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Distinct Characteristics of Lymphoid and Myeloid Clonal Hematopoiesis in World Trade Center First Responders

Myvizhi Esai Selvan[1] | Pei-Fen Kuan[2] | Xiaohua Yang[3] | John Mascarenhas[4] | Robert J. Klein[1] | Benjamin J. Luft[3,5] | Paolo Boffetta[5,6,7] | Zeynep H. Gümüş[1,4,8]

[1]Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York, New York, USA | [2]Department of Applied Mathematics and Statistics, Stony Brook University, Stony Brook, New York, USA | [3]World Trade Center Health and Wellness Program, Stony Brook University, Stony Brook, New York, USA | [4]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA | [5]Division of Infectious Diseases, Renaissance School of Medicine, Stony Brook University, Stony Brook, New York, USA | [6]Stony Brook Department of Family, Population and Preventive Medicine, Renaissance School of Medicine, Stony Brook, New York, USA | [7]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy | [8]Marc and Jennifer Lipschultz Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Correspondence: Zeynep H. Gümüş (zeynep.gumus@mssm.edu)

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To the Editor,

More than two decades after the 9/11 attacks, long-term health consequences for World Trade Center (WTC) rescue and recovery workers continue to emerge. Over 91 000 individuals participated in rescue, recovery, debris cleanup, and restoration of essential services. These first responders, including firefighters, police officers, paramedics, engineers, steel workers, railway tunnel workers, telecommunications specialists, sanitation workers, medical examiners, and volunteers, had no prior training in civil disaster response. These responders faced unprecedented exposure to a complex mix of known or suspected airborne carcinogens, raising concerns regarding their long-term cancer risk. WTC responders inhaled a toxic blend including benzene, formaldehyde, asbestos, silica, cement dust, glass fibers, heavy metals, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzofurans, and dioxins [1]. While the carcinogenicity of these individual compounds is well documented, their collective impact on hematologic malignancy risk remains poorly characterized, creating a critical knowledge gap.

A key mechanism potentially linking environmental exposures to cancer development is clonal hematopoiesis [2], where a subpopulation of blood cells harbors clonal genomic mutations associated with blood cancers, without detectable hematologic disorders or unexplained persistent cytopenia. Clonal hematopoiesis of indeterminate potential (CHIP) involves clonal subpopulations carrying a point mutation or short insertion/deletion with a variant allele fraction (VAF) of at least 2% in genes recurrently mutated in hematologic malignancies. While most research has focused on myeloid lineage CHIP (M-CHIP), lymphoid lineage CHIP (L-CHIP) also occurs and may contribute to lymphoid malignancy risk, though it remains understudied. Beyond cancer risk, CHIP is associated with cytopenias, cardiovascular disease, infection susceptibility, and all-cause mortality, making it a potentially important biomarker for multiple health conditions relevant to WTC responders.

To characterize the full spectrum of CHIP mutations in WTC responders, we performed ultra-deep Whole Exome Sequencing (WES) at 250× on 350 blood samples from 345 participants from the World Trade Center Health Program (WTCHP) General Responders Cohort (GRC) cohort aged 48–90 years (median, 59 years), without a history of hematologic malignancy at enrollment (Figure 1A, Table 1). After rigorous quality control, we identified M-CHIP and L-CHIP mutations (Figure 1B, Table S1) and analyzed their associations with age, ancestry, WTC exposure, HLA zygosity, and various clinical, laboratory,

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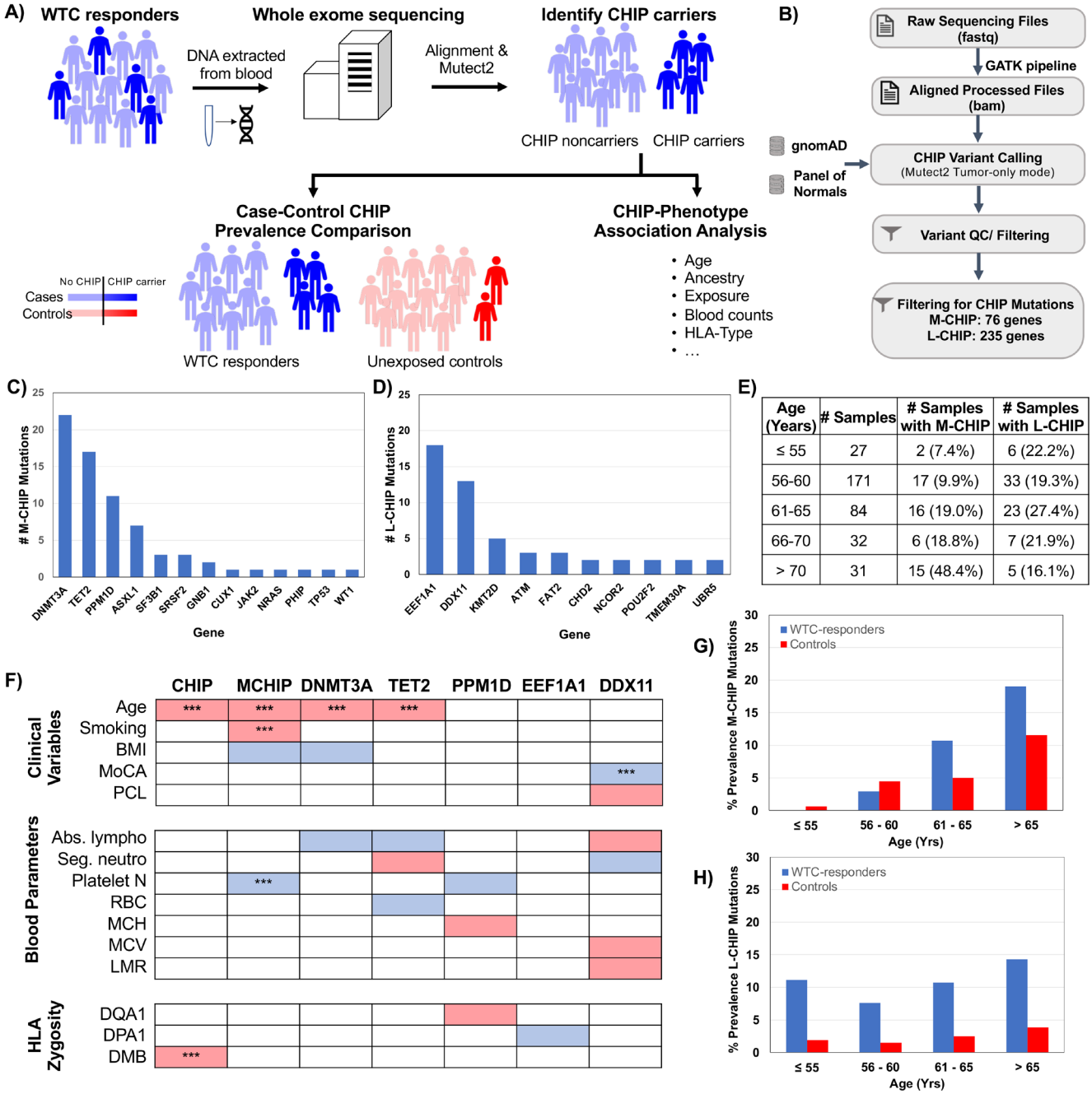

Age (Years)	# Samples	# Samples with M-CHIP	# Samples with L-CHIP
≤ 55	27	2 (7.4%)	6 (22.2%)
56-60	171	17 (9.9%)	33 (19.3%)
61-65	84	16 (19.0%)	23 (27.4%)
66-70	32	6 (18.8%)	7 (21.9%)
> 70	31	15 (48.4%)	5 (16.1%)

FIGURE 1 | (A) Study outline—To understand CHIP prevalence in WTC debris-exposed first responders, we collected blood from participants, extracted DNA, and performed deep WES at 250× on 350 samples. Next, we aligned the exomes to the human genome and called somatic variants using Mutect2 to identify CHIP carriers, the specific CHIP mutations and VAF. Additionally, we compared CHIP prevalence in WTC debris-exposed first responders to healthy controls from the New York City area. Finally, we associated CHIP prevalence with respect to age, ancestry, exposure, cognitive/metal data, HLA zygosity, blood counts and other clinical variables; (B) WES data analysis pipeline to identify CHIP mutations; (C) Number of M-CHIP mutations observed in each gene; (D) Number of L-CHIP mutations observed in top genes (#Mutations > 1); (E) Prevalence of M-CHIP and L-CHIP mutations; (F) CHIP-phenotype associations—Heatmap shows significant associations between overall CHIP, M-CHIP, M-CHIP driven by *DNMT3A*, *TET2*, *PPM1D* mutations, and L-CHIP driven by *EEF1A1*, *DDX11* mutations versus clinical variables, blood parameters and HLA zygosity. Blue and red correspond to significant ($p \leq 0.05$) negative (OR < 1) and positive (OR > 1) correlation. White represents absence of significant correlation. Asterisk represents significant associations ($p \leq 0.05$) in the multivariate regression analysis; (G) M-CHIP mutation prevalence in 345 WTC debris-exposed individuals (blue) and 293 unexposed controls (red) as a function of age; (H) L-CHIP mutation prevalence in 345 WTC debris-exposed individuals (blue) and 293 unexposed controls (red) as a function of age. A statistically significant difference in prevalence was observed between the two groups ($p = 0.031$).

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TABLE 1 | Characteristics of the World Trade Center Health Program (WTCHP) General Responders Cohort (GRC) members selected for WES in this study (the WTC cohort), which, after sample QC that removed duplicates, totaled 345 individuals.

Phenotype	Category	# Samples (%)
Sex (M/F = 12.3)	Male (M)	319 (92.5%)
	Female (F)	26 (7.5%)
Smoking status	Current smoker	15 (4.3%)
	Previous smoker	154 (44.6%)
	Never smoker	176 (51.0%)
Race	White/Caucasian	314 (91.0%)
	Black/ African–American	12 (3.5%)
	Other race	13 (3.8%)
	Unknown	6 (1.7%)
Age (yrs) Median = 59 SD = 5.90	≤ 55	27 (7.8%)
	56–60	171 (49.6%)
	61–65	84 (24.3%)
	66–70	32 (9.3%)
	> 70	31 (9.0%)
Derived exposure level	Very high	15 (4.3%)
	High	55 (15.9%)
	Intermediate	210 (60.9%)
	Low	50 (14.5%)
	Very low	6 (1.7%)
	Missing/no record	9 (2.6%)

mental, and cognitive metrics. CHIP prevalence was also compared to an unexposed New York City control cohort ($n = 293$; Table S2). Detailed methodology is provided in the Supporting Information.

We found that 34.2% (118/345) of WTC participants harbored at least one CHIP mutation. 16.2% harbored M-CHIP mutations (56 participants, 71 mutations, 13 genes), and 21.4% carried L-CHIP mutations (74 participants, 85 mutations, 43 genes) (Table S3). Clonal complexity (≥ 2 mutations) was present in 7.0% (24/345), and 3.5% (12 participants) carried both M-CHIP and L-CHIP mutations. The majority (> 80%) of CHIP-positive participants harbored only a single mutation (Figure S1). Among M-CHIP mutations, 39% were non-synonymous, 30% were stop-gain, 23% were frameshift deletions, and the remainder were frameshift insertions and splicing variants. The majority of L-CHIP mutations (87%) were non-synonymous, 9% were stop-gain, and the rest were frameshift insertions/deletions (Figure S1). The most frequently mutated M-CHIP genes were *DNMT3A*, *TET2*, *PPM1D*, and *ASXL1*, and L-CHIP genes were *EEF1A1*, *DDX11*, *KMT2D*, *ATM*, and *FAT2* (Figure 1C,D). Mutations in *EEF1A1* (21%) and *DDX11* (15%), particularly at (*EEF1A1*:E293K, *EE1F1A*:V315L and *DDX11*:P368S) drove the L-CHIP signal. Among all CHIP mutations, *TET2* exhibited the highest VAF (Figure S2).

Consistent with prior studies [3], M-CHIP prevalence increased with age, especially for *DNMT3A* and *TET2*, which remained significant in multivariate logistic regression (Figure 1E,F, Table S4). Median ages for CHIP-positive, M-CHIP, *DNMT3A*-mutant, and *TET2*-mutant participants were 61, 62, 66.5, and 64 years respectively, compared to 59 years for CHIP-negative participants. Smoking history positively associated with M-CHIP in both univariate and multivariate regression analyses. Associations between BMI and M-CHIP, particularly BMI and *DNMT3A*, may require larger sample sizes to clarify.

As WTC responders age, they face increased risks for neurocognitive and motor dysfunction that resembles neurodegenerative diseases, along with cortical atrophy and cognitive impairment at midlife, associated with both physical exposures at the WTC site and chronic PTSD. Notably, participants with *DDX11* mutations showed significantly higher PTSD Checklist (PCL) scores (indicating greater PTSD severity) and lower Montreal Cognitive Assessment (MoCA) scores (indicating mild cognitive impairment) (Figure 1F). MoCA score association remained significant in multivariate logistic regression. The median MoCA score for participants with *DDX11* mutations was 22, falling within the range indicative of mild cognitive impairment. Given that *DDX11* is a helicase involved in altering RNA secondary structure, and helicase dysfunction has been implicated in neurodegeneration, these findings suggest a link between CHIP and neurocognitive outcomes worthy of further investigation.

In laboratory parameters (Figure 1F, Figure S3), M-CHIP positive cases showed lower platelet counts in both univariate and multivariate regression models compared to CHIP-negative cases. *DNMT3A* and *TET2* mutation carriers had lower absolute lymphocyte counts, and *TET2* mutation was also associated with lower red blood cell (RBC) counts and higher segmented neutrophils. *PPM1D* mutations correlated with lower platelet counts and higher mean corpuscular hemoglobin (MCH). *DDX11* mutation carriers demonstrated elevated absolute lymphocyte counts, mean corpuscular volume (MCV), lymphocyte-to-monocyte ratio (LMR), and lower segmented neutrophil counts.

Comparative analyses against UK Biobank data [4] highlighted both convergent (e.g., *TET2* with lower lymphocyte counts and *PPM1D* with lower platelet counts) and divergent (e.g., M-CHIP associations with lower platelet counts and *TET2* associations with elevated segmented neutrophil counts) patterns. However, multivariate analysis adjusting for age and other factors attenuated most associations. Differences may reflect WTC-debris exposure or methodological factors.

Recent population-level studies suggest that abnormal complete blood counts (CBC) may predict future CHIP development, and CHIP-positive individuals with abnormal myeloid or lymphoid counts face the highest risks for corresponding malignancies. Thus, CHIP-positive WTC responders with elevated myeloid and/or lymphoid blood counts may represent a high-priority subgroup for enhanced surveillance. Given the emerging interest in targeting inflammatory pathways using inhibitors of

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IL-1β, *NLRP3*, and *IRAK1* in CHIP, such interventions in high-risk CHIP-positive WTC participants may help prevent or delay overt myeloid neoplasms, CVD, major bleeding, and infection.

Next, cognizant of CHIP association with immune dysfunction, we examined Human Leukocyte Antigen (HLA) type (both classes I and II) zygosity in relation to CHIP. The heterozygote advantage hypothesis suggests that heterozygous HLA genotypes may confer broader immune response capabilities than homozygous HLA genotypes. CHIP prevalence was statistically significantly associated with *HLA-DMB* homozygosity, which remained significant in multivariate logistic regression, with weaker associations between *PPM1D* and *HLA-DQA1* homozygosity, and inverse associations between *EEF1A1* and *HLA-DPA1* homozygosity. These findings implicate HLA Class II antigen presentation in CHIP risk, supporting a role for immune-genetic interactions.

Note that cross-study comparisons of CHIP prevalence remain challenging due to evolving definitions and lack of standardized analytical pipelines. The 2022 World Health Organization CHIP definition includes somatic mutations in myeloid malignancy-associated genes at VAF ≥ 2% (≥ 4% for X-linked gene mutations in males) in individuals without hematologic disorders or unexplained cytopenia. However, no guidelines exist on corresponding read depth requirements, as mutations with a true VAF of 2% are more likely missed at 30× than 250× depth. Studies also vary on CHIP variants/genes, without international consensus, and no established "gold standard" analysis pipelines exist for CHIP detection. Technical artifact filtering also varies between studies, further complicating cross-study comparisons. Therefore, we compared CHIP prevalence to healthy, unexposed controls from the New York area using the same CHIP calling pipeline. We observed a generally higher CHIP prevalence in the WTC cohort (Figure 1G,H, Table S5). After down-sampling for comparable sequencing coverage, the prevalence of detectable M-CHIP mutations in our WTC cohort was 7.5% (26/345) and L-CHIP was 9.9% (34/345), while in unexposed controls M-CHIP was 3.1% (9/293) and L-CHIP was 2.0% (6/293). Notably, L-CHIP mutations were statistically significantly more prevalent in WTC participants versus controls ($p = 0.031$). However, M-CHIP prevalence did not reach statistical significance ($p = 0.693$). At gene level, *EEF1A1* ($p = 0.024$) and *DDX11* ($p = 0.071$) were elevated in WTC responders (Figure S4).

This is the first comprehensive characterization of CHIP mutation patterns across occupational groups in WTC responders, leveraging extensive clinical, laboratory, cognitive, and HLA zygosity data, and the first characterization of L-CHIP in a WTC-associated cohort. Our findings expand on previous research focused primarily on firefighters [5], given the documented elevated cancer risks for those who were not firefighters [6]. Furthermore, using deep WES allowed an unbiased survey across myeloid and lymphoid genes, creating a valuable resource for future studies as CHIP definitions evolve.

This study has broader implications. Other populations exposed to large-scale fires and collapses, including civilians in modern warfare in populated cities, may also face elevated CHIP risks. Future research should aim to refine cancer risk prediction models that include CHIP status, blood counts, and demographic factors to guide early detection strategies. Although relative risks are increased, the absolute risk of malignancy in CHIP-positive individuals remains low, underscoring the need for careful risk stratification rather than blanket interventions. As CHIP clinics emerge at academic centers, longitudinal data will inform improved risk models, allowing high-risk individuals to be monitored appropriately and potentially enrolled in clinical trials.

Study limitations include occupational confounders in our unexposed controls, inability to detect mosaic chromosomal alterations via WES, modest sample size limiting detection of subtle associations (particularly for L-CHIP), and the risk of false positives from multiple comparisons. Independent validation cohorts will be critical to confirm these findings.

Author Contributions

P.B. and Z.H.G. conceived and designed the study. M.E.S., P.F.K., R.J.K., and Z.H.G. wrote the manuscript. B.J.L. and X.Y. recruited participants and handled sample and data collection. Z.H.G. led sample sequencing at Azenta Inc. M.E.S. performed sequence analyses, and P.F.K. performed statistical analyses. All authors were involved in the interpretation of the results. B.J.L., J.M., and P.B. edited the manuscript. Z.H.G. supervised the study. All authors approved the final manuscript.

Ethics Statement

The study received annual approval under IRB #604113 from the Committees on Research Involving Human Subjects at SBU.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

We will deposit the whole exome sequencing data of the WTC responders in the database of Genotypes and Phenotypes (dbGaP).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Information Table S1.** List of (A) myeloid associated (M-CHIP) mutations and (B) lymphoid associated (L-CHIP) mutations considered in this study. **Supporting Information Table S2**. Characteristics of the 293 unexposed controls from the MSCCR cohort. **Supporting Information Table S3**. All CHIP mutations identified among the 345 WTC samples. (A) M-CHIP mutations identified in WTC samples; (B) L-CHIP mutations identified in WTC samples; (C) Distribution of M-CHIP mutations by genes; (D) Distribution of L-CHIP mutations by genes; (E) M-CHIP mutations identified in downsampled WTC samples; (F) L-CHIP mutations identified in downsampled WTC samples; (G) M-CHIP mutations identified in controls; (H) L-CHIP mutations identified in controls. **Supporting Information Table S4**. CHIP-phenotype associations. (A) CHIP; (B) M-CHIP; (C) L-CHIP; (D) *DNMT3A*; (E) *TET2*; (F) *PPM1D*; (G) *EEF1A1*; (H) *DDX11*. **Supporting Information Table S5**. Prevalence of M-CHIP and L-CHIP mutations in down-sampled 345 WTC debris-exposed first responders and 293 unexposed controls. **Supporting Information Figure S1**. Characteristics of M-CHIP and L-CHIP mutations in 345 WTC debris-exposed first responders. (A) Number of participants with 1, 2, 3, and 4 M-CHIP mutations; (B) Number of different types of M-CHIP mutations; (C) Number of participants with 1,2, 3, and 4 L-CHIP mutations; (D) Number of different types of L-CHIP mutations. **Supporting Information Figure S2**. Variant allele fractions (VAFs) of M-CHIP and L-CHIP mutations. (A) VAF histogram of M-CHIP mutations; (B) VAF histogram of L-CHIP mutations; (C) VAF distribution of top M-CHIP gene mutations; (D) VAF distribution of top L-CHIP gene mutations. Based on VAF, *TET2* exhibited the largest M-CHIP clones, while *EEF1A1* and *DDX11* exhibited the largest L-CHIP clones. **Supporting Information Figure S3**. Comparison of key laboratory parameters between different groups. (A) Absolute lymphocyte counts; (B) Segmented neutrophil counts; (C) Platelet counts; (D) Red blood cell (RBC) counts; (E) Mean corpuscular hemoglobin (MCH); (F) Mean corpuscular volume (MCV) (G) Lymphocyte-to-monocyte ratio (LMR). **Supporting Information Figure S4**. Characteristics of M-CHIP and L-CHIP mutations in 345 WTC debris-exposed responders (blue) and 293 unexposed controls (red). (A) Genes with M-CHIP mutations; (B) Genes with L-CHIP mutations.

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