Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations

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The selective pressures that shape clonal evolution in healthy individuals are largely unknown. Here we investigate 8,342 mosaic chromosomal alterations, from 50 kb to 249 Mb long, that we uncovered in blood-derived DNA from 151,202 UK Biobank participants using phase-based computational techniques (estimated false discovery rate, 6–9%). We found six loci at which inherited variants associated strongly with the acquisition of deletions or loss of heterozygosity in cis. At three such loci (MPL, TM2D3–TARSL2, and FRA10B), we identified a likely causal variant that acted with high penetrance (5–50%). Inherited alleles at one locus appeared to affect the probability of somatic mutation, and at three other loci to be objects of positive or negative clonal selection. Several specific mosaic chromosomal alterations were strongly associated with future haematological malignancies. Our results reveal a multitude of paths towards clonal expansions with a wide range of effects on human health.

Clonal expansions of blood cells containing somatic mutations are often observed in individuals without cancer1–13. Consistent with the idea that clonal mosaicism can be a precancerous state, detectable mosaicism confers a more than tenfold increased risk of future haematological malignancy14–16 and often involves pro-proliferative mutations. Several studies have suggested that inherited variation can influence the likelihood of clonal mosaicism17–21.

The limiting factor in almost all studies of clonal mosaicism has been sample size, with earlier insights arising from analyses of up to around 1,000 mosaic events. Two key factors determine the number of detectable mosaic mutations: the number of individuals analysed, and the ability to detect clonal expansions present at low-to-modest cell fractions. Here we describe insights from an analysis of 8,342 mosaic chromosomal alterations (mCAs) which we identified in single nucleotide polymorphism (SNP) array data from 151,202 UK Biobank participants22 using a sensitive algorithm we developed to make use of long-range haplotype phase information (building on published work23). We also draw upon data on health outcomes during 4–9 years after DNA sampling.

These data provide insights into clonal expansion, including mechanisms by which inherited variants at several loci act in cis to generate or propel mosaicism. We also identify specific mCAs that associate strongly with future haematological malignancies.

Mosaic chromosomal alterations in UK Biobank

We analysed allele-specific SNP-array intensity data previously obtained by genotyping blood-derived DNA from 151,202 UK Biobank participants (40–70 years of age)22; 607,525 genotyped variants remained after quality control (see Methods). We detected mCAs at cell fractions as low as 1% by using long-range phase information that is uniquely available in the UK Biobank23,24. Intuitively, accurate phasing allows the detection of subtle imbalances in the abundances of two haplotypes by combining allele-specific information across a very large number of SNPs (Extended Data Fig. 1). To make maximal use of phase information, we developed a new statistical method for phase-based mCA detection (see Methods and Supplementary Note 1).

We detected 8,342 mCAs (in 7,484 of the 151,202 individuals analysed) at an estimated false discovery rate (FDR) of 6–9% (Fig. 1, Extended Data Fig. 2, Supplementary Table 1, and Supplementary Notes 2, 3; validation rates could differ from this FDR estimate). We confidently classified 71% of the detected mCAs as either loss, copy-number neutral loss of heterozygosity (CNN-LOH), or gain; for the other 29% of events, copy-number state could not be inferred definitively (Fig. 2a and Supplementary Note 1). Most detected mCAs (5,901 of 8,342) were present at inferred cell fractions below 5% (Supplementary Note 4) and would have been undetectable without long-range phasing (Supplementary Note 5). The genomic distribution of detected mCAs was broadly consistent with those found in previous studies12,7,8, as was the observation that individuals acquire multiple mCAs much more frequently than expected by chance (Fig. 2b, Extended Data Fig. 3, Supplementary Tables 2, 3, and Supplementary Note 6); differences (for example, in relative rates of del(20q) calls25) could be explained by differing methodological sensitivity or genotyping platforms (Supplementary Note 4).

Commonly deleted regions (CDRs) below 1 Mb in length may indicate haploinsufficient tumour-suppressor genes for which loss of one copy promotes cell proliferation26. Focal deletions most frequently targeted 13q14, DNMT3A, and TET2, as previously observed26,27; we further observed that most CNN-LOH events on 13q, 2p, and 4q spanned the same CDRs (Fig. 1 and Supplementary Note 7). We

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detected new CDRs at ETV6, NF1, and CHEK2, which are commonly mutated in cancers, and at RPA2 and RYBP. We also detected a CDR at 16p11.2 overlapping a region whose deletion is a known risk factor for autism and other neuropsychiatric phenotypes, though we did not detect this mCA among 2,079 sequenced genomes from the Simons Simplex Collection (SSC)\(^{26,27}\) (Supplementary Note 8). Deletions tended to be concentrated on chromosomes that are seldom duplicated\(^{28}\) (Fig. 2c and Supplementary Table 1), supporting the theory that cumulative haploinsufficiency and triplosensitivity shape clonal evolution\(^{29}\).

We found several notable exceptions to a general pattern in which acquired mutations are most common in the elderly and in males\(^{1,2,3,9}\) (Fig. 2d and Supplementary Table 4). Loss of chromosome X in females\(^ {10}\) was by far the most common event we detected (Supplementary Table 1 and Supplementary Note 2), with frequency increased markedly with advancing age (Supplementary Table 4). (We did not examine loss of chromosome Y, which has been studied elsewhere\(^{21}\)). Stratification of autosomal mCAs by location and copy number revealed an unexpected relationship: although most gain events were (as expected) enriched in elderly individuals and in males, CNN-LOH events tended to affect both sexes equally (Fig. 2e and Supplementary Table 5). Three mCAs exhibited unusual age and sex distributions (FDR 0.05; binomial and \( \chi^2 \)-tests): gains on chromosome X in females\(^ {30}\) was by far the most common event we detected (Supplementary Table 5). Three mCAs exhibited unusual age and sex distributions (FDR 0.05; binomial and \( \chi^2 \)-tests): gains on chromosome X in females\(^ {30}\) was by far the most common event we detected. The mCA at 16p11.2 overlapping a region whose deletion is a known risk factor for autism\(^ {34,35}\) at the estimated common breakpoint of the 10q deletions (Table 1 and Fig. 3a). All 60 individuals with these mosaic 10q deletions had inherited the rs118137427:G risk allele (the allele frequency is 5% in the population), which was always inherited on the same chromosome that subsequently acquired a terminal deletion (Table 1).

To identify a causal variant potentially tagged by the rs118137427:G risk allele, we searched for acquired 10q deletions in WGS data from 520 SSC families (see Methods). We identified two parent–child duos in which both parent and child had acquired the 10q terminal deletion (in mosaic form); all four individuals possessed expanded AT-rich repeats at FRA10B on the rs118137427:G haplotype background\(^ {36,46}\) (Fig. 3c).

Further evidence that the rs118137427:G risk allele tags an unstable version of the FRA10B locus\(^ {36,46}\) was provided by analysis of the variable number tandem repeat (VNTR) sequence at FRA10B (in all 2,079 individuals). This analysis revealed a diversity of novel VNTR sequence motifs (12 distinct primary repeat units carried by 69 individuals from 14 families), all on the rs118137427:G haplotype background (Extended Data Fig. 5a, b and Supplementary Note 8). (The VNTR motifs did not associate with autism status in the SSC cohort.) The motifs had lengths of 38, 39, 42, and 43 bp and exhibited evidence of repeat expansion (probably more than 75 copies in the longest alleles\(^ {36}\)); by contrast, the hg19 reference sequence at FRA10B contains three copies of a 40-bp repeat. Imputing the VNTRs into the UK Biobank showed that they explained 24 of 60 del(10q) cases, despite being present in only about 0.7% of the cohort (Supplementary Table 7). Notably, individuals with del(10q) were as young as other UK Biobank participants, and 51 of 60 were female (binomial \( P = 0.1 \times 10^{-7} \)))) (Fig. 3b); these unusual patterns (which were shared with 16p11.2 deletions) will require further study (Supplementary Note 8).

CNN-LOH events on chromosome (chr)1p strongly associated (\( P = 6.2 \times 10^{-16} \)); lead SNP rs144279563) with three independent, rare risk haplotypes (allele frequencies \(0.01–0.05\%\)) at the MPL proto-oncogene at 1p34.1; the three haplotypes increased risk for 1p CNN-LOH by factors of 53, 63, and 103 (95% confidence intervals (CIs): 28–99, 29–139, and 35–300, respectively) (Table 1, Fig. 4a, and Supplementary Table 8). Other individuals with 1p CNN-LOH mosaicism also shared by examining individuals in the top percentile for counts of lymphocytes, basophils, monocytes, neutrophils, red blood cells, or platelets. We identified many mCAs that were significantly concentrated (FDR 0.05; Fisher’s exact test) in one or more of these subsets of the cohort (Fig. 2f and Supplementary Table 6). Consistent with the idea that these relationships might reflect clonal selection in specific blood cell types, mutations commonly observed in chronic lymphocytic leukaemia (CLL)\(^ {32,33}\) were enriched among individuals with high lymphocyte counts, and JAK2-related 9p events (which are commonly observed in myeloproliferative neoplasms (MPNs)) were most common among individuals with high myeloid cell counts. While future work will be needed to replicate and further explore these findings, our results suggest that mCAs may produce blood-composition phenotypes in individuals with no known malignancy.
long haplotypes containing MPL, suggesting the existence of additional very rare risk variants (Extended Data Fig. 5c). Notably, although gain-of-function mutations in MPL lead to myeloproliferative neoplasms,9,10 the lead SNP on one haplotype, rs369156948, is a protein-truncating variant (PTV) in MPL with no association to haematological malignancies in the UK Biobank (0 cases among 36 carriers).

We were able to identify a likely mechanism for selection of the CNN-LOH events involving MPL. For all 16 events for which we could confidently phase the inherited risk allele relative to the somatic CNN-LOH, the CNN-LOH mutation had replaced the clonal haematopoiesis risk allele with the reference allele (binomial $P = 3 \times 10^{-5}$; Table 1 and Fig. 4a). These results suggest that, among individuals with rare inherited variants that reduce MPL function, recovery of normal MPL gene activity via CNN-LOH provides a proliferative advantage. CNN-LOH events on chr1q associated ($P = 7.4 \times 10^{-4}$, OR = 41 (18–94)) with a rare haplotype (allele frequency = 0.07%)
surrounding the ATM gene at 11q22.3 (Table 1, Fig. 4b, and Supplementary Table 8). For all six CNN-LOH events for which we could confidently phase the risk allele relative to the somatic mutation, the LOH mutation had caused the rare risk allele to become homozygous, suggesting that the risk allele confers a proliferative advantage in the homozygous state (Table 1 and Fig. 4b). (This dynamic contrasts with that of MPL, at which the rare, inherited risk haplotypes were eliminated by LOH and clonal selection.) While sequencing would be required to identify a causal variant, ATM is a clear putative target: ATM encodes a DNA-damage response kinase that promotes DNA repair and limits cell division, and ATM is often inactivated by mutation in cancers.  

In our analysis, acquired 11q deletions also appeared to target ATM (Fig. 1 and Supplementary Note 2).

CNN-LOH and loss events at chr15q associated strongly \( (P = 1.3 \times 10^{-8}) \) with a rare, inherited 70-kb deletion (allele frequency 0.03%) that spanned all of TM2D3 and part of TARSL2 at 15q26.3 (Table 1, Fig. 4c, and Extended Data Figs. 6, 7). For 39 of 41 events with high-confidence phase calls, the CNN-LOH or loss was inferred to produce homozygosity or hemizygosity of the inherited deletion, removing the reference (non-risk) allele from the genome. (This dynamic resembles that of ATM in suggesting clonal selection for the rare, inherited risk allele.) The 70-kb deletion increased risk of 15q mosaicism by a factor of 698 (442–1,102); 45 of 89 carriers exhibited detectable 15q events (32 CNN-LOH; 2 loss, 11 ambiguous between CNN-LOH and loss). Notably, the 70-kb deletion was sometimes inherited on an allele that also had an independent 290-kb duplication of the locus (Extended Data Fig. 6); on this more complex allele, TM2D3 and TARSL2 gene dosage were normal. Carriers of the more complex allele did not exhibit predisposition to mCAs. Further study will be required to determine a proliferative mechanism involving TM2D3, TARSL2, or noncoding elements within the region.

The high penetrances (up to 50%) for the above \( cis \) associations led us to suspect that some risk-allele carriers might harbour multiple subclonal cell populations with the associated alterations. Using a modified version of our methodology, we detected 39 individuals who had acquired two or more CNN-LOH mutations (with different breakpoints and allelic fractions) involving the same chromosome (Extended Data Fig. 8 and Supplementary Note 1). For all 39 individuals with multiple same-chromosome CNN-LOH events, all events involved recurrent selection of the same haplotype (in different clones). Of these 39 haplotypes, 16 carried a risk allele identified by our association scans, 13 appeared to involve other (undiscovered) alleles at the same loci, 5 duplicated 13q14 deletions, and 5 involved other genomic loci (Extended Data Fig. 8). This result indicates strong proliferative advantage conferred by CNN-LOH in these individuals and suggests that mitotic recombination occurs sufficiently to yield multiple opportunities for clonal selection in individuals carrying inherited haplotypes with different proclivities for proliferation.

We also found two common variants on chromosome X that weakly increase risk of X loss while strongly influencing (in heterozygous females) which X chromosome is lost in the expanded clone. These involved a strong association \( (P = 6.6 \times 10^{-22}, 1.9:1 bias in the lost haplotype) \) at Xp11.1 near DXZ4 and a weaker association \( (P = 1.0 \times 10^{-9}, 1.5:1 bias in the lost haplotype) \) at Xq23 near DXZ4 (Table 1, Supplementary Table 9, and Supplementary Note 9). These associations do not appear to be explained by biased X chromosome inactivation\(^\text{28}\) (Supplementary Table 10) and hint at yet another mechanism, different from those we have described.

**Trans associations with mCAs**

Genetic variants near genes involved in cell proliferation and cell cycle regulation predispose for male loss of Y\(^\text{19,21}\), and female loss of X is also heritable \( (h^2 = 26\% \text{ (17.4–36.2\%) } \) in sib-pair analysis\(^\text{22}\), but no associations for X loss have previously been reported, to our knowledge. We confirmed the heritability of female X loss by performing BOLT-REML\(^\text{40}\) analysis (see Methods), obtaining a SNP-heritability estimate of \( h^2 = 10.6\% \text{ (s.e. 3.6\%) } \). Genome-wide association analysis for \( trans \) variants influencing X loss further revealed two genome-wide significant associations at the SP140L and HLA loci (Table 1).
Germline variants affecting cancer risk or chromosome-maintenance phenotypes could in principle increase the risk of clonal expansions. We considered 86 variants that have been implicated in previous genome-wide association studies (GWAS) on CLL, MPN, Y loss, clonal haematopoeisis, and telomere length and tested these variants for association with seven classes of mCAs, stratifying events by copy number and by autosome versus X chromosome. Four variants reached Bonferroni significance (P < 8.3 × 10⁻⁵): two linked variants in TERT41,20,41, a rare frameshift mutation in CHEK220, and a low-frequency 3’ untranslated region (UTR) SNP in TP5321,42 (Supplementary Table 11). The TERT and CHEK2 variants associated with multiple types of autosomal event; by contrast, the TP53 SNP primarily associated with losses (both focal autosomal deletions and X losses). Carriers of the CHEK2 frameshift mutation were especially prone to developing multiple mCAs (one-sided binomial P = 0.008): 8 of 33 carriers with detected autosomal mosaicism had two or more mCAs, generally in multiple clones.

Mosaic chromosomal alterations and subsequent health
 Cancer-free individuals with detectable mosaicism (at any locus) have a more than tenfold elevated risk of subsequent haematological cancer diagnoses1–4. For CLL, a slowly progressing cancer that is known to be preceded by clonal mosaicism years before progression6,44, mosaic alterations observed in patients who go on to develop CLL occur at the same loci as those observed in patients with CLL32,33,45,46. Using data on health outcomes for UK Biobank participants 4–9 years (median 5.7 years) after DNA sampling, we identified nine specific mCAs that were significantly associated (FDR 0.05) with subsequent haematological cancer diagnoses (more than 1 year after DNA collection) in analyses corrected for age and sex and restricted to individuals with normal blood counts at assessment (Fig. 5a and Supplementary Table 12), confirming and providing additional resolution to previous findings1,2. A logistic model combining mosaic status for CLL-associated events with other risk factors—age, sex, CLL genetic risk score47, and lymphocyte count—achieved high CLL prediction accuracy (area under the curve (AUC) = 0.81) in tenfold cross-validation (Fig. 5b and Extended Data Fig. 9). Most of this predictive power came from early clones with trisomy 12, which we could detect at very low cell fractions (Extended Data Figs. 9, 10). Individuals with incident CLL exhibited clonality up to six years before diagnosis, and clonal fraction inversely correlated with time to malignancy (Fig. 5c). We further observed that detectable mosaicism roughly doubled risk for all-cause mortality (corrected for age, sex, and smoking status). This association was explained only partly by cancer deaths (Fig. 5d and Supplementary Table 13) and could reflect effects on cardiovascular illness32, although further study is needed to explore this finding and rule out residual confounding.

Discussion
 Mosaicism typically results from mutation followed by selective proliferation10, and our results uncover diverse biological mechanisms underlying this transformation. We identified very rare inherited variants that affect either the likelihood of mutation (at FRA10B) or its proliferative impacts (due to CNN-LOH in cis), and we also observed trans influences on clonal haematopoeisis in the cell cycle genes TP53, CHEK2, and TERT. Our findings of cis risk loci for CNN-LOH expansions are particularly noteworthy: while some CNN-LOH expansions have previously been observed to provide a second hit to a frequently mutated locus33 or to disrupt imprinting20, here we observed that CNN-LOHs can also achieve strong selective advantage by duplicating or removing inherited alleles. The high penetrances (up to 50%) of the inherited CNN-LOH risk variants we identified challenge what is usually seen as a fundamental distinction between inherited alleles and (more capricious) acquired mutations. A large fraction of carriers of the inherited alleles subsequently acquire and then clonally amplify the mutations in question. The high penetrances imply that mitotic recombination is sufficiently common to predictably unleash latent, inherited opportunities for clonal selection of homozygous cells during the lifespan of an individual, corroborating a recent observation of this phenomenon in skin50. Similarly, we observed Mendelian inheritance patterns for 10q breakage at FRA10B, despite this event involving an acquired mutation.
 Clonal expansions exhibit varying levels of proliferation and biological transformation and thus have a spectrum of effects on health10. We found that many mCAs, including some of those driven by cis-acting genetic variation, had no discernible adverse effects. However, mCAs commonly seen in blood cancers strongly increased cancer risk and could potentially be used for early detection—although we caution that these results are based on relatively short follow-up (4–9 years of cancer outcomes) and need independent replication. As population-scale efforts to collect genotype data and health outcomes continue to expand—increasing both sample sizes and the power of population-based chromosomal phasing—we anticipate ever-more-powerful analyses of clonal haematopoeisis and its clinical sequelae.

Online content
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METHODS
No statistical methods were used to predetermine sample size. The experiments were not randomized and the investigators were not blinded to allocation during experiments and outcome assessment.

UK Biobank cohort and genotyping intensity data. The UK Biobank is a very large prospective study of individuals aged 40–70 years at assessment. Participants attended assessment centres between 2006 and 2010, where they contributed blood samples for genotyping and blood analyses, and answered questions about medical history and environmental exposures. In the years since assessment, health outcome data for these individuals (for example, cancer diagnoses and deaths) have been accrued via UK national registries.

We analysed genetic data from the UK Biobank interim release (about 30% of the full UK Biobank) consisting of 152,729 samples typed on the Affymetrix UK BiLEVE and UK Biobank Axiom arrays with about 800,000 SNPs each and more than 95% overlap. We removed 480 individuals marked for exclusion from genomic analyses based on missingness and heterozygosity filters and one individual who had withdrawn consent, leaving 152,248 samples. We restricted the variant set to biallelic variants with missingness ≤ 10% and we further excluded 111 variants found to have significantly different allele frequencies between the UK BiLEVE array and the UK Biobank array, leaving 725,664 variants on autosomes and the X chromosome. Finally, we additionally excluded 118,139 variants for which fewer than 10 samples (or for chX, fewer than 5 female samples) were called as homozygous for the minor allele; we observed that genotype calls at these variant sites were susceptible to errors in which rare homozygotes were called as heterozygotes. We phased the remaining 607,525 variants using Eagle2 with –Kpbwt = 40,000 and other otherwise default parameters.

We transformed genotyping intensities to log2R ratio (LRR) and B-allele frequency (BAF) values (which measure total and relative allelic intensities) after affine-normalization and GC wave-correction 2,2 in a manner similar to that described (Supplementary Note 1). For each sample, we then computed s.d. (BAF) among heterozygous sites within each autosome, and we removed 320 samples with median s.d. (BAF) > 0.11 indicating low genotyping quality. Finally, we removed an additional 725 samples with evidence of possible contamination 2,2 based on apparent short interstitial CNN-LOH events in regions of long-range linkage disequilibrium (Supplementary Note 1) and one sample without phenotype data, leaving 151,202 samples for analysis.

Detection of mCAs using long-range haplotype phase. Here we outline the key ideas of our approach to mCA detection; full details are provided in Supplementary Note 1. The core intuition is to harness long-range phase information to search for local imbalances between maternal and paternal allelic fractions in a cell population (Extended Data Fig. 1). The utility of haplotype phase for this purpose has previously been recognized 2,2,2, but previous approaches have needed to account for phase switch errors occurring roughly every megabase, a general challenge faced by haplotypers. In the UK Biobank, we have phase information accurately at the scale of tens of megabases 2,2,2, enabling a new modelling approach and considerable gains in sensitivity for detection of large events at low cell fractions (Supplementary Note 5). (Because our method is phase-based, it has the limitation that it cannot detect events contained within regions of homozygosity. While this issue is minor in our study of large events, other approaches originally developed for detection of shorter constitutional or high-cell-fraction CNVs are not subject to this limitation 2,2,2.)

Our technique employs a three-state hidden Markov model (HMM) to capture mCA-induced deviations in allelic balance ([ΔBAF] at heterozygous sites. (By contrast, the hapLOH method 2,2,2 tabulates ‘switch consistency’ between consecutive heterozygous sites.) Our model has a single parameter Θ, which represents the expected absolute BAF deviation at germline hets within an mCA. In computationally phased genotyping intensity data, multiplying phase calls with (signed) BAF deviations produces contiguous regions within the mCA in which the expected phased BAF deviation is either +Θ or −Θ (with sign flips at phase switch errors); outside the mCA, no BAF deviation is expected. The three states of our HMM encode these three possibilities, and emissions from the states represent noisy BAF measurements. Transitions between the +Θ and −Θ states represent switch errors, whereas transitions between +Θ and the Θ state capture mCA boundaries.

Modelling observed phased BAF deviations using a parameterized HMM has the key benefit of naturally producing a likelihood ratio test statistic for determining whether a chromosome contains a mCA. Explicitly, for a given choice of Θ, we can compute the total probability of the observed BAF data under the assumption that mCA-induced BAF deviations have E[|ΔBAF|] = Θ, using standard HMM dynamic programming computations to integrate over uncertainty in phase switches and mCA boundaries. Taking the ratio of the maximum likelihood over all possible choices of Θ (the likelihood of the observed data under the model) yields a test statistic. If the HMM perfectly represented the data, this test statistic could be compared to an asymptotic distribution. However, we know in practice that parameters within the HMM (for example, transition probabilities) are imperfectly estimated, so we instead calibrated our test statistic empirically: we estimated its null distribution by computing test statistics on data with randomized phase, and we used this empirical null to control FDR. Finally, for chromosomes passing the FDR threshold, we called mCA boundaries by sampling state paths from the HMM (using the maximum likelihood value of Θ).

The above detection procedure uses only BAF data and ignores LRR measurements by design (to be maximally robust to genotyping artefacts); however, after detecting mCAs in blood samples, we incorporated LRR data to call detected mCAs as loss, CNN-LOH, or gain. All mosaic chromosomal alterations cause BAF (measuring relative allelic intensity) to deviate from 0.5 at heterozygous sites, and losses and gains cause LRR (measuring total intensity) to deviate from 0, with deviations increasing with clonal cell fraction; accordingly, we observed that plotting detected events by LRR and BAF deviation produced three linear clusters (Fig. 2a), consistent with previous work 2,2,2. We called copy number using chromosome-specific clusters to take advantage of the differing frequencies of event types on different chromosomes. Because the clusters converge as BAF deviation approaches zero, we left copy number uncalled for detected mCAs at low cell fraction (with <95% confident copy number), comprising 29% of all detected mCAs. We then estimated clonal cell fractions as described.

As a post-processing step to exclude possible constitutional duplications, we filtered events of length >10 Mb with LRR >0.35 or with LRR >0.2 and |ΔBAF| >0.16, and we filtered events of length <10 Mb with LRR >0.2 or with LRR >0.1 and |ΔBAF| >0.1. We chose these thresholds conservatively based on visual inspection of LRR and BAF distributions, in which likely constitutional duplications formed well-defined clusters (Supplementary Note 1). (Most constitutional duplications were already masked in a pre-processing step involving a separate HMM described in Supplementary Note 1.)

Enrichment of mCA types in blood lineages. We analysed 14 blood count indices (counts and percentages of lymphocytes, basophils, monocytes, neutrophils, red cells, and platelets, as well as distribution widths of red cells and platelets) from complete blood count data available for 97% of participants. We restricted the analysis to individuals of self-reported European ancestry (96% of the cohort), leaving 140,250 individuals; we then stratified by sex and quantile-normalized each blood index after regressing out age, age squared, and smoking status.

To identify classes of mCAs linked to different blood cell types, we first classified mCAs based on chromosomal location and copy number. For each autosome, we defined five disjoint categories of mCAs that comprised the majority of detected events: loss on p arm, loss on q arm, CNN-LOH on p arm, CNN-LOH on q arm, and gain. We subdivided loss and CNN-LOH events by arm but did not subdivide gain events because most gain events are whole-chromosome trisomies (Fig. 1). For chromosome X, we replaced the two loss categories with a single whole-chromosome loss category. Altogether, this classification resulted in 114 mCA types. We restricted our blood cell enrichment analyses to 78 mCA types with at least 10 occurrences, and we further excluded the chr17 gain category (because nearly all of these events arise from (17p) isochromosomes already counted as 17p–events; Supplementary Note 2).

For each of the 77 remaining mCA types, we computed enrichment of mCAs among individuals with anomalous (top 1%) values of each normalized blood index using Fisher's exact test (two-sided; P values reported throughout this manuscript are from two-sided statistical tests unless explicitly stated otherwise). We reported significant enrichments passing an FDR threshold of 0.05 (Fig. 2f and Supplementary Table 6).

Chromosome-wide association tests for cis associations with mCAs. To identify inherited variants influencing nearby mCAs, we performed two types of association analysis. First, we searched for variants that increased the probability of developing nearby mCAs. For each variant, we performed a Fisher test for association between the variant and up to three variant-specific case-control phenotypes, defined by considering samples to be cases if they contained loss, CNN-LOH, or gain events containing the variant or within 4 Mb (to allow for uncertainty in event boundaries). We tested phenotypes with at least 25 cases; in total, 48 out of 69 = 23 × 3 possible event types had at least 25 carriers, and the rest were excluded from association analyses. We performed these tests on 51 million imputed variants with minor allele frequency (MAF) ≥ 2 × 10−5 (imputed by UK Biobank using merged UK10K and 1000 Genomes Phase 3 reference panels 23), excluding variants with non-European MAF greater than five times their European MAF, which tended to be poorly imputed. We analysed 120,664 individuals who remained after restricting to individuals of self-reported British or Irish ancestry, removing principal component outliers (|z|>4 s.d.), and imposing a relatedness cutoff of 0.05 (using plink --rel-cutoff 0.05) 24. (In our non-GWAS analyses, which focused on mosaic individuals, we did not apply any special handling of related individuals as we were primarily interested in events that result from new clonal cell lines as opposed to maternal inheritance or other close relationships among 4,889 individuals with autosomal mosaicism.)

We also ran a second form of association analysis searching for variants for which mCAs tended to shift allelic balance (analogous to allele-specific
expression). For a given class of mCAs, for each variant, we examined heterozygous mosaic individuals for which the mCA overlapped the variant, and we performed a binomial test to check whether the mCA was more likely to delete or duplicate one allele rather than the other. We restricted the binomial test to individuals in which the variant was confidently phased relative to the mCA (that is, no disagreement in five random resamples from the HMM used to call the mCA).

Given that the two association tests described above are independent, we applied a two-stage approach to identify robust genome-wide significant associations. We used a $P$ value threshold of $10^{-8}$ for discovery in either test and then checked for nominal $P < 0.05$ significance in the other test (retesting that variants that influenced mCAs would exhibit both types of association). At all loci with $P < 10^{-6}$ for either test, the most significant variant with $P < 10^{-8}$ in one test reached nominal significance in the other (Table 1). At identified loci, we further searched for secondary independent associations reaching $P < 10^{-6}$.

In our final analyses, we refined mCA phenotypes to slightly increase power to map associations. For the loci associated with $1p$, $9p$, and $15q$ CN-LOH, we found that association strength improved by expanding case status to include all events reaching the telomere (because several detected telomeric events with uncertain copy number were probably actually CN-LOH events associated with the same germline variants). For the association signal at FRA10B, we refined case status to only include terminal loss events extending from 10q25 to the telomere (because of the breakpoint specificity of this event). We verified that all association tests produced well-calibrated test statistics (Supplementary Note 3).

**Identity-by-descent analysis at MPL and FRA10B.** At loci for which we found evidence of multiple causal rare variants, we searched for long haplotypes shared ideationally among mCA carriers to further explore the possibility of additional or recurrent causal variants. We called IBD tracts using GERMLINE with haplotype extension 40.

**Simons Simplex Collection WGS data set.** The Simons Simplex Collection (SSC) is a repository of genetic samples from autism simplex families collected by the Simons Foundation Autism Research Initiative (SFARI) 53. We analysed 2,079 whole-genome sequences from the first phase of SSC sequencing (median coverage 37.8 $\times$ ) to examine whether mCAs we detected contributed to genetic risk of autism. (The main data set consisted of 2,076 individuals in 519 quartets; we additionally analysed three individuals that did not belong to a complete quartet but were of interest based on high read counts at FRA10B.)

**Detection and calling of 70-kb deletion at 15q26.3.** We discovered the inherited 70-kb deletion associated with 15q CN-LOH and loss by mapping the 15q26.3 association signal (specifically, the rs182643535 tag SNP) in WGS data (Fig. 4c and Extended Data Fig. 6). We then called this deletion in the UK Biobank WGS SNP array data using genotyping intensities at 24 probes in the deleted region (Extended Data Fig. 7).

**Detection and imputation of VNTRs at FRA10B.** For all WGS samples with 10 or more reads at the FRA10B locus, we attempted to perform local assembly of the reads and identify a primary VNTR motif in the assembly. We identified 12 distinct primary motifs carried by 26 individuals in 14 families (Extended Data Fig. 5a, b and Supplementary Note 8). Owing to read dropout in many samples, it is possible that these VNTR motifs may be found in additional samples, and that other VNTR motifs may not have been detected. We imputed the VNTR sequences into UK Biobank using Minimac 3 55. Full details are provided in Supplementary Note 8.

**GWAS and heritability estimation for trans drivers of clonality.** We tested variants with MAF > 1% for trans associations with six classes of mCAs (any event, any loss, any CN-LOH, any gain, any autosomal event, any autosomal loss) on 120,664 unrelated individuals with European ancestry (described above) using BOLT-LMM 3 41, including 10 principal components, age, and genotyping array as covariates. We also tested association with female X loss using an expanded set of 3,462 likely X loss calls at an FDR of 0.1, restricting this analysis to 66,685 female individuals. In our targeted analysis of 86 variants implicated in previous GWAS, we applied a Bonferroni significance threshold of $8.3 \times 10^{-8}$ based on 86 variants and 7 phenotypes. We estimated SNP heritability of X loss using BOLT-LMM 62, including 10 principal components, age, and genotyping array as explanatory variables. In the second model, we added CLL genetic risk (computed using 14 high-confidence GWAS hits that had both been previously published 3 11 and reached $P < 5 \times 10^{-8}$). In the third model, we added lymphocyte count. In the final model, we added two explanatory variables for 13q and > 12 events.

We assessed the accuracy of each model on two benchmark sets of samples. We restricted our primary analyses to individuals with normal lymphocyte counts ($1.35 \times 10^{9}/l$ at assessment (that is, exhibiting at most slight clonality); in auxiliary analyses, we removed this restriction (and expanded the full prediction model to include 11q, +12, 13q, 13q CN-LOH, 14q, 22q+, and the total number of other autosomal events). We performed tenfold stratified cross-validation to compare model performance. We assessed prediction accuracy by merging results from all cross-validation folds and computing area under the receiver operating characteristic curve (AUC) (Fig. 5b), and we also measured precision-recall performance (Extended Data Fig. 9). (We caution that while AUC is commonly used to assess discriminative power, AUC does not have a direct clinical interpretation 48.)

**Estimation of mortality risk conferred by mCAs.** We analysed UK death registry data provided by UK Biobank for 4,619 individuals reported to have died since assessment. We censored deaths after 31 December 2015, as suggested by UK Biobank, leaving 4,518 reported deaths over a median follow-up time of 6.9 years (range 5–10 years). We examined the relationship between mCAs and mortality, aiming to extend previous observations that mosaic point mutations increase mortality risk 3 11. For this analysis, we were insufficiently powered to stratify mCAs by chromosome owing to the weaker effects of mCAs on mortality risk and the relatively small number of deaths reported during follow-up. We therefore stratified mCAs only by copy number and computed the hazard ratio conferred by each event class using a Cox proportional hazards model. We restricted these analyses to individuals with self-reported European ancestry, and we adjusted for age and sex as well as smoking status, which was previously associated with clonal haematopoiesis 13 11,59 and associates with mosaicism in the UK Biobank (Table 1). We did not exclude individuals based on blood counts in these analyses (owing to the potential for rare mCAs to affect the corresponding authors upon request.)
Data availability. Mosaic event calls are available in the Supplementary Data. Access to the UK Biobank Resource is available via application (http://www.ukbiobank.ac.uk/). Approved researchers can obtain the SSC population data set described in this study by applying at https://base.sfari.org.

Extended Data Fig. 1 | Examples of mosaic events called using phased genotyping intensities. a–c, UK Biobank mCA sample 2791 has a mosaic deletion of chr13 from approximately 31–53 Mb that cannot be confidently called from unphased BAF and LRR data (a, c). However, the existence of an event is evident in the phased BAF data (b), and the regional decrease in LRR indicates that this event is a deletion. In b, mean phased BAF is plotted for SNPs aggregated into bins spanning $n = 25$ heterozygous sites; the same bins are used for c. Error bars, s.e.m. d–f, Sample 1645 has a mosaic CNN-LOH on chr9p from the 9p telomere to about 26 Mb that cannot be confidently called from unphased BAF and LRR data (d) but is evident in phased BAF data (e). A phase switch error causes a sign flip in phased BAF at approximately 20 Mb. The lack of a shift in LRR in the region (f) indicates that this event is a CNN-LOH. In e, mean phased BAF is plotted for SNPs aggregated into bins spanning $n = 50$ heterozygous sites; the same bins are used for f. Error bars, s.e.m. g–i, Sample 2464 has a full-chromosome mosaic event on chr12 that cannot be confidently called from unphased BAF and LRR data (g, i) but is evident in phased BAF data (h). Several phase switch errors cause sign flips in phased BAF across chr12. The slight positive shift in mean LRR (i) indicates that this event is most likely to be a mosaic gain of chr12. In h, mean phased BAF is plotted for SNPs aggregated into bins spanning $n = 50$ heterozygous sites; the same bins are used for i. Error bars, s.e.m.
Extended Data Fig. 2 | Estimation of true FDR using age distributions of individuals with mCA calls. We generated age distributions for (i) ‘high-confidence’ detected events passing a permutation-based FDR threshold of 0.01 (bright red); (ii) ‘medium-confidence’ events below the FDR threshold of 0.01 but passing an FDR threshold of 0.05 (darker red); and (iii) ‘low-confidence’ events below the FDR threshold of 0.05 but passing an FDR threshold of 0.10 (darkest red; not analysed but plotted for context). We compared these distributions to the overall age distribution of UK Biobank participants (grey). On the basis of the numbers of events in each category, approximately 20% of medium-confidence detected events are expected to be false positives. To estimate our true FDR, we regressed the medium-confidence age distribution on the high-confidence and overall age distributions, reasoning that the medium-confidence age distribution should be a mixture of correctly called events with age distribution similar to that of the high-confidence events, and spurious calls with age distribution similar to the overall cohort. We observed a regression weight of 0.31 for the component corresponding to spurious calls, in good agreement with expectation, and implying a true FDR of 7.5% (6.2–8.8%, 95% CI based on regression fit on $n = 6$ age bins).
Extended Data Fig. 3 | Clonal cell fractions of co-occurring events generally suggest co-existence within the same cell population. For each pair of significantly co-occurring events (Fig. 2b), we compared the clonal fractions of the two events within each individual that carried both events. Each point in the plots corresponds to an individual carrying the pair of events under consideration; individuals are colour-coded by the total number of events they carry. For nearly all pairs of events, the clonal fractions of the two events were very similar in most individuals carrying both events, suggesting that the events occurred in the same clonal cell population. A few exceptions do seem to exist; for example, 22q− versus 13q CNN-LOH cell fraction; here, the cell fractions suggest that 13q CNN-LOH events may be present in a subclone. This observation is consistent with acquired uniparental disomy of 13q providing a second hit within a del(13q14) clonal expansion, as we see in Extended Data Fig. 8. (We did not include del(13q14) vs. 13q CNN-LOH in this plot because inference of clonal fractions is complex for these overlapping events; see Extended Data Fig. 8.)
Extended Data Fig. 4 | Replication of previous association between JAK2 46/1 haplotype and 9p CNN-LOH in cis due to clonal selection. The common JAK2 46/1 haplotype has previously been shown to confer risk of somatic JAK2 V617F mutation such that subsequent 9p CNN-LOH produces a strong proliferative advantage15–18,20 (right). In our analysis, CNN-LOH on 9p is strongly associated with JAK2 46/1 ($P = 1.6 \times 10^{-13}$, OR = 2.7 (2.1–3.5); Fisher’s exact test on $n = 120,664$ individuals) with the risk haplotype predominantly duplicated by CNN-LOH in hets (52 of $n = 61$ heterozygous cases; binomial $P = 1.8 \times 10^{-8}$). Left, the genomic modification is illustrated in the top panel and association signals are plotted in the bottom. The lead associated variant is labelled, and variants are coloured according to linkage disequilibrium with the lead variant (scaled for readability).
**a** Variable Number Tandem Repeats (VNTRs) at FRA10B identified in WGS data

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**b** Identity-by-descent graph at FRA10B for UK Biobank del(10q) individuals colored according to imputed VNTRs

- VNTR-42-a
- VNTR-43-b
- VNTR-38-a
- IBD > 2.5 cM

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**c** IBD graph at MPL for UK Biobank 1p mosaic individuals

- Edges = IBD > 2.5cM (edge weights increase with IBD length)
- Red nodes = carriers of rare MPL nonsense mutation (rs369156948)
- Green nodes = carriers of long rare haplotype (tag: rs144279563)
- Blue nodes = carriers of long rare haplotype (tag: rs182971382)
Extended Data Fig. 6 | Germline CNVs at 15q26.3. a, Read depth profile plot of WGS samples in the terminal 700 kb of chr15q. Three individuals in one family carry an approximately 70-kb deletion at 15q26.3, and a fourth carries the same deletion along with an approximately 290-kb duplication (probably on the same haplotype, based on population frequencies of these events; see Extended Data Fig. 7). These four individuals (highlighted in blue) segregate with the rs182643535:T allele in the WGS cohort. Inset: the parental carrier in the family, individual 10921, has detectable mosaicism in two distinct 15q CNN-LOH subclones (one starting at 41.64 Mb with 4.6% cell fraction, the other starting at 71.64 Mb with an additional 2.0% cell fraction). b, Expanded read depth profile plot, with deletion-only individuals highlighted in blue and the del + dup individual highlighted in green. Breakpoint analysis indicates that the deletion spans chr15:102151467–102222161 and contains a 1,139-bp mid-segment (chr15:102164353–102165491) that is retained in inverted orientation. The duplication spans chr15:102026997–102314016.
Extended Data Fig. 7 | Mosaic chromosomal alterations and germline CNVs at 15q26.3. Using identified breakpoints of the germline 70-kb deletion and 290-kb duplication (Extended Data Fig. 6), we computed mean genotyping intensity (LRR) in UK Biobank samples within the 70-kb deletion region (24 probes) and within the flanking 220-kb region (97 probes). Individuals are plotted by flanking 220-kb mean LRR versus 70-kb mean LRR and coloured according to mosaic status for somatic 15q mCAs. UK Biobank samples carrying the 70-kb deletion, 290-kb duplication, and both (del+dup) are all easily identifiable in distinct clusters. The plot also appears to contain clusters with higher copy number. Of the three CNV-carrying alleles, the simple 70-kb deletion is the only one that predisposes to mCAs. Most mosaic events containing the 70-kb deletion are CNN-LOH events that make cells homozygous for the 70-kb deletion; two individuals have somatic loss of the homologous (normal) chromosome, making cells hemizygous for the 70-kb deletion.
Extended Data Fig. 8 | Phased BAF plots of chromosomes with multiple CNN-LOH subclones. All of the plots exhibit step functions of increasing $|\Delta \text{BAF}|$ towards a telomere, which is the hallmark of multiple clonal cell populations containing distinct CNN-LOH events that affect different spans of a chromosomal arm (all extending to the telomere). Distinct $|\Delta \text{BAF}|$ values (called using an HMM) are indicated with different colours. Flips in the sign of phased BAF usually correspond to phase switch errors. Two samples exhibit high switch error rates: 14q individual 3067 (explained by non-European ancestry), and 1p individual 23 (explained by very high $|\Delta \text{BAF}|$; extreme shifts in genotyping intensities result in poor genotyping quality). All five individuals with multiple CNN-LOH events on chr13q appear to contain switch errors over 13q14, but these switches are actually explained by overlapping 13q14 deletions; see Supplementary Note 1 for detailed discussion.
Extended Data Fig. 9 | CLL prediction accuracy: receiver operating curves and precision-recall curves. CLL prediction benchmarks using tenfold stratified cross validation on: only individuals with lymphocyte counts in the normal range (1 × 10^9/L to 3.5 × 10^9/L), as in our primary analyses (n = 36 cases, 113,923 controls) (a, b); and individuals with any lymphocyte count (n = 78 cases, 118,481 controls) (c, d). a matches Fig. 5b, and b shows the precision-recall curve from the same analysis. c and d correspond to an analogous analysis in which we removed the restriction on lymphocyte count and also used additional mosaic event variables for prediction (11q–, 14q–, 22q–, and total number of autosomal events). In both benchmarks, individuals with previous cancer diagnoses or CLL diagnoses within 1 year of assessment were excluded; however, some individuals with very high lymphocyte counts pass this filter (and probably already had CLL at assessment despite being undiagnosed for more than 1 year), hence the difference in apparent prediction accuracy between the two benchmarks.
Extended Data Fig. 10 | Mosaic chromosomal alterations detected in CLL cases sorted by lymphocyte count. Individuals are stratified by cancer status at DNA collection (no previous diagnosis versus any previous diagnosis), and mCAs (red, loss; green, CNN-LOH; blue, gain; grey, undetermined) are plotted per chromosome as coloured rectangles (with height increasing with BAF deviation).
Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

1. Sample size
   Describe how sample size was determined.

   We analyzed all samples in the UK Biobank available at the time we began the study (the interim release, ~30% of the full UK Biobank data set). We reasoned that this sample size would be sufficient given (a) the success of previous studies of similar or smaller sizes (e.g., Jacobs et al. 2012, Laurie et al. 2012, Machiela et al. 2015, Vattathil & Scheet 2016) and (b) our new, more sensitive detection methodology.

2. Data exclusions
   Describe any data exclusions.

   We removed 480 individuals marked for exclusion from genomic analyses based on missingness and heterozygosity filters and 1 individual who had withdrawn consent, leaving 152,248 samples. We further removed 320 samples with median s.d.(BAF)>0.11 indicating low genotype quality. Finally, we removed an additional 725 samples with evidence of possible contamination (based on apparent short interstitial CNN-LOH events in regions of long-range linkage disequilibrium) and 1 sample without phenotype data, leaving 151,202 samples for analysis.

3. Replication
   Describe whether the experimental findings were reliably reproduced.

   All attempts at replication were successful: we replicated the genetic associations we identified at 10q and 15q, and we replicated our results concerning the age and sex distributions of particular events. Further replication is needed for the other genetic associations we identified (which were too weak allow reasonable replication power) and the associations with blood phenotypes and health outcomes.

4. Randomization
   Describe how samples/organisms/participants were allocated into experimental groups.

   We did not allocate samples into experimental groups.

5. Blinding
   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   We did not collect samples, and we did not allocate samples into groups.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.
6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

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- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- A statement indicating how many times each experiment was replicated
- The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- The test results (e.g. P values) given as exact values whenever possible and with confidence intervals noted
- A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

7. Software

Describe the software used to analyze the data in this study.

We performed genotyping QC and cis association tests using PLINK 1.90, haplotype phasing using Eagle 2.3, heritability estimation and trans association tests using BOLT-REML / BOLT-LMM 2.3, identity-by-descent detection using GERMLINE 1.5.1, and imputation using Minimac3 (1.0.14). We also used custom algorithms described in Methods and the Supplementary Note.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). Nature Methods guidance for providing algorithms and software for publication provides further information on this topic.

8. Materials and reagents

Policy information about availability of computer code

**Policy information about availability of materials**

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

- No unique materials were used.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

- No antibodies were used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

- No eukaryotic cell lines were used.

b. Describe the method of cell line authentication used.

- No eukaryotic cell lines were used.

c. Report whether the cell lines were tested for mycoplasma contamination.

- No eukaryotic cell lines were used.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

- No eukaryotic cell lines were used.
Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals
   Provide details on animals and/or animal-derived materials used in the study.

   No animals were used in the study.

Policy information about studies involving human research participants

12. Description of human research participants
   Describe the covariate-relevant population characteristics of the human research participants.

   The study did not involve human research participants. (Only previously-collected data from UK Biobank was analyzed.)