increases the chance of developing hematological malignancy in the future, with only 10% of people with CHIP will be diagnosed (Reed et al., 2023). However, the problem lies in the difficulty in accurately separating the 10% of CHIP patients who are most likely to be in a premalignant state from those who are not due to the heterogeneity of this condition and the etiology of the associated hematological cancers.

In all cells, somatic mutations build up throughout time (Blokzijl et al., 2016; Hoang et al., 2016). These include minor insertions or deletions, common base substitutions, and structural variations (SV), which are copy-number changes of large chromosomal areas. An estimated ∼20 somatic mutations in the entire genome (Osorio et al., 2018) and ∼0.1 mutations in protein-coding exons (Welch et al., 2012) are acquired annually by HSCs, most of which are SNVs. Only long-lived HSCs in the bone marrow may self-renew throughout an organism's lifetime (Wilkinson et al., 2022). As a result, only mutations that occur in HSCs will typically last in a person's entire life. Humans are predicted to possess between 350,000 and 1,400,000 coding mutations in their HSC pool by the age of 70, as each person has between 50,000 and 200,000 HSCs. Clonal expansions in blood should be widespread as people age if even one of these mutations can give the HSC in which it occurs a selection advantage (Jaiswal et al., 2019).

**2.0. Somatic mosaicism and its role in Human diseases**

The existence of genetically different cell populations within an individual as a result of postzygotic mutations is known as somatic mosaicism (SM). A person who has a mosaic, or has distinct DNA in various bodily cells, is the result of combining cells with mutations and cells without mutations (Martínez-Glez, et al., 2020). Over time, these mutations can cause clonal expansions, especially in stem cell compartments, which can affect aging and disease susceptibility. These mutations, which affect different genomic sizes ranging from single nucleotides to entire chromosomes, are not inherited like germline mutations, but they can have significant phenotypic consequences (affecting only a portion of the body) depending on timing and tissue affected (Olafsson and Anderson 2021). It is now a widespread genetic variant with broad implications for human disease. Recent developments in deep sequencing, single-cell genomics, and sensitive bioinformatic pipelines have demonstrated that somatic mosaicism is ubiquitous across tissues and life stages, with implications for human disorders ranging from developmental disorders to age-associated diseases and cancer. Previously, the detection of mosaic variants was limited by technological limitations (Lodato and Walsh, 2023). According to Iourov and Heng (2022), SM is today recognized as phenomena that influences human growth, diversity, aging, and a variety of human disorders.

Chromosome aneuploidies, structural rearrangements, mobile element insertions, and mistakes in DNA replication all contribute to somatic mosaicism(Thorpe et al., 2020). The anatomical distribution and severity of the phenotype are significantly influenced by the cell lineage and time of the mutation. While later mutations may be limited to specific tissue compartments, early embryonic postzygotic mutations can be broadly disseminated and phenotypically comparable to constitutional variants (Lee, et al., 2021). For instance, a postnatal mutation may cause a single vascular malformation, but an early PIK3CA mutation may impact the brain, skin, and vasculature (Keppler et al., 2015). Even low-frequency mutations are amplified into disease-relevant burdens by clonal growth fueled by selection advantage (Chatsirisupachai et al., 2024). SVs, short indels, copy-number changes, or significant chromosomal modifications may also be a part of somatic events (Lodato and Vijg 2023). According to Lodato and Walsh (2015), mosaicism is now known to play a role in a number of human cancers, including developmental abnormalities, overgrowth syndromes, neurological disorders, cancer propensity, age-related clonal expansions, and organ-specific conditions like gout and liver cirrhosis. The timing, location, and type of the mutation all affect the phenotypic effects of mosaicism, which frequently lead to tissue-specific symptoms and varying expressivity. Somatic mutations can result in limited symptoms, as demonstrated by monogenic illnesses such as tuberous sclerosis and segmental neurofibromatosis (Choi et al., 2022). Similarly, somatic mutations in brain cells have been linked to the etiology of polygenic disorders including neurodevelopmental and neuropsychiatric disorders, indicating that mosaicism may be the cause of some instances that were previously thought to be inherited (Nishioka et al., 2018). Somatic mosaicism is a key factor in the development and spread of tumors in cancer biology, which leads to intra-tumoral heterogeneity and treatment resistance. Review of research by Manders et al. (2022) concludes that the patterns of somatic mutation accumulation over the human lifespan suggest that somatic mutations in all organs grow linearly with age. The study highlights mutational signals linked to endogenous and external mutagens, including UV radiation, and implicates changing rates; the trajectory is determined by stochastic base decay, APOBEC enzymes, and alkylating chemicals. Notably, prenatal cells display higher mutation rates than postnatal cells, likely due to rapid embryonic cell divisions.

Additionally, CH of indeterminate potential (CHIP) is a well-documented example of somatic mosaicism. According to Walsh et al., 2021, 15–20% of individuals over the age of 70 carry at least one somatic mutation linked to cancer in genes (e.g., in DNMT3A, TET2, ASXL1) at significant allele frequencies. CHIP is associated with increased epigenetic age, heightened inflammation, elevated cardiovascular disease risk, and modestly increased all-cause mortality (Nachun et al., 2021). In summary, these investigations highlight the widespread occurrence of SM, which is influenced by both extrinsic and intrinsic mutational processes and contributes to a variety of diseases as well as normal development. Aging, disease vulnerability, and functional decline are closely related to its effects, which extend across nuclear and mitochondrial genomes and impact tissues ranging from the brain to hematological systems.

**3.0. Origins of hematopoiesis and clonal hematopoiesis**

In order to create and replenish the blood system, hematopoiesis—the synthesis of blood cells components—occurs during embryonic development and throughout maturity. Blood development in vertebrates involves two developmental ontologies: the primitive and the definitive hematopoiesis (Ranbir 2022). During early embryonic development, erythrocytes and macrophages are produced by an erythroid progenitor, which is involved in primitive hematopoiesis (Baron 2014). As the embryo grows, red blood cells produced by primitive hematopoiesis which help oxygenate the tissues (Dzierzak and Bigas 2018). Early in development, blood islands in the extra-embryonic yolk sac are where transient, erythroid progenitor cells initially emerge in mammals and birds. These cells are incapable of renewal and lack pluripotency (Ciau-Uitz et al., 2014). Later in development, and noticeably at different times in different species, definitive hematopoiesis takes place. Erythroid-myeloid progenitors (EMPs) are progenitors produced by a brief wave of definitive hematopoiesis that takes place in the blood islands of the majority of organisms (Frame et al., 2013). Human stem cells (HSCs), which are multipotent and can produce all of the adult organism's blood lineages, are subsequently involved in definitive hematopoiesis. In vertebrates, definitive HSCs originate in the developing embryo's aorta-gonad-mesonephros (AGM) area and then go to the fetal bone marrow and liver (Kobayashi et al., 2023). Two transcription factors, Gata1 and Pu.1 (now known as Sfpi1 in mice and Spi1b in zebrafish), play a major role in primitive hematopoiesis. They have a cross-inhibitory connection that controls primitive erythroid and myeloid fates (Rothenberg et al., 2019). Another transcription factor belonging to the runt family which is crucial for hematopoiesis is called Runx1 (Lam and Zhang et al., 2012). The hemangioblast, the predecessor to both primitive erythroid progenitors and endothelial cells is coordinated by a variety of transcription factors during development —Tal1, Gata2, Lmo2, Fli1, and Etsrp (Doré and Crispino et al., 2011). Important transcription factors that regulate the expression of other genes involved in hemangioblast formation are encoded by a number of genes (Mitsis et al., 2020). Two major cell-signaling pathways crucial for embryonic development are the Wnt and Notch pathways. The pathways are important for HSC function and in control of cell fate specification and pattern formation (Liu et al., 2022; Reichrath and Reichrath, 2022).

**4.0. Genetics and genomics of CH**

Somatic genetic alterations observed in CH include point mutations in cancer-related genes, mosaic chromosomal alterations, or a combination of these (Vijg et al., 2017). Clonal hematopoiesis may occur in the context of selective pressures such as cytotoxic therapies and tobacco smoking, and the inability to rectify DNA replication errors among aging (Franco and Godley 2025). With respect to HSCs' neutral drift, the random genetic drift of evolutionarily neutral alleles at the molecular level contributes to CH (Stolzenbach et al., 2022). Figure 1 illustrates HSC mutation acquisition over a lifespan and the consequences. In human tissues, somatic mutation, clonal selection, and oncogenesis are interconnected processes that are subject to change over time and have gradual effects (Martincorena 2019). A key component of our comprehension of SM is the quantification of tissue stem cell proliferation, differentiation, somatic mutation, and selection dynamics. Throughout development and the postnatal period, normal stem cells accumulate somatic variation (Derks and Boxtel et al., 2023). Genetic drift or selection causes stem cell clones to change in size over time (Lyne et al., 2021). Expanded clones without known driver events may be more common than those with known driver events, according to analysis of somatic variant distributions, which also indicates that CH is significantly more common than suggested by known drivers (Sigurdsson et al., 2017). This finding raises several questions, including whether CH drivers develop accidentally or if their acquisition is aided by higher turnover and/or somatic mutation rates. Do the incidence and clinical characteristics of stem cell clones with known and unknown causes vary?

In order to track the long-term dynamics of both healthy and premalignant HSCs, mutations are thought to be a molecular clock that gradually accumulates with age (Egeren 2021; Williams 2022). Scientists have estimated the clonal proliferation rate and employed sequencing for both driver and passenger mutations. Using information from serial blood sample sequencing or separately isolated HSC colonies, a number of researchers have developed Bayesian logistic growth models that rebuild hematopoietic lineage hierarchies (Weinstock et al., 2023). These studies collectively imply that known driver genes are not involved in somatic events (Lee-Six 2018; Fabre et al., 2022). Researchers indicate a number of factors related to the origins and subsequent dynamics, including spontaneous attrition of less suitable CH clones and genotype specificity (Uddin et al., 2012). One example is the DNMT3A clones, which most likely exhibit quicker clonal expansion at younger ages before slowing down at older ages. Later on in life, splicing factor-mutated CH emerges are seen (Robertson et al., 2022). Lastly, malignant and nonmalignant outcomes are more frequently associated with CH clones that meet the VAF criterion for CHIP/CCUS (VAF > 2%). According to a study by Zeventer et al., 2023 a total of 92.4% of clones develop at a steady exponential pace. The growth rates of these clones vary greatly depending on the mutation, ranging from 5% (DNMT3A and TP53) to over 50% annually (SRSF2P95H). Clone growth rates with the same mutation varied by about ±5% year. Different patterns of lifetime clonal activity are shown by phylogenetic analysis of hematopoietic colonies using time-series data. Early in life, the DNMT3A-mutant clones grew more preferentially, and as they aged, their growth slowed. On the other hand, TET2-mutant clones appeared at all ages, while splicing gene mutations spurred growth later in life. Neutral drift dynamics is the pattern of stem cell turnover, according to quantitative analysis (Snippert 2010). According to the study, Lgr5hi cell divisions in intestinal stem cells happen symmetrically and do not lend credence to a concept where two daughter cells—one Lgr5hi cell and one transit-amplifying [TA] cell per division—adopt different fates. Lastly, neutral drift acting on a limited population of active hematopoietic stem cells causes clonal hematopoiesis, which can occur with or without potential driving mutations and is typical in the elderly (Zink et al., 2017). Instead of a particular genetic advantage brought about by a mutation, the expansion of a hematopoietic stem cell (HSC) clone could be the result of random variations in cell division and survival. According to Genovese et al. (2014), drift adding to the total pool of blood mutations and may raise the chance of hematologic malignancies or other age-related illnesses. The genetic contribution(fitness and selection) to CH fitness and selection is illustrated in Figure 2.

**4.1.**Driver genes

A key component of tumor growth (a model for SM), waves of expansion of increasingly disordered clones at different stages are caused by the accumulation of driver mutations in cancer genes in conjunction with external stimuli (Kent and Green 2017). This model assumes that before transformation, the randomly distributed SM must accumulate in normal cells. In this situation, two questions are crucial. How quick do the chosen clones grow, and when do selection events take place in life? Genotype-dependent clonal growth or attrition is influenced by both external and intrinsic selection factors. Radiation and chemotherapy have a significant impact on the selection pressures of clonal ascendancy and dominance (Bolton 2020). According to earlier research, patients receiving platinum-based chemotherapy and radiation therapy have a higher incidence of TP53- and PPM1D-mutant CH genes after being exposed to cytotoxic chemotherapy (Singh et al., 2020). Pre-existing CH clones are frequently selected for and transformed by chemotherapy exposure (Franco 2025). Toxin-related cellular stressors may have a role in the development and spread of CH in a genotype-specific way, as evidenced by the moderate correlation between tobacco exposure and ASXL1 gene mutant CH (Levin et al., 2022). Co-occurring conditions like autoimmune illness, HIV infection, and aplastic anemia may potentially serve as triggers. In the context of cytotoxic T-cell-mediated autoreactive HSC destruction in aplastic anemia, CH genotypes seem to have a competitive advantage (Neal and Seishi 2015). Lastly, another factor that promotes clonal growth is sex differences. Population cohorts have shown variations in peripheral blood counts (Paltiel et al., 2025). Male sex is linked to poorer outcomes in myeloid malignancy mutations in splicing factors, and males with CHIP are more likely than females to have ASXL1 mutations, whereas females are more likely to have DNMT3A gene mutations (Karantanos et al., 2021). The acquisition and spread of mutations across a human lifetime are depicted in Figures 3a and 3b. The CH driver genes, variations, and roles are compiled in Table 1. In ultra-deep sequencing of 74 cancer genes in small (0.8-4.7 mm2) biopsies of sun-exposed eyelids, the burden of somatic mutations averaged 2-6 mutations/megabase/cell in multiple cancer genes (Martincorena et al., 2019). Several genes were under strong positive selection even in physiologically normal skin, including most of the key drivers of cutaneous squamous cell carcinomas. The study highlights variability in the driver landscape among individuals and variability in sizes of clonal expansions across genes. In summary genetic factor have a major role determining the function and trajectories of clones.

**4.2.** Biological factors and germline predisposition to CH

Advanced biological aging and viruses are other biological elements that contribute to CH. Report suggest HIV infection may raise the incidence of cancer and CH (Gillis et al., 2024). Research on human CH has shown that clonal growth increases exponentially from middle age to old age (Osorio et al., 2018). According to other studies on HSC, older HSCs have a variety of phenotypic variations from younger HSCs at the population level, which are linked to decreased function, fitness, and lineage potential (Pang and Schrier 2017). The mutations and clinical, concomitant diseases linked with the CH category are listed in Table 2. In summary, these findings indicate that the natural history of CH is life-long and influenced by both intrinsic and extrinsic variables, which are not antagonistic but co-operative. Further, they provide fundamental insights into the interactions between SM, aging, and clonal selection.

Germline susceptibility in few illnesses with a wide variety of variations and dispositions is briefly described in the paragraph that follows. Numerous familial predisposition syndromes such as inherited bone marrow failure syndromes (IBMFSs) have elevated rates of CH, suggesting a connection between germline variations and selective pressure for the acquisition of certain SM. Ineffective hematopoiesis and a higher incidence of acute myeloid leukemia (MDS/AML) and myelodysplastic syndromes are characteristics of IBMFSs. A family susceptibility to MDS/AML is linked to mutations in the genes *CEBPA*, *DDX41*, *GATA2*, *RUNX1*, and *SAMD9/9L* (Tsai and Lindsley et al., 2020). Recurrent mCA (isochromosome 7q and deletions at 20q) or inactivating mutations in EIF6 are characteristics of Schwachman Diamond Syndrome (CH). These mutations functionally repair hereditary deficiencies in translational efficiency and inappropriate p53 activation (Kawashima et al., 2023). Additionally, somatic compensation has been reported in patients with germline SAMD9/9L and Fanconi anemia (Choijilsuren et al., 2021). Telomeropathies, which include skewed X chromosome inactivation in addition to CH, are characterized by somatic reversion, which corrects or eliminates the germline genetic error. The promoter of the *TERT* gene allele variant exhibits additional mCAs and CHUD acquired mutations (Holohan et al., 2014; Kouroukli et al., 2023). Furthermore, rare variants with higher penetrance for CH and common variants with lower penetrance have been found through genome-wide association studies. For example, an 8-bp intronic deletion in TERT has been linked to a 1.37-fold increase in CH driver mutations, indicating telomere maintenance (Tapper et al., 2015). Another study found that JAK2 gene-mutant MPN was linked to frequent coding variations in TERT (Matsuguma et al., 2019). Additional reports include the core promoter of gene *TCL1A* variations that affect clonal expansion rates as measured by passenger-approximated clonal expansion rate. These variations were linked to slower growth of TET2-mutant CH and significantly lower odds of CHIP involving mutations in genes *TET2*, *ASXL1*, *SF3B1*, and *SRSF2* in comparison to *DNMT3A* (Testa et al., 2025). Finally, gene TCL1A-mediated reduction in fitness for certain HSC clones specifically increases the likelihood of DNMT3A clones (Jakobsen et al., 2024). These studies implicate role of biological and germline factors in the form of co-morbid diseases to contribute or act as second hit in the progression and course of CH.

**5.0.CH nosology-Myeloid and Lymphoid**

Numerous hematological conditions, including neoplasms, are thought to be precursors of other hematological conditions. For instance, since about 25% of MDS cases and 10% to 20% of myelofibrosis cases ultimately advance to acute myeloid leukemia (AML), MDS and primary myelofibrosis are regarded as early phases that may lead to AML. According to Steensma et al. (2018), myeloma can also develop into active multiple myeloma, which can thereafter develop into plasma cell leukemia. Although CH is common in the general population and associated with a number of health hazards, little is known about its prevalence and effects in long-term survivors of AML, particularly those who have survived for at least five years. CH in AML long-term survivors (with a median follow-up of 11.6 years) is reported by Krauß et al., (2025). Out of the 61.9% of survivors, 35.9% had CH of uncertain potential (VAF ≥2%) and 26% had small-clone CH (SC‐CH; variable allele frequency [VAF] <2%). Additionally, CH was more prevalent among survivors who had chemotherapy (75.7%) as opposed to those who received allogeneic stem cell transplantation (alloSCT-54.0%) and among age-matched healthy controls. CH prevalence increased with chronological age in survivors of chemotherapy, but it was more closely associated with hematopoietic age (donor age plus years since transplantation) in alloSCT recipients. Mutation patterns were also affected by the type of treatment; following chemotherapy, TP53 and PPM1D gene variations were more common. Diabetes in alloSCT patients and co-morbid rates of subsequent malignancies in survivors of chemotherapy were associated with CH with VAF ≥10%. Another observation is that acute myeloid leukemia, myelodysplastic syndromes (MDS), and MPNs frequently include mutations that are commonly mutated in clonal hematopoiesis, including *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, *TP53*, and *SF3B1* genes (Buscarlet et al., 2017). Therefore, it is not unexpected that individuals with CH are more likely than those without such mutations to acquire these tumors. Additionally, these mutations are observed in circulating immune cells such as lymphocytes, monocytes, and granulocytes (Mitchell et al., 2021). These findings highlight the high frequency and possible clinical significance of CH in AML long‐term survivors. Monoclonal B-cell lymphocytosis (MBL) and monoclonal gammopathy of unknown significance (MGUS) are precursor illnesses of lymphoid malignancy. In the MBL cells of 11 patients with CD19+/CD5+/CD20dim, Agathangelidis et al. (2018) found L-CHIP mutations in 7 CLL driver genes, including *NOTCH1*, *FBXW7*, and *POT1* genes. mCAs frequently exhibit chromosomal abnormalities that contribute to lymphoid malignancy (lymphoid mCAs [L mCAs]) (Sekar et al., 2024). Although L-CHIP is less prevalent than its myeloid cousin, its incidence rises with age. With certain L-CHIP mutations, like *NOTCH1*, the genotype distribution is more evenly distributed in L-CHIP (von Beck et al., 2023). Similar to M-CHIP, L-CHIP was more common as people aged. Niroula et al. 2021 report the prevalent as (1.3% ) as compared to 5.8% in M-CHIP and equally distribution of variants across a greater number of genes According to Brown et al. (2023), L-CHIP was linked to a higher risk of diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and general non-Hodgkin lymphoma (NHL). While cnLOH is similarly distributed between the sexes, gender disparities in LH mCAs are observed because copy number increase or loss is more common in men (OR = 1.42) (Jacobs et al., 2012). The key distinctions between myeloid and lymphoid CH are outlined in Table 3.

Additionally, CHIP could be involved in tumor immune responses. According to mouse models, removing Tet2 in myeloid cells increased anti-melanoma T-cell activity and decreased tumor growth, whereas deleting Dnmt3a in CD8⁺ T cells avoided T-cell depletion and enhanced response to PD-1 checkpoint inhibition (Reed et al., 2023). Clinical examples are equally convincing. Ktena et al., (2022) report that the recipients of bone marrow transplantation who received donor cells with DNMT3A-mutated CHIP had higher rates of graft-versus-host disease and lower tumor relapse rates. This is probably because the donor immune cells mounted stronger responses against the tumor and host tissues. In another study report, chronic lymphocytic leukemia patients responded exceptionally well to CAR-T therapy carrying the **TET2** mutation from CHIP, and the CAR construct (Fraietta et al., 2018). The TET2-null CAR-T clone was effective at clearing leukemia due to its expanded central memory CD8⁺ population, reduced exhaustion, and enhanced cytokine production

**6.0 .Detection methods**

A precondition for CH of hematology diagnosis is routine hematological diagnosis based on medical history and concomitant conditions. Standard laboratory tests for AML, including spinal taps, lumbar punctures, and bone marrow aspiration biopsies. The flowchart also includes the microscopy section, blood chemistry, and coagulation testing (Tripathi and Chuda-statpearls 2025). When diagnosing AML, the proportion of blasts in the blood or bone marrow is especially crucial. Thus, leukemia cell classification is made possible by cytochemistry tests like flow cytometry and immunohistochemistry (Li 2022). Imaging tests include computed tomography (CT) scans, magnetic resonance imaging (MRI), PET/CT scans, CT-guided needle biopsies, ultrasounds, and X-rays enable internal capture of the afflicted organs, which aids in diagnosis(Chou et al., 2014). Somatic variation has been documented at all genomic sizes and includes point mutations, expansion of trinucleotide repeats, copy-number loss/gain, uniparental disomy, mitotic recombination, aneuploidy, translocation, and retrotransposition (Martínez-Glez, et al., 2021). Because of this, there are specific methods for the sensitive identification of specific types of variation, and the methods' abilities to identify specific somatic variation types vary widely. The sampling of tissues for the CH mosaicism investigation is subject to many limitations and cautions. One important consideration while examining mosaic samples is the dissection's purity. The presence of normal cells in the injured area significantly impairs downstream analysis' ability to detect mosaic alterations. The situation may be compounded by the fact that cellular migration frequently takes place in certain tissues during development (Walsh et al., 1992; Pleasure 2000). Cellular migration may affect only one cell, causing neighboring cells to originate from distinct sources. Cellular migration may put a strong biological constraint on the apparent frequency of driver somatic mutations in affected tissues (e.g., brain). Other factors may lower the measurable fraction of mosaic cells in a sample. Two potential causes include cell-type-specific lethality and a mosaic deficiency of essential paracrine or juxtacrine signaling molecules. Paracrine or juxtacrine signaling factors are necessary for cell survival (Leibrock et al., 1989; Hohn, 1990). Mosaic loss of these factors could result in affected tissue that is dependent upon surrounding normal tissue for survival, reducing the total number of mutant cells.

Large mosaic events in single cells can be detected using techniques based on microscopy. Large structural rearrangements, duplications, deletions, and intra- and inter-chromosomal translocations can all be detected using chromosomal banding techniques like fluorescent in situ hybridization (FISH). Only aberrations greater than 3–10 Mb can be resolved by the banding procedures. Resolution of a variation of FISH, known as multicolor FISH, range from 100 kilobases(kb) to several kb (Imataka and Arisaka 2015). Single nucleotide polymorphism microarrays (SNP microarrays) and array CGH (aCGH) can identify copy number variations across sizable portions of the genome (Pinkel and Albertson 2005). For minor CNVs, array-based methods provide greater sensitivity over the whole genome (resolve regions less than 100 kb). Low-level somatic events can also be detected using SNP microarrays (Bignell et al., 2004). The field of human genetics has undergone a radical transformation in the last decade due to the application of sequencing techniques to individual cells, bulk tissue, or a particular number of cells.CH is diagnosed by sophisticated DNA sequencing, often as part of a blood test, which identifies specific genetic alterations in blood cells (Belotserkovskaya et al., 2023). Somatic genetic variants have been identified by whole-exome or whole-genome sequencing of bulk tissue from paired damaged and unaffected sections of the tissues (Choi et al., 2009). Multiplex ligation-dependent probe amplification (MLPA), which employs several sequence-specific probes covering a certain area, is another method for detecting specific CNAs, including single exon events, even though it is not array-based (Ma et al., 2021). Another technique that uses genome-wide high-resolution enzymatic restriction digests of DNA to detect structural variations is optical genome mapping (OGM) (Levy et al., 2024).
CH is typically detected during or after blood work, sometimes as part of more thorough hematological or cancer evaluations (Elbert and Weeks 2023). Furthermore, hematologic malignancy or other clonal illnesses might be problematic when mutations occur without the typical indications or symptoms. Measuring the percentage of cells affected by specific somatic changes helps determine the extent of the mosaic mutation and the developmental period at which it happened. Yadav and De (2014) evaluated the many methods that have been developed to de-convolute SM into distinct populations. As an alternative to bulk tissue, single cells or small clusters of cells can be sequenced. Additionally, researchers have used digital PCR (dPCR) technologies, which allow for greater sensitivity (1 mutation in 10,000 normal cells, or 10⁻⁴), and single-cell approaches to detect SNVs or indels in single cells (Poirion et al., 2018). Furthermore, for the diagnosis and disease monitoring of hematological malignancies, qPCR and dPCR are typically well-suited to identify particular recurrent genetic alterations, such as single gene mutations (e.g., JAK2 p.V617F) and distinct fusions (e.g., BCR::ABL1) (Galimberti et al., 2022; Chatterjee et al., 2024). Somatic variations can be identified, validated, and analyzed from these data using a variety of software tools. The reader is directed to reviews from other reliable sources because they are outside the purview of the review. Table 4 summarizes the several techniques used for CH detection.

**7.0. CH in Haematological disorders and Non-haematolgical disorders**

7.1.Haematological disorders

Molecular drivers of myeloid CH are common initiators of myeloid malignancy. CHIP, CCUS, and M-mCA are associated with an increased risk of subsequent myeloid malignancy(Gu et al., 2023).The estimated risk rate of malignant transformation is ~0.5% to 1% per year in CHIP/CCUS (DeZern et al., 2019). The risk of transformation to myeloid malignancy is determined by the presence of specific molecular and hematologic feature. CHIP/CCUS with mutations in splicing factor genes *TP53*, *IDH1*, *IDH2*, and *RUNX1* have the highest risk of evolution to myeloid neoplasia (Taborda et al., 2024). The clonal hematopoiesis risk score (CHRS) is a clinical tool to estimate the risk of progression to myeloid malignancy in CHIP/CCUS based on the presence of molecular and hematologic features (Mohammad et al., 2025). CHRS characterizes CHIP/CCUS into high-, intermediate-, and low-risk groups based on the presence or absence of various features. Additionally, cytogenetic abnormalities may initiate myeloid malignancy. Chronic lymphocytic leukemia (CLL) is often initiated by copy number abnormalities (Puiggros et al., 2014), and L-mCAs due to trisomy 12 (Abruzzo et al., 2018), deletion of 13q (Khalid et al., 2021), and copy-neutral loss of heterozygosity at the NOTCH1 locus (Edelmann, et al., 2019). It is observed that CHIP/CCUS commonly precedes myeloid malignancy and lymphoid malignancy (Brogana et al., 2025). CH is also implicated in Classical Philadelphia Chromosome-Negative Myeloproliferative Neoplasm, chronic idiopathic neutropenia (CIN) and Aplastic Anemia (Kjær et al., 2020; Tsaknakis et al., 2021; Ogawa 2016). Mutations in *JAK2*, *CALR*, and *MPL* are major disease drivers for MPNs, and can initiate or promote MPNs with or without other co-mutations (Grabek et al., 2020). Tsaknakis et al., 2021 report mutations across six genes with a median VAF of 12.75% in genes *DNMT3A*, *TET2*, *IDH1*/*2*, *SRSF2* and *ZRSR2* respectively. CH-related mutations alter the number and function of non-leukemic T-cells or even disrupt the immune system (Belizaire et al., 2023). Inflammation may directly affect the proliferation and self-renewal of HSCs. Finally, studies reveal an association between CH in the peripheral blood stem cell (PBSC) harvest (Gillis et al., 2024) and t-MN in non-Hodgkin lymphoma (NHL) (Gibson et al., 2017). In hematopoietic stem cell transplantation (HSCT), CH detected in the donor or recipient can influence outcomes (Gibson et al., 2017; Williams et al., 2024). Patients with lymphoma and myeloma with CHIP at the time of autologous transplantation had inferior survival and increased risk of therapy-related myeloid malignancy.

7.2. Non-haematolgical disorders

Since CHIP mutations might change the function of circulating immune cells, it is conceivable that CHIP may have an impact on aging-related nonmalignant disorders (Brown et al., 2023). There is evidence that the genes *DNMT3A*, *JAK2*, and *TET2* are involved in immune function (Cobo et al., 2021). CHIP is relevant to "inflammaging," the age-related increase in systemic inflammation. There are common loss-of-function gene mutations in both *DNMT3A* and *TET2* genes which encode enzymes crucial for DNA methylation in innate immunity (Cobo et al., 2022). Tet2-deficient murine macrophages challenged with bacterial endotoxins or low-density lipoprotein show increased expression of the chemokines Cxcl1, Cxcl2, and Cxcl3 as well as the interleukin-8 (IL-8) and Il1b and Il6 in comparison to wild-type macrophages (Xie et al., 2022). Their function is confirmed by other studies of increased circulating levels of IL-8, IL-6, and IL-1B in people with TET2 mutations (Lassalle et al., 2023). Mice lacking Dnmt3a have mast cells that are more active during allergic reactions when stimulated with immunoglobulin E. This is accompanied by an increase in IL-6, IL-13, and tumor necrosis factor α levels (Leoni et al., 2017). Mutations in *JAK2* gene causes constitutive signaling from specific growth factor receptors and STAT transcription factor activation, which in turn causes strong activation of T cells and granulocytes, enhanced inflammation in macrophages, and activation of neutrophil extracellular traps (Haage et al., 2024). *SF3B1* mutant carriers have been shown to have greater levels of circulating IL-18, whilst *ASXL1* mutation carriers have been found to have higher levels of circulating IL-6 (Marnell et al., 2021). 50% of DNMT3A-mutated CHIP carriers harbor DNMT3A mutations in their T cells, whereas 30% of most patients with JAK2V617F1 MPNs harbour JAK2 mutations in their T cells (Huang et al., 2024). Also, there is growing evidence that the function of T- and B-cells depends on genes linked to CHIP. For instance, angioimmunoblastic T-cell lymphoma and other lymphomas involving CD41 T-helper cells frequently include mutations in *TET2* and *DNMT3A* genes (Yao et al., 2020).

7.3.Atherosclerotic cardiovascular diseases

An increased risk of ischemic stroke and incident chronic heart disease (CHD) is associated with CHIP. The hazard ratio (HR) for CHIP carriers for these illnesses was approximately 2%. Clone size was linked to risk level because CHIP carriers with VAF had a 10% higher risk of getting CHD than those with smaller clones (Singh et al., 2024). The HRs for CHD was similar in carriers of the *DNMT3A*, *TET2*, and *ASXL1* gene mutations. However, the HR was significantly greater in those with JAK2 V617F mutations (Nangalia et al., 2015). According to research, mice whose bone marrow was transplanted without functional Tet2 alleles had greater lesions in cases of atherosclerosis of the aortae of Ldlr2/2 mice (Fuster, et al., 2017). The identical phenotype observed in mice with Tet2 deficient in solely the myeloid compartment, indicates that myeloid dysfunction was sufficient to induce the phenotype. Gene-expression investigations on murine macrophages showed that Tet2 deletion was associated with increased expression of Il1b, Il6, Cxcl1, Cxcl2, and Cxcl3 (Cull et al., 2017). Changes in macrophage inflammatory responses and accelerated atherosclerosis could result from JAK2 mutations (Dotan et al., 2022). It is unclear how PPM1D mutations contribute to atherosclerosis, despite evidence that Tp53 depletion causes accelerated atherosclerosis in mice (Branca et al., 2020). These mutations are often selected after chemotherapy or radiation therapy (Yura et al., 2021). Clonal evolution and CH-mediated diseases are summarized in Figure 4. A frequent coding variant in IL6R is associated with lower levels of C-reactive protein and a decreased risk of CHD (Cupido et al., 2022). Despite never developing myeloid malignancies as would be expected, families with heterozygous TET2 null allele carriers develop Hodgkin lymphoma (Feng et al., 2019). This suggests that SM acquired later in life may have different effects from TET2 germline mutations. Given that one of the seven carriers evaluated for clinical atherosclerotic disease had developed CHD, it may be inferred that germline TET2 mutations are most likely not the source of cardiovascular disease. It is well known that MPNs with a JAK2-mutated gene are far more likely to develop venous and arterial thrombosis. This finding is corroborated by increased rates of neutrophil extracellular trap formation in granulocytes with a JAK2 mutation, which is believed to be a catalyst for thrombus formation (Shammo et al., 2016). Research on mice revealed that in murine models of heart failure, hematopoietic cell mutations in DNMT3A, TET2, or JAK2 resulted in deteriorating cardiac function (Wang et al., 2021).

7.4.Other human diseases

According to studies that first linked CHIP to atherosclerotic cardiovascular disease, also implicated moderate correlation between CHIP and type 2 diabetes (T2D) (Tobias et al., 2023). Tet2-deficient mice have higher insulin resistance associated with age and obesity, along with enhanced pro-inflammatory signaling, according to mouse models, suggesting that CHIP increases the risk of type 2 diabetes (Fuste et al., 2020). According to a different study, macrovascular issues are more common in T2D patients with SV-induced clonal hematopoiesis (Schafer and Mann 2024). One age-related illness with a major inflammatory component is chronic obstructive pulmonary disease (COPD). According to Miller et al., (2023), CHIP raises the risk of both the incidence and severity of COPD. TET2 mutations were enriched in seronegative RA (P = 0.009) and CHIP was linked to a lower overall survival in RA participants (P = 0.013), providing additional evidence for the context-dependent relationship between CHIP and inflammation and its possible therapeutic implications (Hiitola et al., 2025). Increased IL-1β signaling in Tet2-deficient rats in response to urate crystal exposure is indicative of CH (CHIP/CCUS) in gout (Weeks and Ebert 2023). Patients with CHIP who have a VAF ≥ 10% are twice as likely to have cirrhosis, nonalcoholic hepatic steatosis, and chronic liver disease (Wong et al., 2023). Researches in brain sciences report CHIP patients are likely to develop Alzheimer's disease. This association may be due to the phagocytic activity of bone marrow-derived microglial-like cells, which are more prevalent in CHIP patients' brains than in controls' (Thomas 2023). According to a study by Bouzid et al., 2023, in a cohort whose dementia prevalence was 37.9% the proportion of the individuals with CHIP increased significantly with age. Furthermore, they found that tau neurofibrillary tangles and brain β-amyloid (Aβ) in autopsy samples were negatively correlated with CHIP and AD neuropathological characteristics. CHIP is linked to the incidence of hemorrhagic stroke and small vessel ischemic stroke subtypes (HR=1.24 [95% CI, 1.01–1.51]; P=0.04). Finally, TET2 was most strongly linked, according to gene-specific association data, to both ischemic and total stroke, while both TET2 and DNMT3A were linked to an elevated risk of hemorrhagic stroke (Bhattacharya et al., 2022).In summary CH is implicated in several hematological, lymphoid and organ disorders of liver, bone, lungs and brain indicative of multicellularity and mosaicism.

**8.0.Diagnosis and Interventions of clonal hematopoiesis**

In the absence of established interventions to eliminate expanded clones, the benefit of testing for and informing patients of an incidental finding of clonal hematopoiesis is still unclear, particularly when considering the potential psychological impact of such an unmodifiable risk factor for disease. Currently, no universal recommendations to patients about all hematopoietic clones exist since many clones will be of no consequence. Few situations, though, call for notification, such as CHIP patients who might be discovered to have clinical or mutational traits linked to an increased risk of hematologic malignancy, such as abnormal blood count indices or high-risk mutational traits such as chromosomal aneuploidy, higher VAF, more than one known myeloid neoplasm driver mutation, or higher risk genes like IDH1/2, TP53, or spliceosome components. It is highly advised that CHIP associated to the JAK2 V617F mutation be disclosed because of the elevated risk of cardiovascular disease or thrombosis that this mutation confers(Bhattacharya and Bick 2021). In summary, the decisions to notify individuals about CHIP should take into account the patient’s life expectancy, personal preferences, and cultural context. The potential to discover CH is recommended in consent discussions for genetic testing whenever possible, and individuals are given the option to be or not be informed of CHIP as an incidental finding.

A number of institutions are currently thinking about setting up specialty clinics to evaluate patients with CH; however the administrators and doctors working on this project are frequently facing difficulties because of a few problems. First, there is sometimes a lack of clarity regarding the germline or somatic nature of an identified mutation particularly when VAF-TP53 mutations are high (40%) (Churpek et al., 2015; Trottier et al., 2019). The second uncertainty stems from family factors and the non-hematological effects of germline variations. Several Institutions have established partnerships with geneticists who can set up non-hematopoietic tissue testing (e.g., fibroblast cell line as a germline control or skin biopsy). When additional illness states, such cardiovascular and autoimmune problems or neurodegenerative disorders, turn out to be more prevalent, they also consult with other specialists. Partnerships with hematologists interested in other malignancy precursor states (e.g., monoclonal B-cell lymphocytosis or MGUS) may help secure adequate resources and enable CH interventions in institutions and clinical settings where genetic testing is not routinely performed (Salem, et al., 2015). Solid tumor experts recommend a significant percentage of patients for hematological evaluation because up to 30% of those examined have CH (Coombs et al., 2017). Discretion may be made possible by the use of parallel sequencing, which involves sequencing a primary tumor (such as a solid tumor) and blood as a control to rule out germline variations. In addition, patients with non-hematologic neoplasms could be evaluated for prolonged or pronounced cytopenias in the setting of oncologic therapy.

In the context of the majority of CHIP instances, current treatments for myeloid neoplasia, such as lenalidomide or DNA hypomethylating drugs, are unlikely to be sufficiently selective or offer a positive risk-benefit balance. However, in some situations with big clones, the medications may delay the development of sickness and lower the total clonal burden, which could eventually be advantageous. IDH inhibitors and splicing inhibitors (like E782055) are examples of targeted medicines that are currently in use. Because high concentrations of vitamin C have been shown to restore TET2 function and disrupt aberrant leukemic stem cell self-renewal in preclinical models, an interventional trial of intravenous vitamin C is currently underway in TET2 mutant CCUS (NCT 03682029) (Cimmino et al., 2017).

The cardiovascular risk linked to CH is more significant from a public health perspective than the comparatively uncommon neoplastic development (Libby and Sidlow et al., 2019). Anti-inflammatory strategies are therefore beneficial in averting cardiac problems (Swirski 2018). Last but not least, it has been shown that the anti-interleukin 1b antibody canakinumab can stop history of myocardial infarction and stroke in individuals with increased C-reactive protein (Ridker et al., 2017). Colchicine, an antimacrophage drug, was found to be beneficial in reducing recurrent cardiac events in patients who had myocardial infarction in a placebo-controlled research (Tardif et al., 2019). Currently, the primary treatment for people with CH is blood count monitoring and management of known risk factors for heart disease. CHRS estimates myeloid malignancy risk and may be used to guide risk-specific management. There are still some important considerations, such as which individuals should have their bone marrow aspirated during the initial evaluation and how frequently prospective blood count monitoring should be done based on each patient's unique progression risk (Bolton et al., 2019). Although there is no agreement on precise methods, it appears reasonable that a patient with CCUS and several high-VAF mutations, including a splicing variant, should be observed more frequently than, say, a patient with just a DNMT3A non-R882 mutant clone of 2.5% VAF. Furthermore, it is still unclear which patients with clonal hematopoiesis should have further exercise stress testing or computed tomography coronary calcification assessment, as well as the ideal blood pressure and cholesterol targets. Lastly, a subset of patients would naturally experience psychological anxiety or worry upon learning about CH, similar to other clinical circumstances where a "watchful waiting" or active surveillance method is implemented (Rittenmeyer et al., 2016).

**9.0.Discussion**

The hematopoietic system has served as the standard illustration of stem cell biology for many years. Similar design principles were expected for other tissues: a hard-wired hierarchy with a rare, infrequently dividing (quiescent) stem cell at its base that produces its offspring via unidirectional differentiation pathways and asymmetric divisions. However, depending on their size, function, internal structure, and exposure to external assaults, different tissues and organs face quite varied threats to their integrity. Relevant concerns regarding genomic integrity are raised by the persistence of oxidative DNA damages, including 8-oxoG, in neural tissues despite cellular repair processes (Poetsch 2020). Leukemia and other genetic abnormalities further suggest that human genomes are dynamic. The mechanism of genetic antagonistic pleiotropy (AP) in which controlled mutagenesis increases gene regulation at the price of genomic integrity could provide a tenable explanation. Genes displaying AP are identified as key drivers in aging studies (Gems and Kern 2024). As seen in CH, the positive and negative effects of AP could manifest at various stages of a person's life. According to newer genetic technologies, SM is a key factor behind several human morbidities. Furthermore, SM seems to be a mechanism for human development, aging, and inter-individual variability. This paradox may be explained by a conceptual framework known as "fuzzy inheritance and the genome architecture theory," which suggests that SM not only causes disease but also enhances cellular adaptability and human diversity (Heng and Heng 2019). Overall, the research suggests that rather than individual genes determining system inheritance, the human genome serves as a distinct unit of selection for macroevolution. In conclusion, a range of internal and external forces continue to cause random genomic changes in the human genome with beneficial and detrimental effects. Only a small percentage of people over 50 will eventually create an enlarged clone (>2% VAF), despite the nearly universal occurrence of mutations in this population. This suggests that the competitiveness of non-mutated versus mutated HSC varies between individuals. In order to discover new causes and mutations, future research should take into account people from a variety of genetic ancestral backgrounds, given the wide range of variants in CH that have been discovered to date and germline vulnerability to CH with notable founder effects. The hematopoietic microenvironment is essential for preserving HSCs, controlling differentiation, controlling the production of blood cells, and causing hematological diseases (Seshadri and Qu (2016). New insights on CH will be gained by examining the variety of clonal niches seen in the bone marrow and how they support various facets of hematopoiesis. Furthermore, the intricate relationship between driver mutations and the tumor microenvironment is essential to comprehending the onset and progression of cancer and this relationship may extend to CH (Yuan et al., 2024). An indication of the underlying biology and genetics is the annual increase in the list of age-related and concomitant CH disorders. We will be able to manipulate the biology of CH at the developmental, genetic, and clinical levels by using animal models in the tree of life. These study results represent tenable research directions or hints that will facilitate the creation of interventional treatments. The emerging understanding of CH as a prevalent age-dependent occurrence and efforts to better identify and distinguish oncogenic clonal proliferation from benign must be coupled with worries about the danger of subsequent malignancies (Goldman et al., 2023).

**10.Conclusion**

The ontology of the hematopoietic system, stem cell biology, and medicine are few of the areas impacted by advances in our knowledge of CH. Understanding the fundamental biology and adaption mechanisms of aging hematopoiesis, as well as the mechanisms behind malignant transformation, is made possible by CH. Additionally, it could provide fresh insights into common characteristics of age-related illnesses like heart disease. It is proposed that CHIP may function as a biomarker of unhealthy aging worldwide. Researchers are also interested in the interaction of niche dynamics with somatically altered HSCs. Furthermore, nothing is known about the mechanisms underlying clonal growth in HSCs with Tet2 and Dnmt3a mutations, as well as the majority of other CHIP mutations. The ability to prospectively measure rates of clonal proliferation in individual MPN patients is limited, and there are still knowledge gaps, especially regarding the role of germline genetic factors on MPN pathogenesis and phenotypic variability. Therefore, the relevance of widespread screening for CHIP may become clear-cut if clones can be medically repressed. The assessment of CH at the nuclear level, namely chromatin, nucleosome occupancy, transcription factor occupancy, and RNA polymerase occupancy, has been made possible by scale-up techniques and technological advancements in the field of sequencing, such as hairpin duplex-enhanced fidelity sequencing and single-cell total RNA miniaturized sequencing. Methods such as single-cell 3C-seq techniques and Fiber-seq are making it possible to investigate genetic variations and CpG methylation. These advancements will be crucial to our comprehension of the clonal advantage mechanisms bestowed by SM and necessary for the creation of focused therapies. Insights into the effects of evolutionary processes on clonality and a few stochastic waves, as well as the importance of driver genes and mutations, are provided by this review, which updates the basic and clinical aspects of CH through a genetics and genomics lens. In future, hematologists may spend more time preventing malignant disasters and less time controlling them with further basic and translational research.

**Ethics declaration -** Since it a review no Human/animal studies were involved.

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**Tables and Figures**

Table-1. List of CH driver genes, variants and function

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sl.no** | **Gene** | **Common variant associated**  | **Biological function** | **References** |
| 1 | *JAK2*  | Val617Phe | Non-receptor tyrosine kinases which play a central role in cytokine and growth factor signaling.  | Bernstein et al., 2023 |
| 2 | *DNMT3A*  | Arg882Pro | DNA methyltransferase that is thought to function in de novo methylation, rather than maintenance methylation. |
| Arg882His |
| Arg882Cys |
| Glu774 |
| Trp306 |
| 3 | *SRSF2*  | Pro95Arg | Serine/arginine (SR)-rich family of pre-mRNA splicing factors, which constitute part of the spliceosome.  |
| Pro95Leu |
| Pro95His |
| 4 | *ASXL1*  | Arg417 | Encodes a chromatin-binding protein required for normal determination of segment identity in developing embryo. |
| Gln708 |
| 5 | *MTA2*  | Asp289Gly | Component of NuRD, a nucleosome remodeling deacetylase complex identified in the nucleus of human cells. |
| 6 | *TET2*  | Arg1452 | Methylcytosine dioxygenase which catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine.  |
| 7 | *SPRED2*  | Val56Phe | SPRED family of proteins which regulate growth factor-induced activation of the MAP kinase cascade. |
| 8 | *SF3B1*  | Lys700Glu | Subunit 1 of the splicing factor 3b protein complex.  |
| 9 | *PPM1D*  | Arg581 | PP2C family of Ser/Thr protein phosphatases-negative regulators of cell stress response |
| 10 | *TP53* | R273H R248QR249S  | Tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. | Chen 2022 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Methodology** | **Applicability** | **Detection of early and clonally expanded mutations** | **Advantages** | **Limitations** | **Reference** |
| Bulk sequencing | Any tissue | Majority | Mutation Sensitivity | Lacks Information on cell lineagesLow coverageCannot detect low-frequency mutations artefacts (10−4) | Coorens et al., 2025 |
| Duplex sequencing | Any tissue | Minority | Mutation spectrum as low as (0.5–2×) duplex coverage | MinorityLacks Information on cell lineagesDetect SNVs and indels Missing high-frequency mutations at low (0.5–2×) coverage |
| Single-cell WGA | Any tissue | Dependson cell number | Single-cell level in any tissue | Less than 50% sensitivity  |
| LCM clones | No | Depends on clone number | Accuray Single-cell level | Applicable to tissues with visible clonal substructures |

 Table-2. Summary of Mosaicism detection methods and their advantages and applications.

 Table-3. CH categories associated mutations and clinical, co-morbid disorders.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Fitness-inferred CH genes | **Gene** | **Mutation** | **Clinical disorder associated** | **Co-morbid disorders** | **References** |
| *BRCC3* | Truncating | Heme malignancyAcute lymphoblastic leukemiaCommon lymphoid malignanciesMultiple myeloma and related disorderChronic myeloid leukemialeukemiaMyeloid leukemiasMyelodysplastic diseasesMyeloproliferative neoplasms | InfectionsInfluenzaPneumoniaAcute upper respiratory infectionsAcute lower respiratory infectionsIntestinal infectious diseases | Bernstein et al., 2023. |
| *DNMT3A* | Truncating/Missense |
| *TET2* | Truncating/Missense |
| *ASXL1* | Truncating |
| *JAK2* | Missense |
| *ZBTB33* | Missense |
| *PPM1D* | Truncating |
| *SRSF2* | Truncating/Missense |
| *SF3B1* | Truncating/Missense |
| *GNAS* | Missense |
| Non- fitness-inferred CH genes | *SETD2* |  | Acute lymphoblastic leukemia Common lymphoid malignanciesChronic myeloid leukemia Myeloid leukemias Myelodysplastic diseasesMyeloproliferative neoplasms | InfectionsInfluenzaAcute upper respiratory infectionsIntestinal infectious diseases |
| *NF1* |  |

Table-4. Summary of differences betweeen Myeloid and Lymphoid Haematopoiesis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CH | **Frequency of CHIP (40-70 years)** | **Frequency of mCAs (40-70 years)** | **Frequent CHIP mutations and distribution** | **Frequent mCAs** | **Stage of Mutation**  |
| Myeloid Clonal Haematopoiesis | 5.8 % | 0.4% | DNMT3A, TET2, and ASXL1 mutations account for 87% of M-CHIP variants  | LOH,TCL1A, Del20q, LOH\_JAK2, Del5q, Tri8 | HSCs and immature myeloid precursors |
| Lymphoid Clonal Haematopoiesis | 1.3% | 0.8% | DUSP22, FAT1,KMT2D, SYNE1, and ATM mutations account for ~20% of L-CHIP variants | Tri12,LOH\_ITPKB, Del13q, LOH\_MIR16-1, LOH\_NOTCH1, Del10q | HSCs immature lymphoid precursors, and mature lymphocytes |









