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Supplementary information

Comprehensive analysis of chromothripsis in 2,658 human cancers using whole-genome sequencing

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Supplementary Figures

Comprehensive analysis of chromothripsis in 2,658 human cancers using whole-genome sequencing

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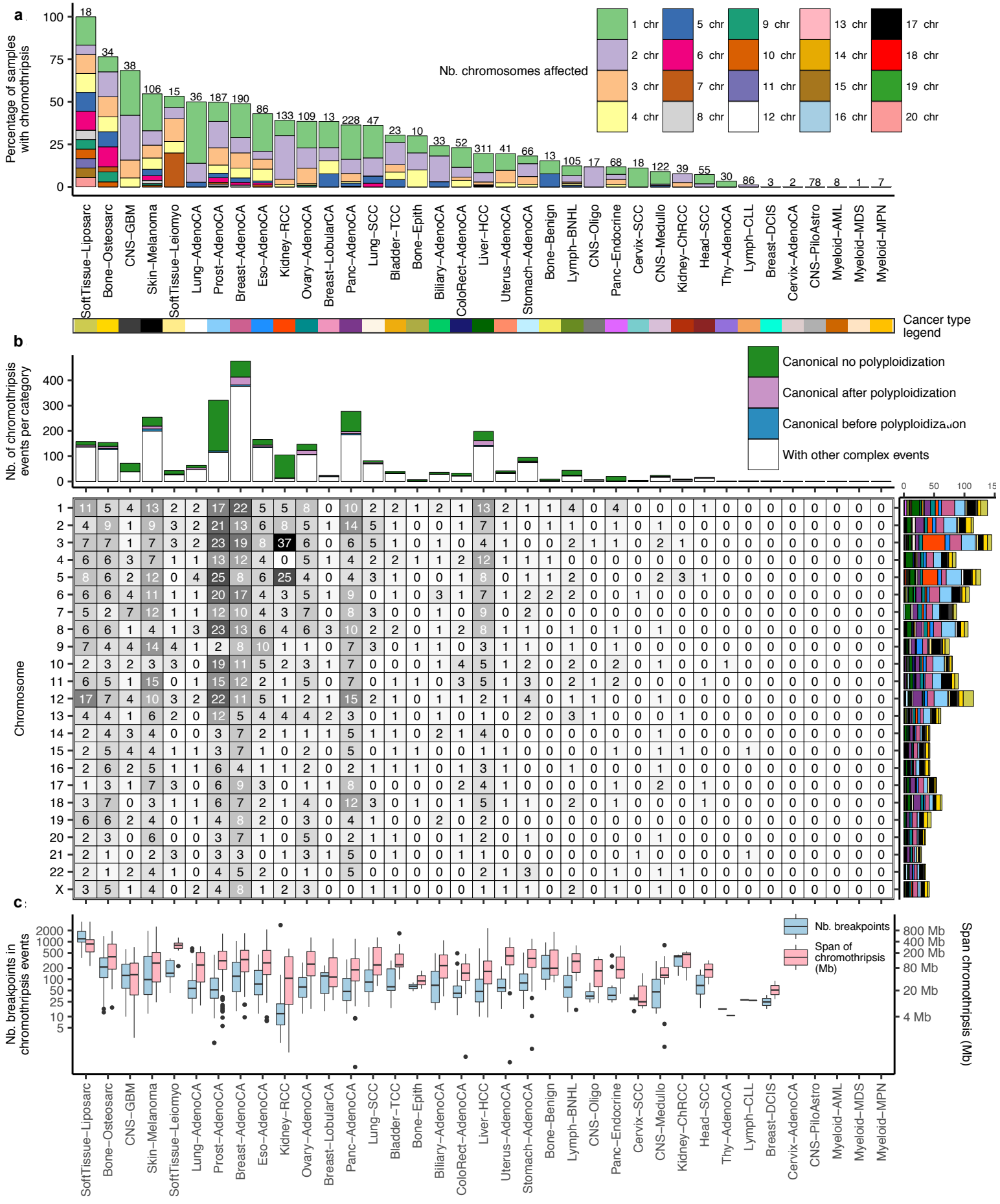
[11]The members of this working group are listed at the end of the paper.

[12]The members of this consortium are listed in the Supplementary Note.

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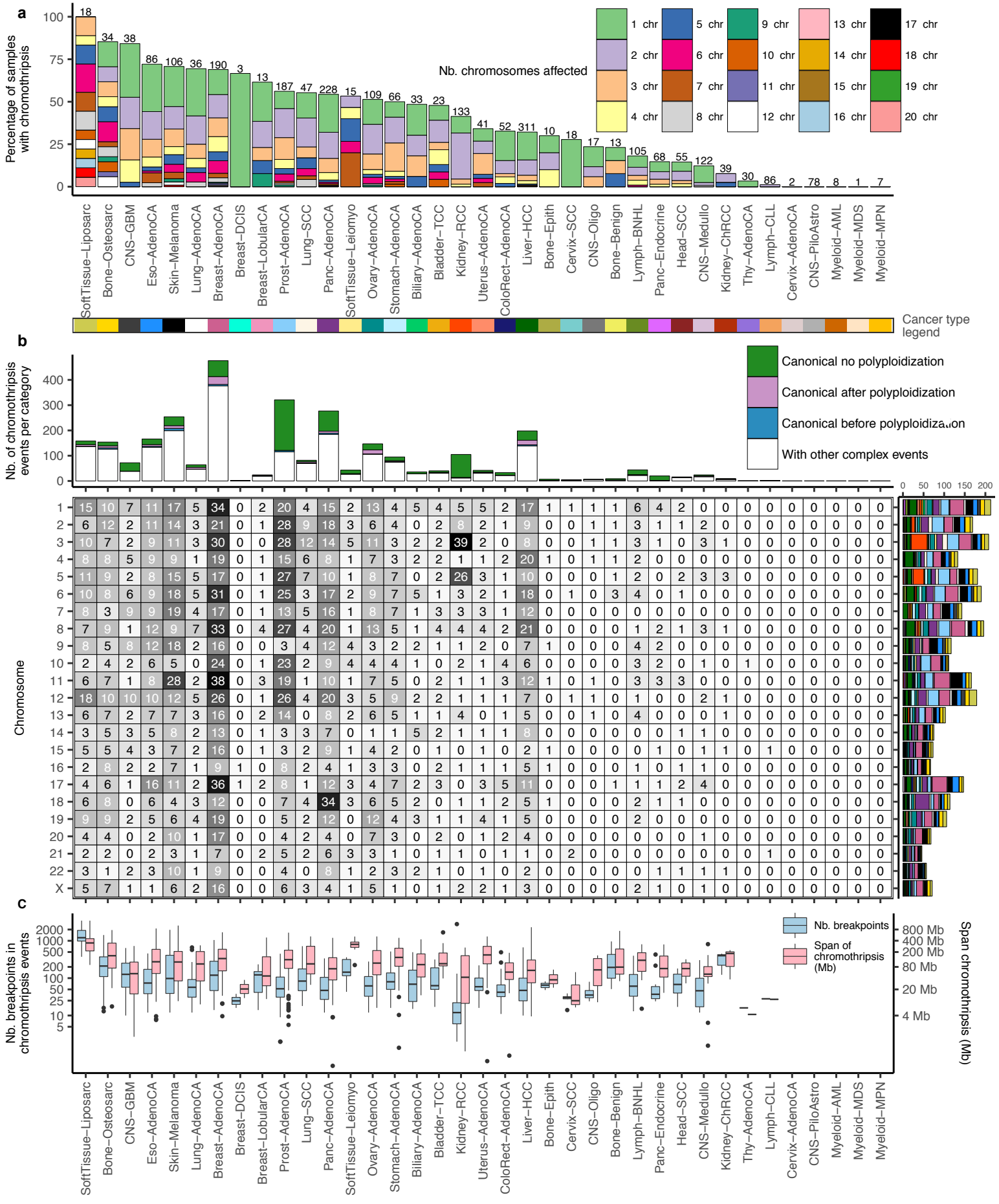
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Supplementary Figure 1



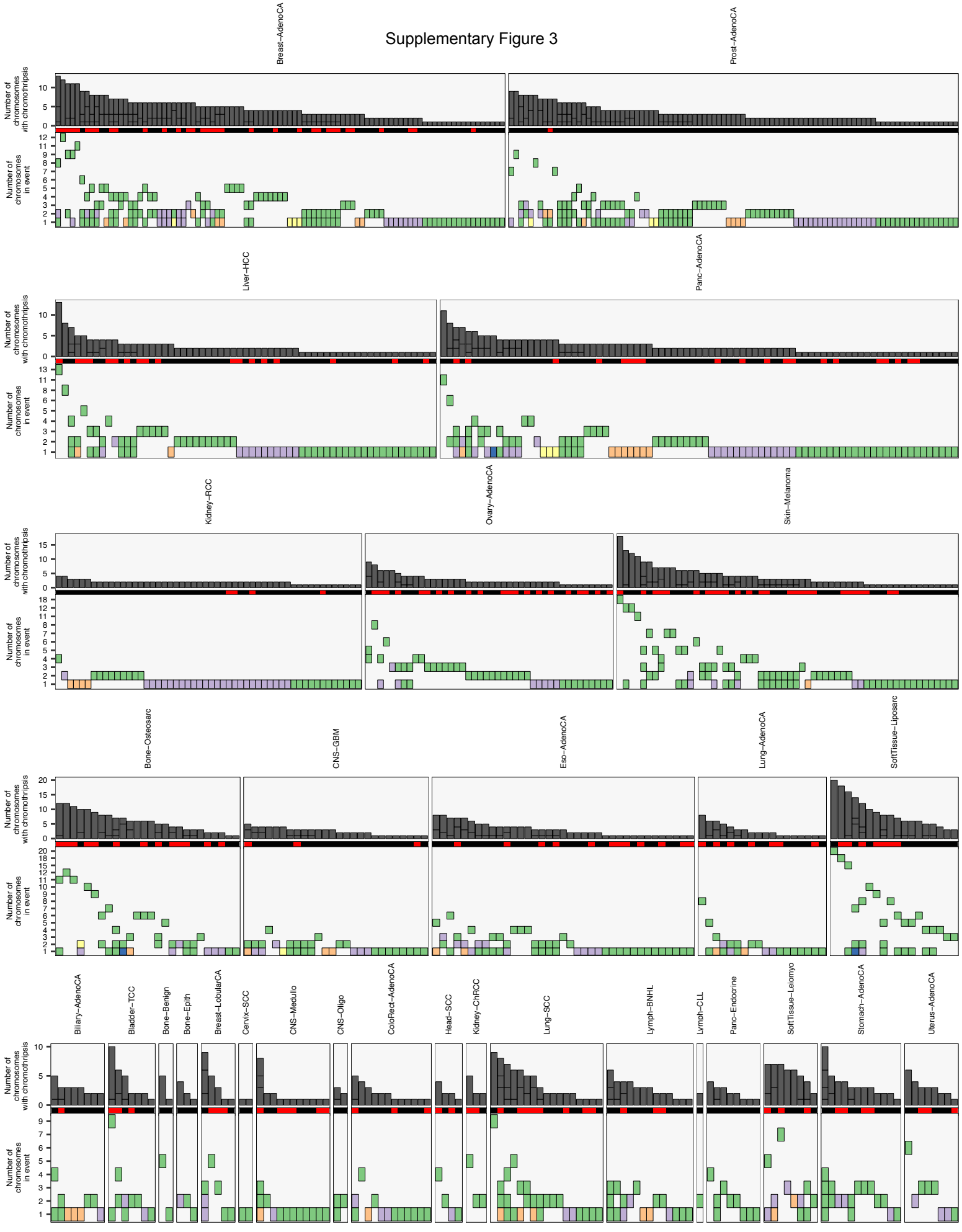
Supplementary Figure 1. Landscape of chromothripsis across 37 cancer types including high-confidence calls only. (**a**) Percentage of patients harboring chromothripsis events. The total number of tumors examined for each cancer type is indicated on top of the bars, whereas the colors of the bars indicate the number of chromosomes affected by chromothripsis. (**b**) Number of chromothripsis regions categorized on the basis of the oscillating copy number patterns and the temporal profile of the events with respect to polyploidization, and their distribution across the genome. (**c**) Distribution of the number of breakpoints (blue), and span of the chromothripsis events (pink). Box plots in (**c**) show median, first and third quartiles (boxes), and the whiskers encompass observations within a distance of 1.5 times the interquartile range from the first and third quartiles.

Supplementary Figure 2

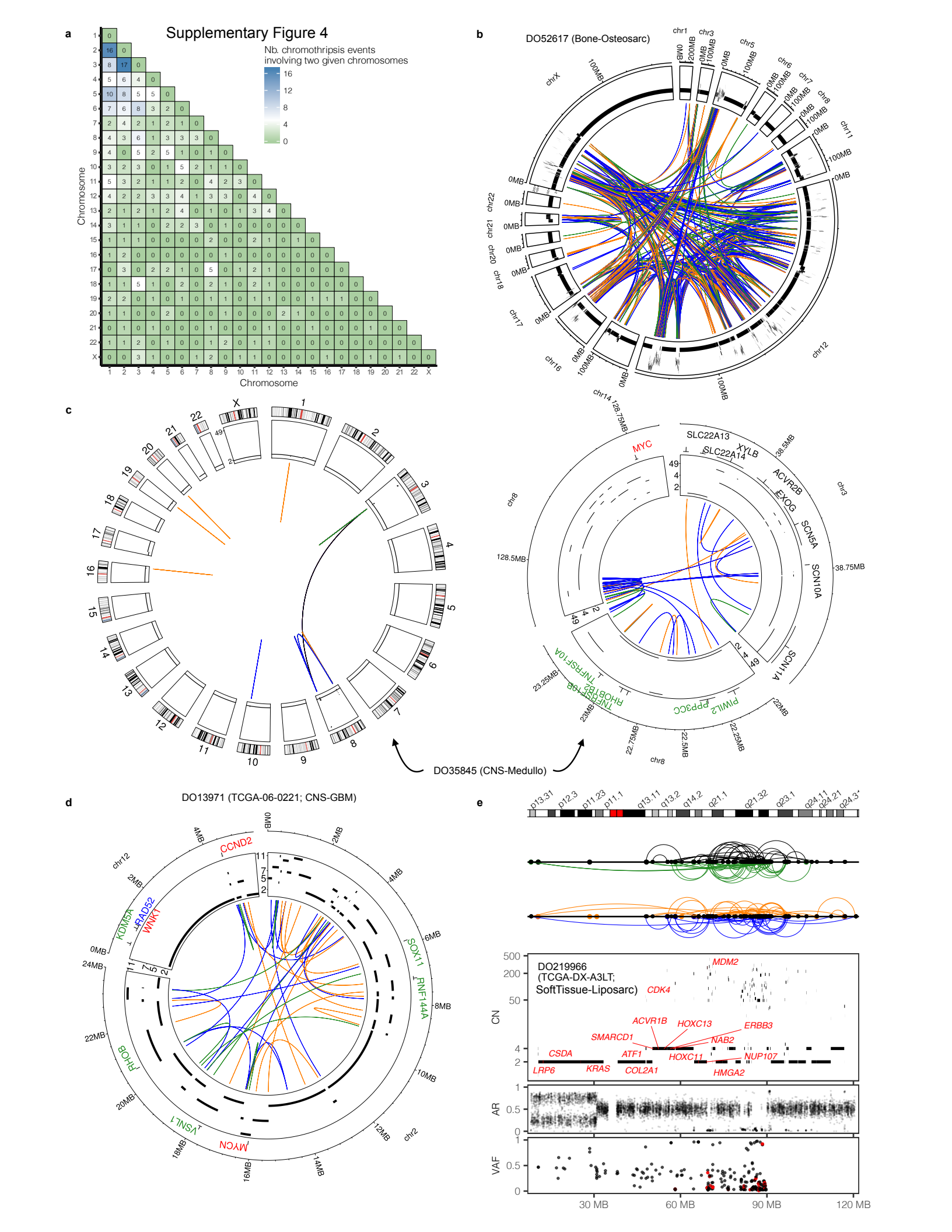


Supplementary Figure 2. Landscape of chromothripsis across 37 cancer types including the high- and low-confidence calls. (**a**) Percentage of patients harboring chromothripsis events. The total number of tumors examined for each cancer type is indicated on top of the bars, whereas the colors of the bars indicate the number of chromosomes affected by chromothripsis. (**b**) Number of chromothripsis regions categorized on the basis of the oscillating copy number patterns and the temporal profile of the events with respect to polyploidization, and their distribution across the genome. (**c**) Distribution of the number of breakpoints (blue), and span of the chromothripsis events (pink). Box plots in (**c**) show median, first and third quartiles (boxes), and the whiskers encompass observations within a distance of 1.5 times the interquartile range from the first and third quartiles.

Supplementary Figure 3

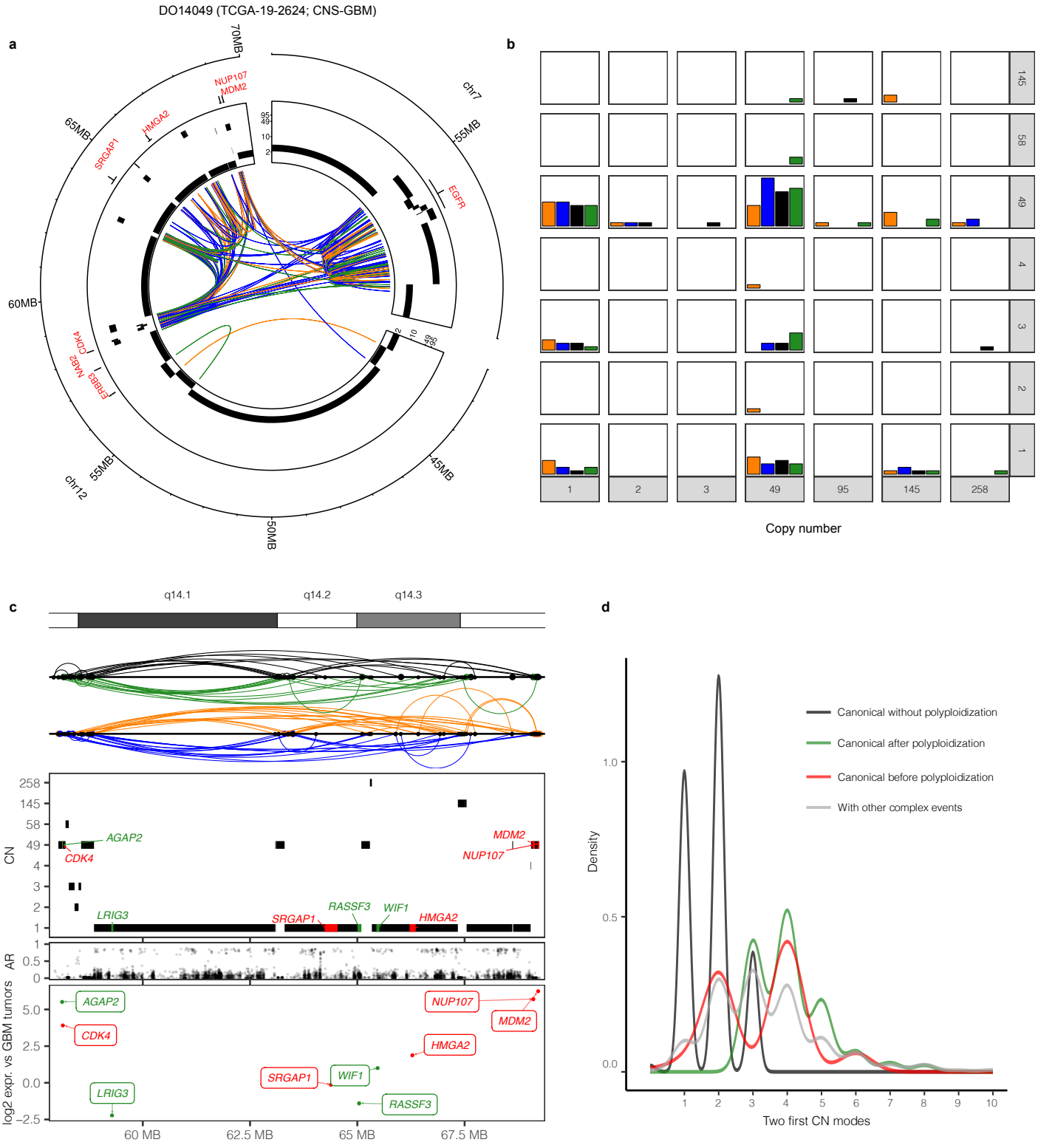


Supplementary Figure 3. Distribution of the number of chromosomes harboring high-confidence chromothripsis. The top barplot reports the total number of chromosomes with chromothripsis (including low- and high-confidence regions) per tumor (*x*-axis). The middle heatmap indicates whether the ploidy of the tumor was estimated to be >=3 (red) or not (black). The bottom heatmap reports the total number of independent chromothripsis events detected in a given tumor (*y*-axis). The colour of each cell represents the number of chromosomes involved in each independent event.


Supplementary Figure 4
a
Nb. chromothripsis events
involving two given chromosomes
Chromosome
Chromosome
b
DO52617 (Bone-Osteosarc)
c
DO35845 (CNS-Medullo)
SLC22A13
SLC22A14
XYLB
ACVR2B
EXOG
SCN5A
SCN10A
SCN11A
MYC
PIWIL2
PPP3CC
TNFRSF10A
RHOBTB2
d
DO13971 (TCGA-06-0221; CNS-GBM)
CCND2
KDM5A
RAD52
WNK1
SOX11
RNF144A
RHOB
VSNL1
MYCN
e
DO219966
(TCGA-DX-A3LT;
SoftTissue-Liposarc)
MDM2
CDK4
ACVR1B
HOXC13
ERBB3
SMARCD1
NAB2
CSDA
ATF1
HOXC11
NUP107
LRP6
KRAS
COL2A1
HMGA2
CN
AR
VAF
30 MB
60 MB
90 MB
120 MB

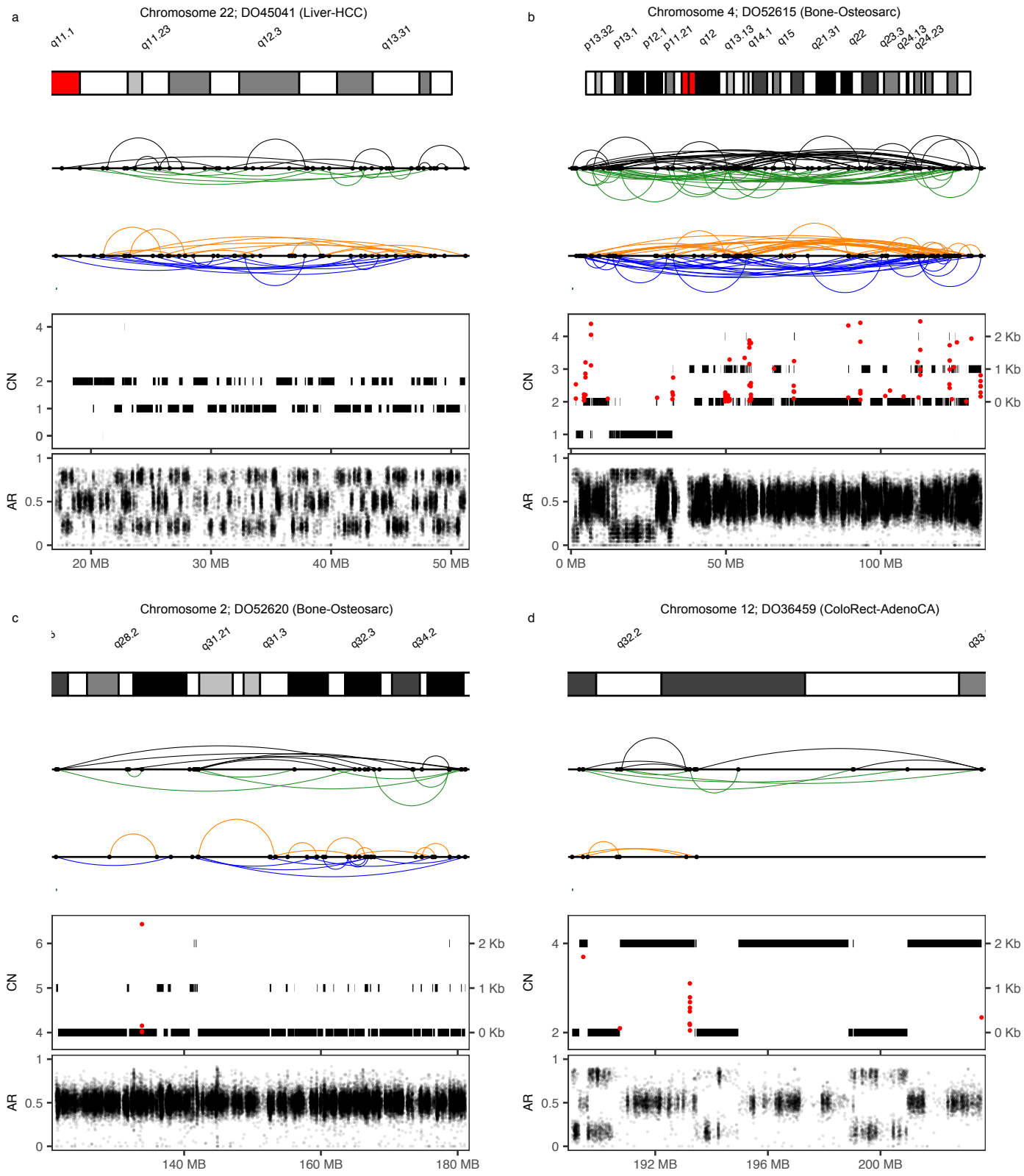
Supplementary Figure 4. (**a**) Number of chromothripsis events involving two given chromosomes across the entire set of high-confidence calls. (**b**) Unscaled Circos plot showing a massive chromothripsis event in patient DO52617 (Bone-Osteosarc) involving 16 chromosomes**.** (**c**) Example of a chromothripsis event in patient DO35845 (CNS-Medullo) affecting a few megabases in chromosomes 3 and 8, with an oscillating copy number pattern between states 4 and 49. This case also illustrates the amplification of *MYC*. Panel (**a**) shows the SVs detected across the entire genome, whereas panel (**b**) corresponds to the regions affected by chromothripsis (scaled Circos plot). (**d**) Scaled Circos plot representing the chromothripsis event in patient DO13971 (TCGA-06-0221; CNS-GBM) involving chromosomes 2 and 12, leading to the concomitant amplification of *MYCN* and *CCND2*. (**e**) Concomitant amplification of *CDK4* and *MDM2* in chromosome 12 in patient DO219966 (TCGA-DX-A3LT; SoftTissue-Liposarc). The bottom panel represents the variant allele fraction (VAF) for somatic SNVs. APOBEC-associated mutations are colored in red.

Supplementary Figure 5



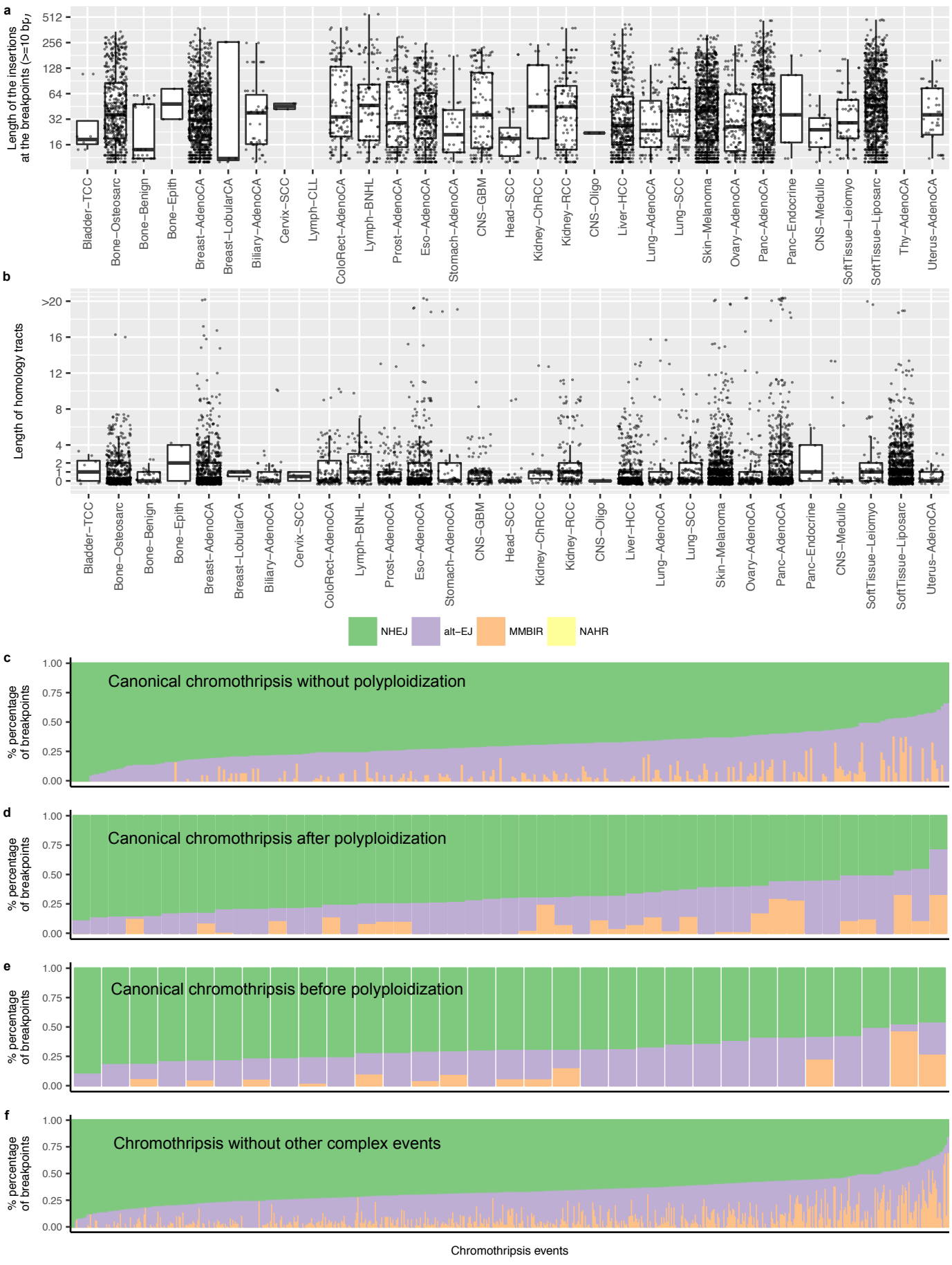
Supplementary Figure 5. (**a**) Example of a focal chromothripsis event in patient DO14049 (TCGA-19-2624; CNS-GBM) involving chromosomes 7 and 12 leading to the concomitant amplification of *CDK4*, *MDM2*, and *EGFR*. A previous study where this tumor was analysed using single-cell sequencing reported that genomic alterations in the *EGFR* locus defined different subclones[48]. These results are concordant with our calls in that the chromothripsis event affecting the *EGFR* locus presents CN oscillations across two states in the regions containing *MDM2* and *CDK4*, whereas the oscillating pattern is distorted at the *EGFR* locus, consistent with the presence of secondary subclonal rearrangements. The lack of a clear oscillation between two CN states would be expected from bulk sequencing data if secondary rearrangements had further altered the *EGFR* locus in different subclones. Although the canonical pattern of chromothripsis is not fully apparent at the *EGFR* locus when using bulk data, we could correctly detect chromothripsis at that locus by using interchromosomal SVs. (**b**) Copy-number step plot[6]. Each cell represents the distribution of types (see Fig. 1C) for those SVs connecting segments of the CN equal to the values indicated in the *x* and *y*-axis. (**c**)**.** Example of a chromothripsis event in chromosome 12 in patient DO14049 (TCGA-19-2624; CNS-GBM) leading to the concomitant amplification of *CDK4*, *MDM2*, and *NUP107* likely as a result of DM formation. (**d**) Distribution of the two first CN modes for the chromothripsis events categorized as canonical without polyploidization (black), canonical after polyploidization (green), canonical before polyploidization (red), and chromothripsis events in the context of other complex events (gray). Cases with CN modes higher than 10 were not depicted for clarity.

Supplementary Figure 6



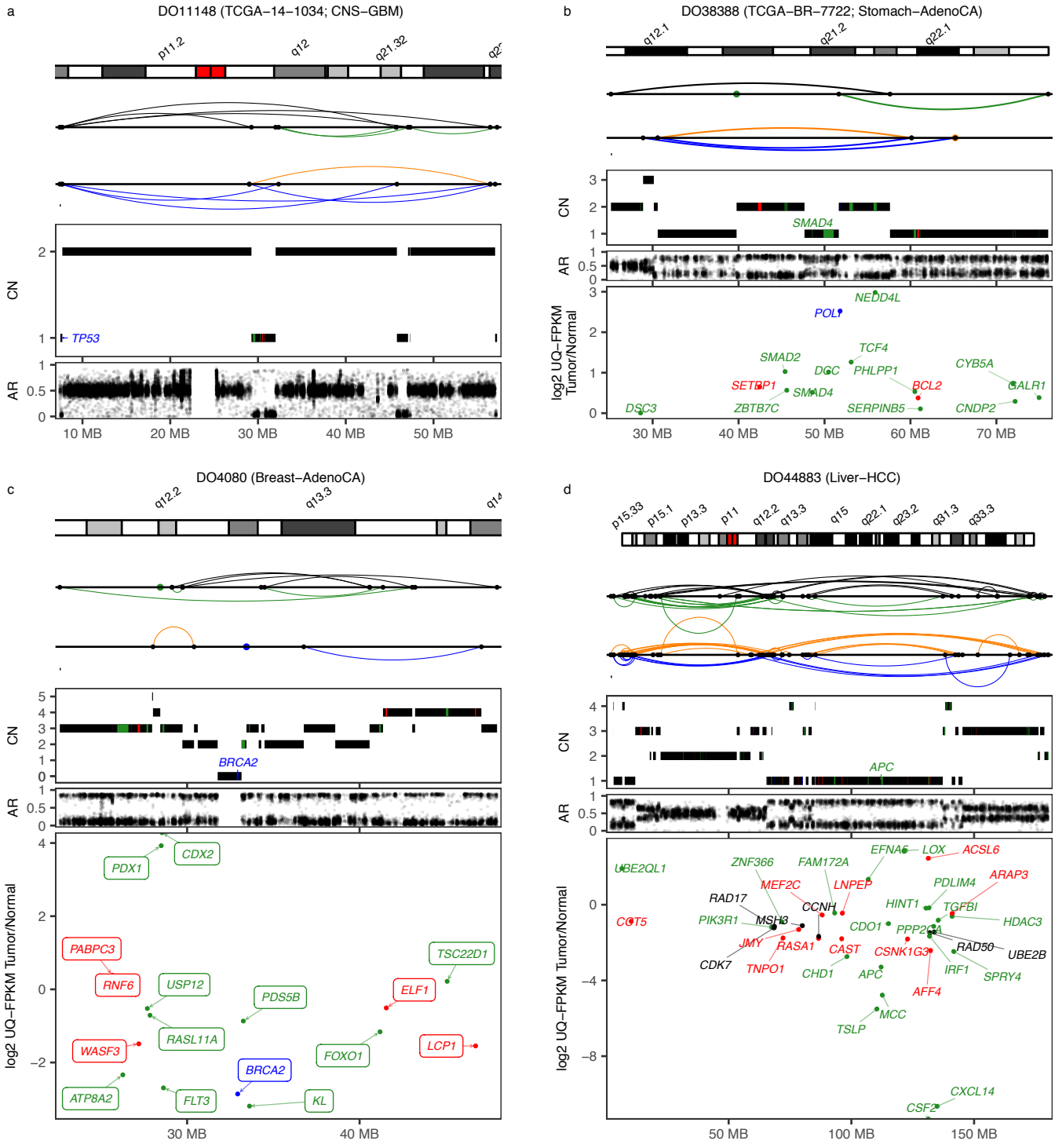
Supplementary Figure 6. Examples of chromothripsis regions. (**a**) canonical chromothripsis without polyploidization (chromosome 22; DO45041, Liver-HCC), (**b**) canonical without polyploidization displaying APOBEC-mediated kataegis (chromosome 4; DO52615, Bone-Osteosarc), (**c**) canonical chromothripsis after polyploidization (chromosome 2; DO52620, Bone-Osteosarc), and (**d**) canonical chromothripsis before polyploidization (chromosome 12; DO36459, ColoRect-AdenoCA). Clustered APOBEC-associated mutations are shown as red dots.

Supplementary Figure 7



Supplementary Figure 7. Analysis of the DNA repair mechanisms for the high-confidence chromothripsis events**.** (**a,b**) Distribution of the length of the insertions and homology sequences, respectively, detected at the breakpoints for the high-confidence cases with at least 80% of the breakpoints detected pertaining to chromothripsis. Percentage of breakpoints for each DNA repair mechanism across all cases displaying canonical chromothripsis without polyploidization (**c**)**,** canonical chromothripsis after polyploidization (**d**)**,** canonical chromothripsis before polyploidization (**e**), and chromothripsis co-localized with other complex rearrangements (**f**). Box plots in (**a,b**) show median, first and third quartiles (boxes), and the whiskers encompass observations within a distance of 1.5 times the interquartile range from the first and third quartiles.

Supplementary Figure 8



Supplementary Figure 8. Chromothripsis-mediated loss of tumor suppressors. (**a**) Evidence of chromothripsis-mediated loss of one *TP53* allele in patient DO11148 (TCGA-14-1034; CNS-GBM). The remaining allele harbors a deleterious mutation (pathogenic missense SNV, p.R337C; COSM11071). (**b**) Chromothripsis-mediated loss of one *SMAD4* allele in patient DO38388 (TCGA-BR-7722; Stomach-AdenoCA). The remaining allele harbors a deleterious mutation (pathogenic missense SNV, chr18: 48,591,925 G>A). (**c**) Biallelic *BRCA2* deletion in patient DO4080 (Breast-AdenoCA) confirmed by the low expression levels of *BRCA2*). This tumor also exhibited the mutational signature 3, which is known to be related to *BRCA1*/*BRCA2* deficiency. (**d**) Monoallelic loss of *APC* in patient DO44883 (Liver-HCC).

Supplementary Note

Comprehensive analysis of chromothripsis in 2,658 human cancers using whole-genome sequencing

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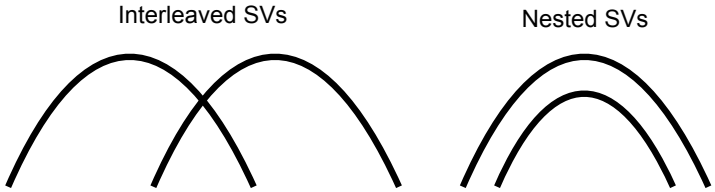
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1. Chromothripsis detection using ShatterSeek

1.1 Algorithm description

Here, we detail the chromothripsis detection pipeline implemented in ShatterSeek for identifying chromothripsis patterns from whole-genome sequencing data. The code can be found at https://github.com/parklab/ShatterSeek. Our chromothripsis calls for each PCAWG sample can be explored through interactive Circos plots at: http://compbio.med.harvard.edu/chromothripsis/.

A key feature of ShatterSeek is based on the fact that the regions affected by chromothripsis should be characterized by clusters of breakpoints belonging to SVs that are interleaved, *i.e.*, the regions bridged by their breakpoints overlap instead of being nested, as is expected from random joining of genomic fragments (Supplementary Note Fig. 1).



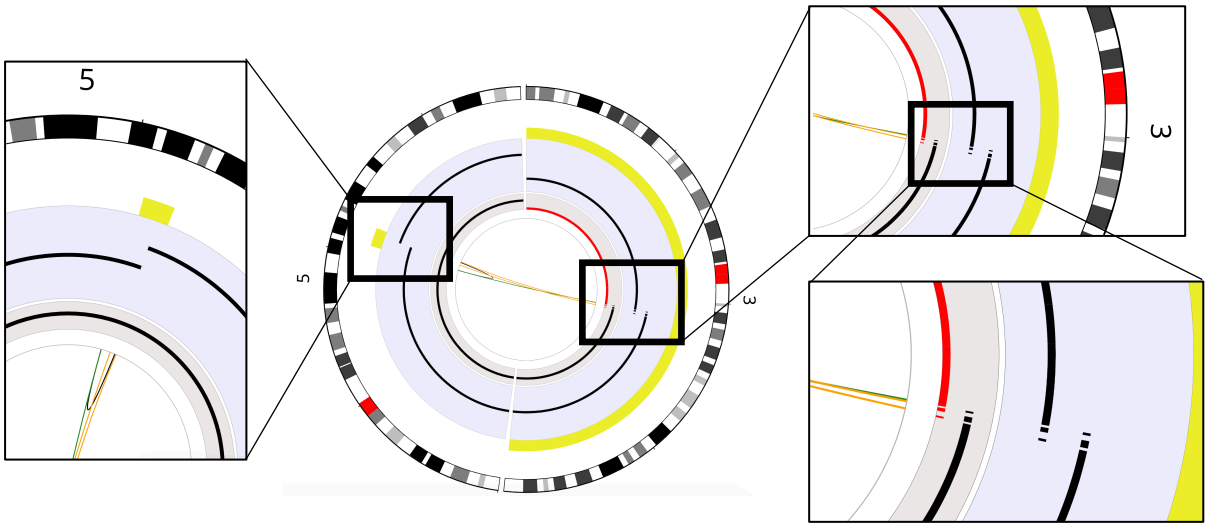
Supplementary Note Figure 1. Illustration of the pattern of interleaved SVs used in ShatterSeek to detect candidate chromothripsis regions displaying clusters of intrachromosomal SVs.

This approach allows us to encompass the many cases that do not display simple oscillations, *e.g.*, partially oscillating CN profiles with interspersed amplifications, and oscillations spanning multiple CN levels due to aneuploidy[1,2]. Therefore, we firstly scanned the cancer genomes for the presence of clusters of interwoven SVs. To find clusters within a given chromosome, ShatterSeek constructs an undirected graph whose nodes correspond to SVs and whose edges connect interleaved SVs. Thus, clusters of SVs were detected by finding the connected components in the graph. The connected component in each chromosome with the highest number of SVs was considered for further analysis. We confined our analyses to the entire mappable genome with the exception of chromosome Y. We use the term ‘chromothripsis region’ to refer to cases where chromothripsis affects only one chromosome, whereas we term ‘chromothripsis event’ the set of chromothripsis regions involved in a single catastrophic event. Thus, a chromothripsis event can affect a single chromosome, or encompass genomic regions from multiple chromosomes.

Rearrangements in chromothripsis should also follow a roughly even distribution for the different types of fragment joins (*i.e.*, duplication-like, deletion-like, head-to-head and tail-to-tail inversions, depicted in blue, orange, black, and green, respectively, in Fig. 1a, in the main text, throughout the entire article, and in the Supplementary Information) and have breakpoints randomly distributed across the affected region[3–5]. Hence, once the SV clusters were detected,

we tested whether the distribution of DNA fragment joins diverged from a multinomial distribution with equal probabilities for each category using the goodness-of-fit test for the multinomial distribution (chiq.test function from the R package *stats*), as described by Korbel and Campbell[4] (fragment joins test). In addition, we used the binomial test corrected for mappability to evaluate the enrichment of SVs in each chromosome (chromosomal enrichment test). We also evaluated whether the distribution of breakpoints differed from an exponential distribution as described by Korbel and Campbell[4] (exponential distribution of breakpoints test). The *P* values from these three tests were corrected using the FDR method. The level of significance was set to q ≤ 0.2. Finally, the genomic regions delimited by the distal breakpoints composing the clusters of interleaved SVs were further examined for the presence of contiguous genomic segments oscillating between two CN states.

We decided to only consider the criteria of loss of heterozygosity proposed by Korbel and Campbell [4] when examining the set of chromothripsis calls detected in diploid genomes. We did not consider this criterion to call chromothripsis across the entire tumor cohort because we noticed that some *bona fide* chromothripsis cases identified in low-purity samples (*e.g.,* Fig. 2c in the main text) might not meet the cut-off value for statistical significance due to the infiltration of normal tissue. In such cases, the allelic ratios (*i.e.*, B allele frequencies) for heterozygous SNPs would not divert significantly from 0.5, and thus, would hamper the observation of alternating LOH patterns associated to copy losses[6]. This phenomenon is exacerbated when chromothripsis occurs in aneuploid tumors due to increased CN, and hence, chromothripsis events do not necessarily lead to LOH (see *e.g.,* Supplementary Fig. 6c).



Supplementary Note Figure 2. Evidence of a chromothripsis event in tumor DO17178 (TCGA-AK-3454; Kidney-RCC) involving few interchromosomal SVs between chromosomes 3 and 5. Such type of chromothripsis events in Kidney-RCC tumors have been previously reported (Mitchell *et al.*, Cell, 2018). This case was missed by ShatterSeek because the SVs involved in the event do not generate a cluster of interleaved SVs. It was however identified through visual inspection.

Integration of SV and CN information was crucial for filtering candidate regions with clusters of breakpoints originating from tandem duplications or deletions rather than from chromothripsis (Supplementary Data Files 3-4). Whereas these cases often satisfied the CN-based criterion

used to call chromothripsis in some previous studies (*e.g.*, 10 segments oscillating between 2 CN states)[7–9], the predominance of one type of SV permitted us to dismiss chromothripsis as their generating mechanism. In addition, considering both SV and CN information resulted in higher sensitivity for detecting those chromothripsis events involving relatively few SVs or CN segments and/or are co-localized with other complex events (Supplementary Data Files 1-2).

1.2 Confidence of chromothripsis calls

After visual inspection of a number of chromothripsis calls, we considered as high-confidence chromothripsis those regions satisfying at least one of the following sets of cut-off values for the statistical criteria described above: (i) at least 6 interleaved intrachromosomal SVs, 7 adjacent segments oscillating between 2 CN states, the fragment joins test, and either the chromosomal enrichment or the exponential distribution of breakpoints test; and (ii) at least 3 interleaved intrachromosomal SVs and 4 or more interchromosomal SVs, 7 adjacent segments oscillating between 2 CN states and the fragment joins test. Given that the oscillating CN pattern is often only partly retained in chromothripsis events in Bone-Osteosarc, SoftTissue-Leiomyo, and SoftTissue-Liposarc tumors due to subsequent amplification events[1,10,11], we also considered as high-confidence chromothripsis regions those detected in these cancer types involving at least 40 intra- or interchromosomal SVs, and satisfying the fragments joins test (this change in criteria affects six samples, but, because many of them have multiple events, only one sample that previously was not identified as having chromothripsis was identified as having one event).

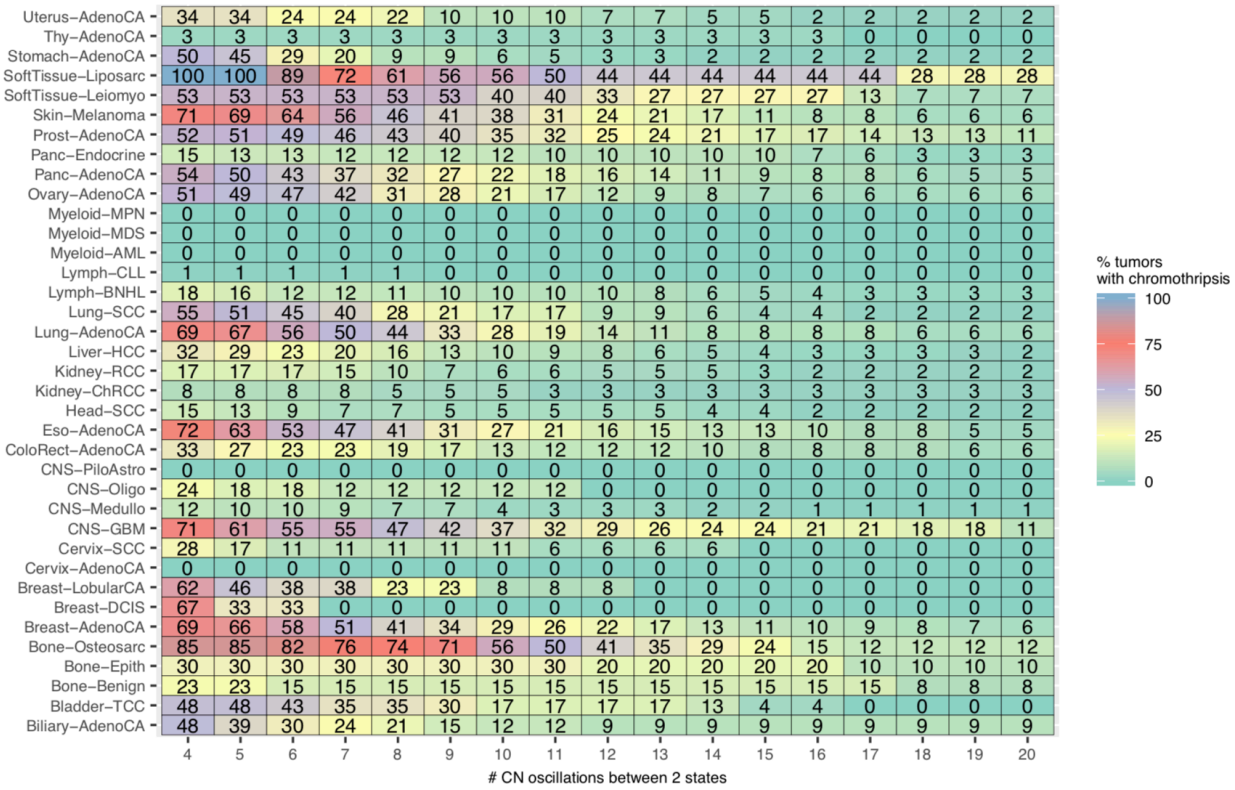
We classified as low-confidence those chromothripsis regions meeting the following cut-off values: at least 6 interleaved intrachromosomal SVs, 4, 5 or 6 adjacent segments oscillating between 2 CN states (following the criteria previously used[2]), the fragment joins test, and either the chromosomal enrichment or the exponential distribution of breakpoints test. Therefore, the main difference between the low- and high-confidence calls resides in the number of oscillating CN segments.

We chose 7 CN oscillations as the cut-off value to define high-confidence for the following reasons: 1) combined with other criteria, it gave estimates that are largely concordant with previous findings for diploid cases as well as rates given in two recent studies[2,12]; 2) it removed most of the tandem duplication (false positive) cases; 3) a minimum number of 4 CN oscillations (assuming that other criteria were satisfied) used previously[2] were too relaxed because many focal cases did not look sufficiently convincing when visualized; 4) we observed that longer oscillations are frequently interrupted by secondary CN alterations (as noted in multiple studies, *e.g.,* Behjati *et al*.[1]) and thus requiring too many consecutive oscillations removed cases that are convincingly chromothripsis except for the interruption.

One should note that a cut-off value of 7 might be too stringent, as some experimentally generated chromothripsis events would be missed[3]. However, our analysis showed that 7 represents a reasonable compromise between sensitivity and specificity. The high *vs* low confidence classification was performed to account for the possibility that we may have missed

many events; but the estimates discussed throughout the main text are for high-confidence calls unless otherwise stated.

The impact of the threshold for the required number of CN oscillations is shown in the heatmap below, where we display the percentage of tumors with a chromothripsis call as a function of the CN oscillation parameter. This sensitivity analysis reveals that the chromothripsis rates are much higher than previously anticipated even when requiring at least 10 uninterrupted CN oscillations (Supplementary Note Fig. 3). The rates of chromothripsis as a function of the number of breakpoints involved, number of chromosomes affected, and the minimum number of uninterrupted CN oscillations between 2 CN states can be explored interactively at http://compbio.med.harvard.edu/chromothripsis/.



Supplementary Note Figure 3. Percentage of tumors with chromothripsis as a function of the minimum number of uninterrupted CN oscillations required to make a call.

1.3 False positive and false negative rate analysis

After visual inspection of all cases, we removed 165 high-confidence events (8.5% of high-confidence events; 106 tumors) and 136 low-confidence calls (10.4% of low-confidence events). We included 93 events across 45 tumors after visual inspection (*e.g.,* Supplementary Note Fig. 2). All these cases are labelled in the column “comment” in Supplementary Table 1 and in the accompanying website.

Supplementary Note Table 1. Confusion matrix for ShatterSeek.

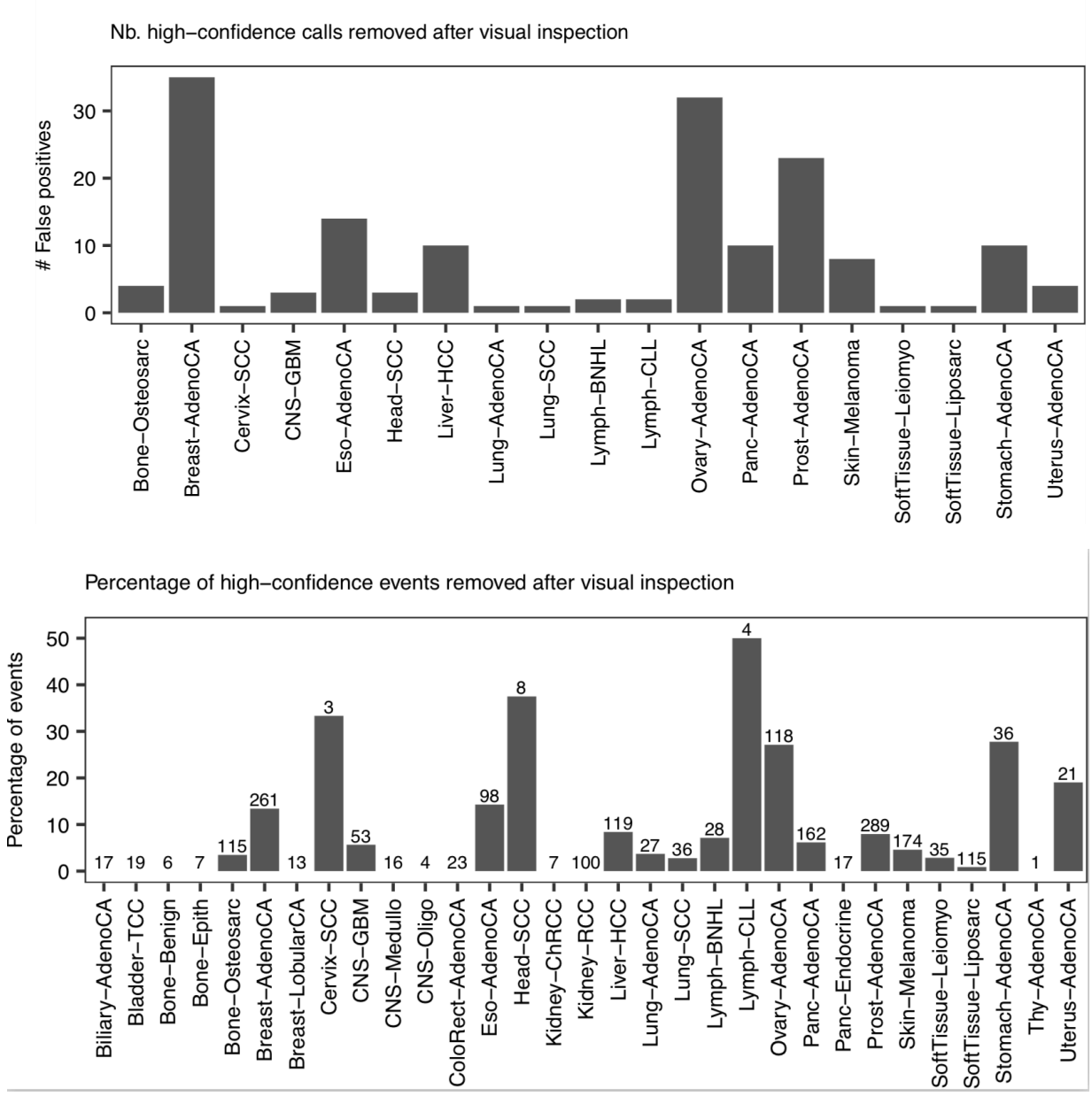
		Visual inspection	
		High-confidence chromothripsis	No chromothripsis
ShatterSeek	High-confidence chromothripsis	689	106
	No chromothripsis	45	1703

We estimate a FP rate for our method when evaluated at the tumor level of 5.9% for high-confidence calls, which is comparable to that of previous studies (Notta *et al.*[2] reported a FP rate of 7% for Chrom-AL; Supplementary Note Table 2). The difference between the FP rate of Chrom-AL and our method is largely due to differences in SV rates across cancer types (Supplementary Note Figs. 4-5). We also note that we assembled a highly stringent chromothripsis call set to guarantee that we were not overcalling, and hence, it is possible that a considerable fraction of the events we removed might be true chromothripsis cases.

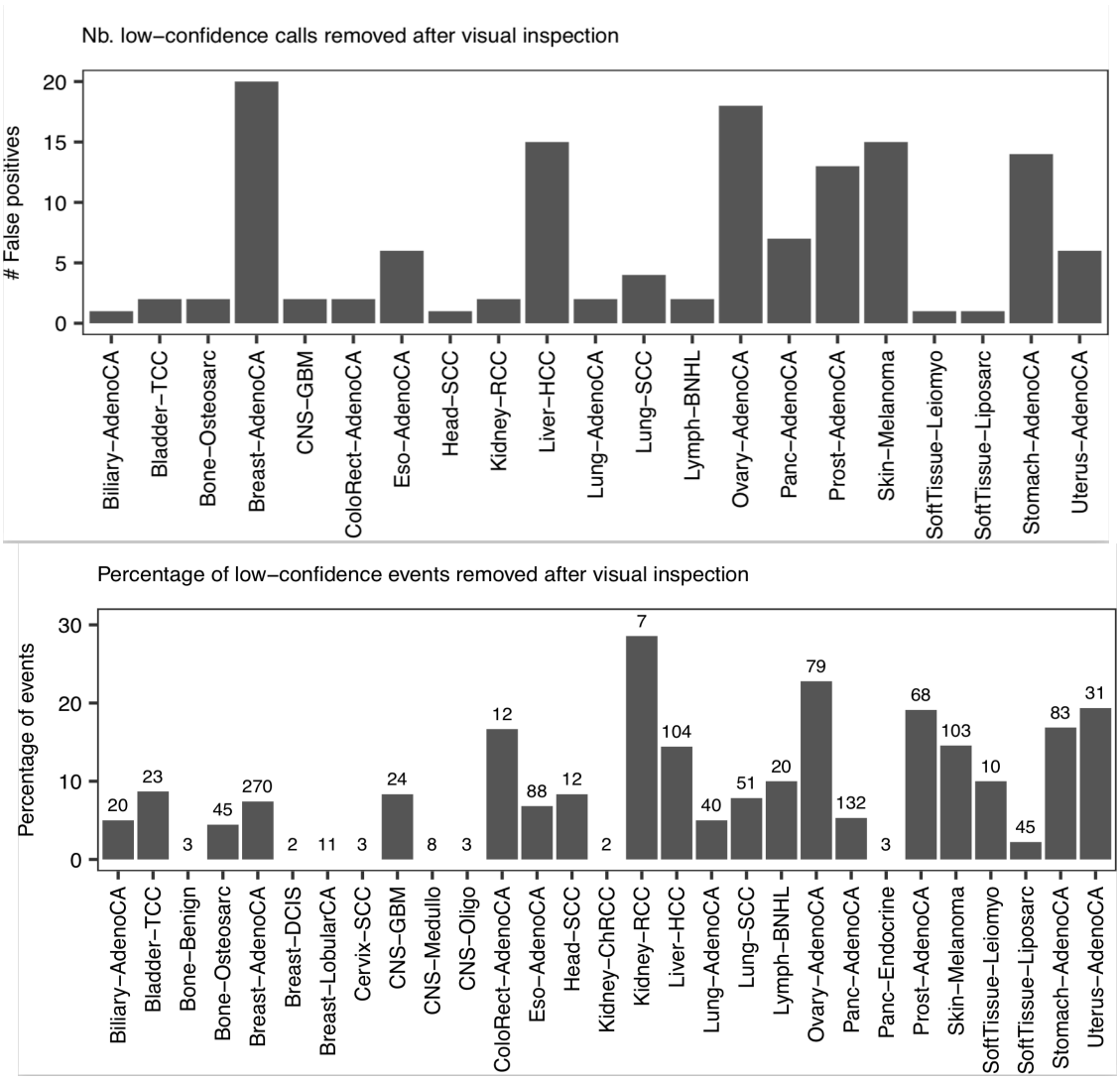
Our false negative rate was estimated to be 5.8%, which is also comparable to that reported by Notta *et al.*, *i.e.,* 8%. We detected 93 false negatives in 45 tumors (Supplementary Note Fig. 6). These cases were mainly events involving two or three chromosomes that generate few CN oscillations and often led to the deletion of one chromosome arm. Therefore, these cases were missed because they involved few interchromosomal SVs, and hence, ShatterSeek failed to detect a cluster of interleaved intrachromosomal SVs at the affected regions (see Supplementary Note Fig. 2 for an example).These events were common in Kidney-RCC, as other studies have reported recently[13].

We note that the false positive and false negative rates of Chrom-AL were determined by visual inspection[2], as we also do. Given that we detected chromothripsis in the same tumors as Notta *et al*.[2] (see section 2.8), we next examined the false positive and false negative rates on a per tumor type basis to better understand the differences in false positive rates.

We observe that for tumor types where other sources of hypermutation are frequent (*e.g.,* Homologous Recombination -HR- deficiency) our approach shows a higher false positive rate. This is expected because, although these hypermutated tumors show clusters of tandem deletions and duplications that are not interleaved, our algorithm sometimes fails to dismiss cases where other structural variations (generally inversions) occur on top of the tandem duplications or deletions. Identifying clusters of *interleaved SVs* is crucial to correctly dismiss false positive cases—clusters of breakpoints generated by other mechanisms but showing CN oscillations. Of the 2,591 chromosomes in the PCAWG cohort that show CN oscillations, we only called chromothripsis in 69% thereof (1787 events), *i.e.,* the interleaved SV criterion removes 31% of events. Visual inspection of these events revealed that the CN oscillations were consequence of tandem duplications and deletions. A visual representation for all these events is given in Supplementary Data File 3. Overall, these results indicate that the difference in the false positive rate of our algorithm and Chrom-AL[2] is due to tumor-type specific genomic instability patterns. Note that our false negative rate for Panc-AdenoCA, the tumor type studied by Notta *et al*., is comparable, *i.e.,* 5.8%.

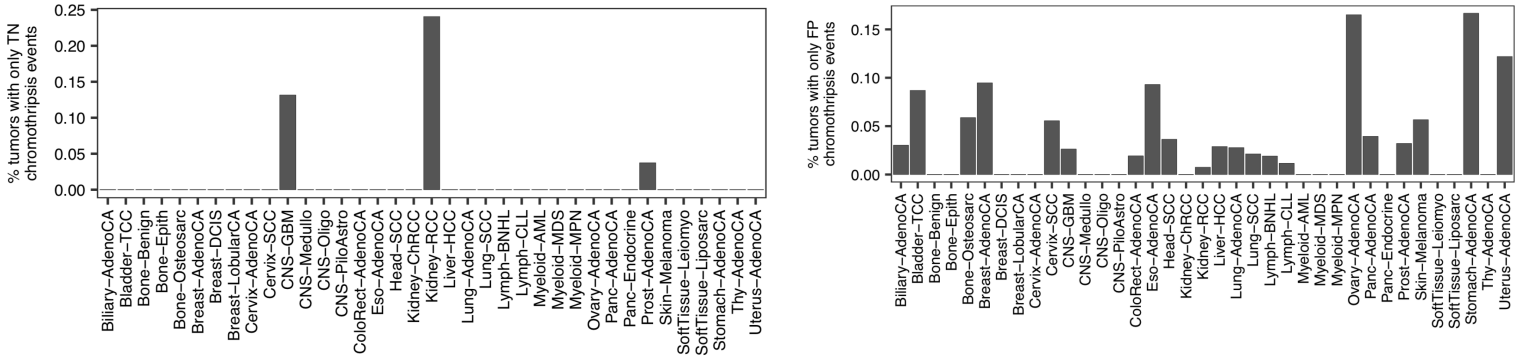


Supplementary Note Figure 4. Total number (top) and percentage (bottom) of high-confidence chromothripsis events (*e.g.,* chromosomes where chromothripsis was detected by ShatterSeek, not tumors) that were deemed false positives after visual inspection. Note that false positives are often detected in tumors that show true positive chromothripsis events in other chromosomes. In fact, of the 210 tumors where we detected false positives events, 103 thereof harbor true positive chromothripsis events in other genomic regions. The numbers on top of the bars on the bottom plot indicate the total number of high-confidence events detected in the tumors of the type indicated on the *x*-axis.



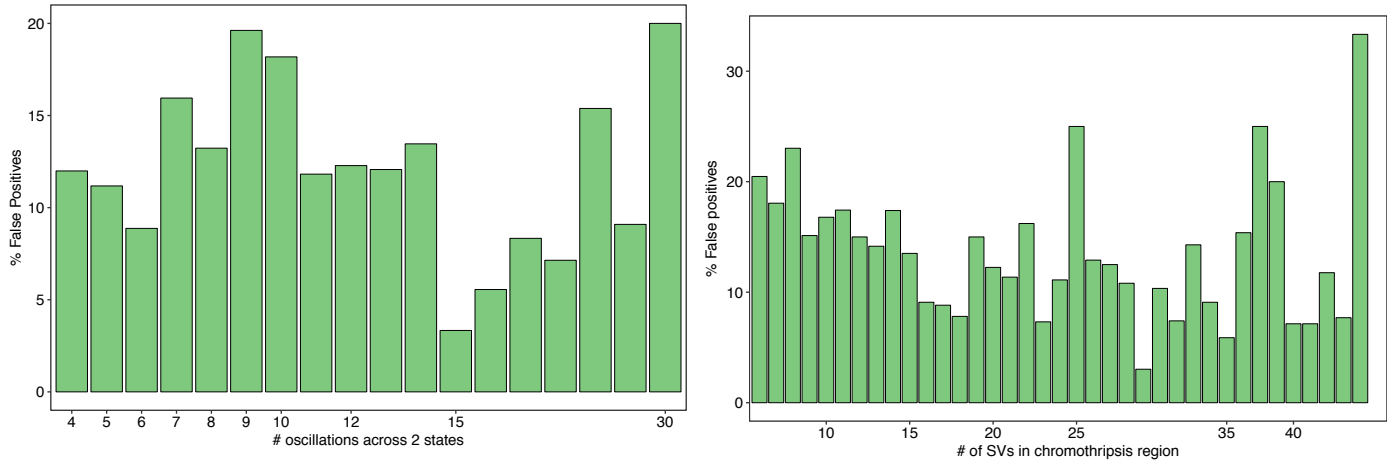
Supplementary Note Figure 5. Total number (top) and percentage (bottom) of low-confidence chromothripsis events (*e.g.,* chromosomes where chromothripsis was detected by ShatterSeek, not tumors) that were deemed false positives after visual inspection. The numbers on top of the bars on the bottom plot indicate the total number of low-confidence events detected in the tumors of the type indicated on the *x*-axis.

In total, 45 tumors were included (true negatives, left-hand side plot in Supplementary Note Fig. 6), and 108 were removed (false positives, right-hand plot in Supplementary Note Fig. 6) after visual inspection. For most cancer types, the percentage of false positive tumors is below 5%, and true negatives belonged to three tumor types only.



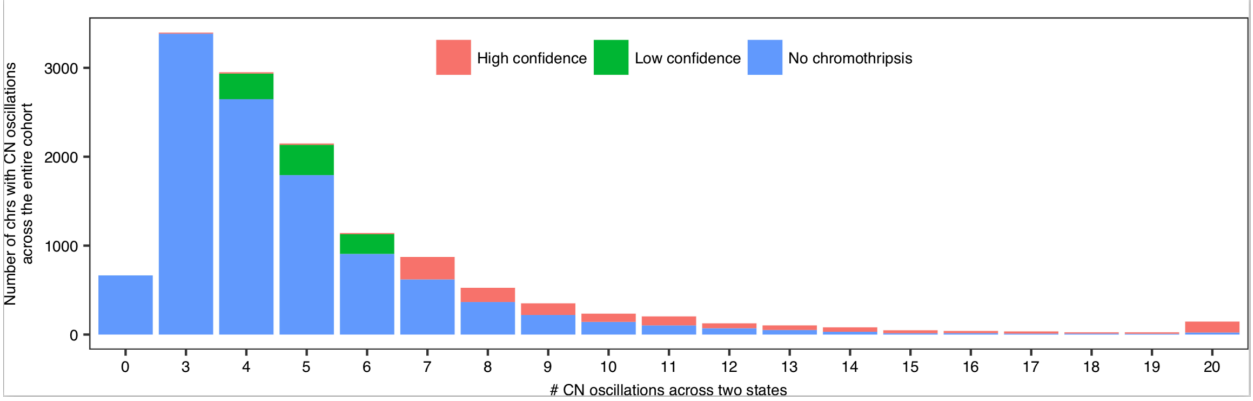
Supplementary Note Figure 6. Left. Percentage of tumors in the entire cohort with true negative events only. It can be seen that true negative events are enriched in Kidney-RCC, where chromothripsis events are recurrently formed by few interchromosomal SVs between chromosomes 3 and 5, thus leading to few CN oscillations (<10) and the loss of the *VHL* gene[13]. **Right.** Percentage of tumors in the PCAWG cohort with false positive calls only and that were not considered as harboring chromothripsis in this study. The chromothripsis rates are decreased by less than 5% in most tumor types after removing false positive cases by visual inspection. False positives are enriched in tumor types where hypermutation occurs frequently due to *e.g.,* HR deficiency, including Breast-AdenoCA and Ovary-AdenoCA.

We next examined whether the false positives we detect are characterized by a low number of CN oscillations, or by a low number of SVs (Supplementary Note Fig. 7). It can be seen that the false positives are evenly distributed across CN oscillations and number of SVs, indicating that false positives are not enriched for cases involving few SVs or displaying few oscillations.



Supplementary Note Figure 7. Percentage of false positive events stratified on the basis of the number of CN oscillations in the event (left), and number of SVs involved in the event (right). The bars indicate the percentage of chromothripsis events called by ShatterSeek showing a given number of CN oscillations or SVs that were classified as false positives.

Finally, we assessed the fraction of regions showing clusters of SVs and a certain number of CN oscillations in the tumors examined where we make a chromothripsis call. We hypothesized that if our algorithm and visual inspection steps were not specific to chromothripsis, we would expect the algorithm to call a high rate of chromothripsis events for chromosomes displaying few CN oscillations. We found that the fraction of regions with 3-7 oscillations where we call chromothripsis is small, especially for those with 3-4 oscillations (Supplementary Note Fig. 8), indicating that our algorithm does not call chromothripsis arbitrarily in regions with few oscillations.

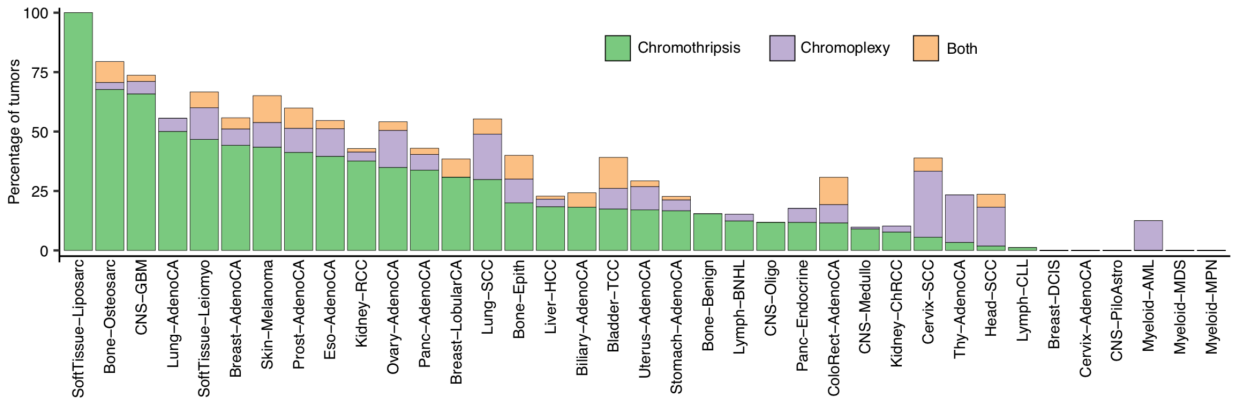


Supplementary Note Figure 8. Number of chromosomes harboring SV clusters across the entire cohort (13,120 regions across the 2,428 tumors with at least 1 SV that we examined; *y*-axis) showing the number of CN oscillations indicated in the *x*-axis. The x-axis indicates the number of CN oscillations in these regions. Regions with >20 oscillations were aggregated to the bar with the label “20”.

1.4 Chromothripsis and chromoplexy

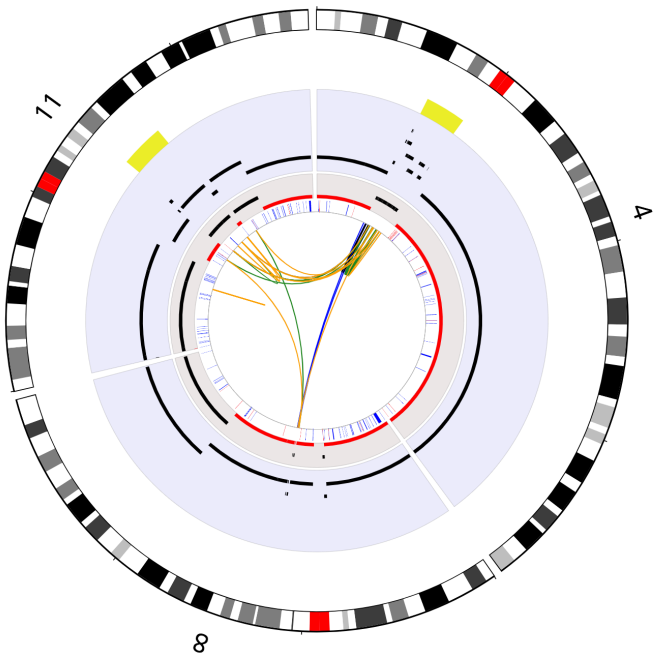
Chromoplexy is defined as a chain of balanced translocations, thus displaying balanced CN profiles rather than oscillating CN profiles, with the exception of those cases where DNA resection or segmental loss occurs[14]. Given that chromoplexy events where segmental losses occur might generate chromothripsis-like patterns, we next sought to analyse to what extent ShatterSeek misclassifies chromoplexy events as chromothripsis. To this, we detected chromoplexy events in all tumors considered using ChainFinder version 1.0.1.[14] We required at least three chromosomes involved in a chain to make a chromoplexy call. We detected 306 chromoplexy chains in 253 tumors (10% of tumors; Supplementary Note Fig. 9). We found that chromothripsis and chromoplexy occurred frequently in different genomic regions of the same tumor; only 12 tumors had regions where both ShatterSeek and ChainFinder made a call. This represents 3.2% (23/734) of the tumors with high-confidence chromothripsis events. We detected both chromoplexy and chromothripsis in the same region in 1 Biliary-AdenoCA, 1 Bone-Epith, 1 Breast-AdenoCA, 1 Breast-LobularCA, 1 ColoRect-AdenoCA, 1 Eso-AdenoCA, 2 Liver-HCC, 2 Panc-AdenoCA, and 2 Prost-AdenoCA tumors. Visual inspection of these cases revealed that both chromoplexy and chromothripsis events occurred in these tumors (see

Supplementary Note Fig. 10 for an example), and that both algorithms made correct calls even in cases where both mechanisms overlapped. By analizing the SVs in chromoplexy chains, we found that only 1% (when considering high-confidence chromothripsis regions only) of the SVs involved in chromoplexy mapped to regions affected by chromothripsis; 4.5% when also including low-confidence calls.



Supplementary Note Figure 9. Percentage of tumors harboring chromothripsis events only (green), both chromoplexy and chromothripsis in different regions of their genomes (orange), and chromoplexy events only (purple).

Given these results, coupled to the fact that we used high thresholds for the minimum number of chromosomal segments exhibiting CN oscillations, we are confident that there is not a substantial contamination of chromoplexy events in our chromothripsis call set. However, we cannot completely exclude the possibility that chromothripsis might have occurred in some



Supplementary Note Figure 10. Example of a tumor (Bone-Epith, CGP_donor_1602529) where both chromothripsis and chromoplexy affected the same region. An interactive version of this plot can be found at: http://compbio.med.harvard.edu/chromothripsis/

cases on already-rearranged chromosomes by chromoplexy and *vice versa*. These cases would belong to the "with other complex events" category in our classification of chromothripsis events.

1.5 Chromothripsis and chromoanasynthesis

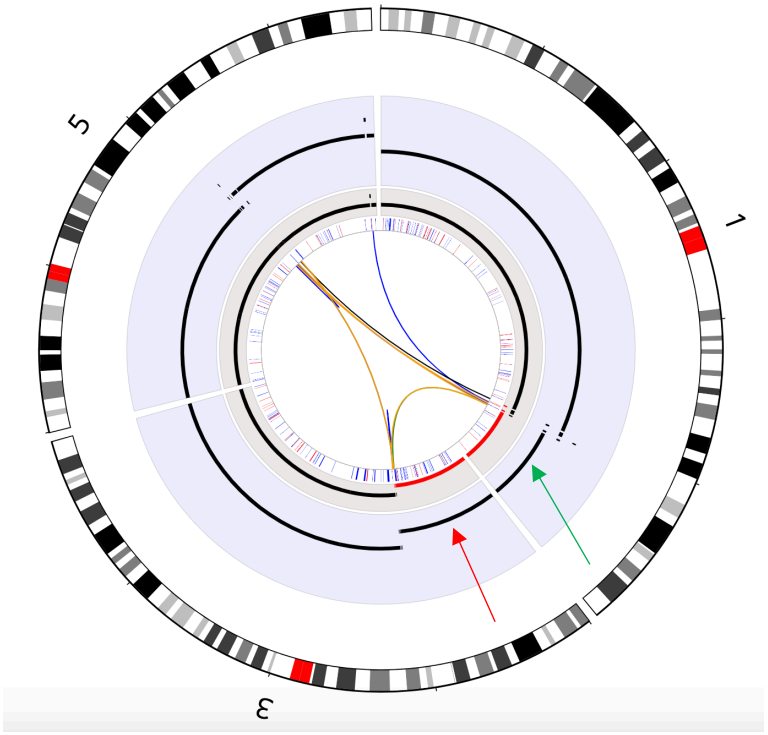
Another mechanism that often generates chromothripsis-like patterns is chromoanasynthesis[15]. We note that the distinction between chromothripsis and chromoanasynthesis is often simple for diploid genomes in the absence of secondary rearrangements. When there is aneuploidy, the distinction is less clear because the CN and LOH patterns for a chromothripsis event in an aneuploid genome are comparable to that of a chromoanasynthesis even in a diploid tumor. Hence, it is not always possible to assess systematically the difference between these two scenarios (with the genome-wide ploidy and microhomology at breakpoints and SV connections, it may be possible to make educated guesses in some situations, but not always very reliably). Another complication is that some genomes appear to contain both chromothripsis and chromoanasynthesis events, often connected to each other (see Fig. 4 in the main text). Therefore, we used the canonical cases to estimate the fraction of chromoanasynthesis cases in our call set, which was found to be in the order of ~5% (see the main text for further details).

To identify templated insertions, we followed the set of criteria described by Li *et al*.[16], namely: orientation and microhomology at the breakpoints, connections between amplified segments, and the size of the amplified segments.

1.6 Defining the extent of chromothripsis events

We considered that two or more intrachromosomal chromothripsis regions belong to the same catastrophic event if these regions +/- 10Kb are linked by at least two interchromosomal SVs. Given that we did not always detect rearrangements between all regions belonging to the same chromothripsis event in cases where at least three chromosomes were involved, we applied transitive reasoning to identify the full extent thereof. For instance, if the chromothripsis regions in chromosome 1 and 2 are linked, and those detected in chromosome 2 are also linked to a chromothripsis region in chromosome 3, we consider that the chromothripsis patterns detected in these three chromosomes belong to the same event.

In each chromosome, the genomic region encompassed between the breakpoints at both ends of the complex rearrangement was considered as the region affected by chromothripsis. However, we note that manual review is required in cases where a chromothripsis event leads to the loss of the entire genomic region upstream or downstream the SV cluster till the chromosome ends, as in these cases those regions are not comprised within the SV cluster (see two examples in Supplementary Note Figs. 2 and 11)[13].



Supplementary Note Figure 11. Example of an event that required manual inspection to determine that the regions downstream (chromosome 1; green arrow) and upstream (chromosome 3; red arrow) of the cluster of SVs generated by a multichromosomal event were lost due to chromothripsis. Tumor DO19733 (Kidney-RCC; TCGA-CW-5585). An interactive version of this plot can be found at: http://compbio.med.harvard.edu/chromothripsis/

1.7 Classification of chromothripsis events

Chromothripsis events were classified as canonical if at least 60% of contiguous CN segments alternate between two copy number states. We inferred the mutational timing using the pattern of the copy number variation and the loss of heterozygosity as previously proposed[17], and used by others[2]. The basic idea is that if chromothripsis occurs before genome doubling, the copy number oscillations, for instance, would go from 1-2-1-2-1-2 to 2-4-2-4-2-4; if after genome doubling, it would be 3-4-3-4-3-4-3 because it would affect only one chromosome[17]. Canonical chromothripsis events with alternating CN profiles between CN states ≥ 3 were considered to have occurred after polyploidization. Canonical events with CN profiles alternating between two CN states encompassed in the set {0,1,2,3} were labeled as canonical without polyploidization. For the canonical chromothripsis events occurring in polyploid tumors, we can determine whether chromothripsis occurred before or after polyploidization. Chromothripsis events that preceded polyploidization display a CN pattern that oscillates between CN states that are multiple of 2 (*e.g.*, 2 and 4 in the case of whole genome duplication; Supplementary Fig. 6d). For example, if the CN oscillation occurs between 2 and 4 copies in a tetraploid tumor, we infer that polyploidization occurred after chromothripsis. Chromothripsis patterns detected in complex

rearrangements where less than 60% of adjacent copy number segments alternate between two copy number states were considered to colocalize with other complex events likely generated by mechanisms other than chromothripsis (see Fig. 1 in main text).

1.8 Effect of tumor purity and heterogeneity

Tumor purity and intra-tumor heterogeneity are potential confounding factors in the estimation of chromothripsis rates as they reduce the sensitivity of SV and CN detection. Tumor purity is highly variable across cancer types (Supplementary Table 1). However, we found that the chromothripsis rates we estimate are not correlated with average tumor purities across cancer types (Supplementary Figs. 1-2, and Supplementary Table 1). This is probably because most chromothripsis events generate many CN alterations and SVs, and the probability of missing the majority of these events is low even with relatively low purity. In many cases, we were able to detect chromothripsis events in low-purity samples (see Fig. 2c in the main text, where the purity was 0.22) or in tumors with multiple subclonal populations (Supplementary Fig. 5a). However, it is possible that chromothripsis events present in a reduced fraction of cancer cells are missed by our pipeline, resulting in under-estimation of the chromothripsis frequency.

2. Comparison of ShatterSeek to other methods

2.1 Comparison with previous calling criteria

Supplementary Note Table 2. The table below lists the major papers that involved chromothripsis calls, along with the algorithms and criteria used for its detection.

	Title	Year	Journal	Authors (first, senior)	Algorithm
Original chromothripsis paper	Massive genomic rearrangement acquired in a single catastrophic event during cancer development	2011	Cell	Stephens, Campbell	Custom (simulations)
Multiple myeloma	Chromothripsis identifies a rare and aggressive entity among newly diagnosed multiple myeloma patients	2011	Blood	Magrangeas, Minville	Custom software. Criteria based on CN oscillations
Colorectal cancer	Chromothripsis is a common mechanism driving genomic rearrangements in primary and metastatic colorectal cancer	2011	Genome Biology	Kloosterman, Cuppen	Custom software. CN oscillations; comparison w.r.t. Stephens *et al*. cases (Cell, 2011)

	Title	Year	Journal	Authors (first, senior)	Algorithm
Germline chromothripsis	Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline	2011	Human Molecular Genetics	Kloosterman, Cuppen	Custom software. CN oscillations; comparison w.r.t. Stephens *et al*. cases (Cell, 2011)
Medulloblastoma	Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with *TP53* mutations	2012	Cell	Rausch, Korbel	10 CN oscillations. According to Korbel (personal communication), this approach works well for medulloblastomas, but it might not work for other cancer types.
Medulloblastoma	Sequencing of neuroblastoma identifies chromothripsis and defects in neuritogenesis genes	2012	Nature	Molenaar, Versteeg	"Genomes were annotated as having chromothripsis-like characteristics when the sum of intra-chromosomal somatic junctions (as reported by JunctionDiff and filtered as above) within a single chromosome was larger or equal to 20. Focused amplified regions (cgCGH scores ≥3) within a chromosome were excluded from this sum. Using these characteristics, we annotated 10 out of the 87 patients as chromothripsis-like"
Prostate cancer	Poly-gene fusion transcripts and chromothripsis in prostate cancer	2012	Genes Chromosomes Cancer	Wu, Collins	Custom code based on Stephens *et al*. (Cell, 2011)
Criteria inference chromothripsis	Criteria for inference of chromothripsis in cancer genomes	2013	Cell	Korbel & Campbell	Criteria for inference of chromothripsis are proposed
Pan-Cancer analysis array data	Functional genomic analysis of chromosomal aberrations in a	2013	Genome Research	Kim, Park	Custom code partly based on Korbel and Campbell (Cell, 2013)

	Title	Year	Journal	Authors (first, senior)	Algorithm
	compendium of 8000 cancer genomes				
Esophageal adenocarcinomas	Genomic catastrophes frequently arise in esophageal adenocarcinoma and drive tumorigenesis	2014	Nature Communications	Nones, Barbour	Custom code based on Korbel and Campbell (Cell, 2013)
Leukemia	Constitutional and somatic rearrangement of chromosome 21 in acute lymphoblastic leukaemia	2014	Nature	Li, Harrison	Custom code based on Korbel and Campbell (Cell, 2013)
GBM	Whole genome sequence analysis links chromothripsis to *EGFR, MDM2, MDM4*, and *CDK4* amplification in glioblastoma	2015	Oncoscience	Furgason, Bahassi	ShatterProof (score cut-off value 0.37)
Pancreatic cancer	Whole genomes redefine the mutational landscape of pancreatic cancer	2015	Nature	Waddell, Grimmond	Custom (not specified); only reference to Campbell and Korbel (Cell, 2013)
CAST *in vitro*	A cell-based model system links chromothripsis with hyperploidy	2015	Molecular Systems Biology	Marvin, Korbel	Custom code based on Korbel and Campbell (Cell, 2013)
Chromothripsis and kataegis in vitro	Chromothripsis and kataegis induced by telomere crisis	2015	Cell	Maciejowski, de Lange	Custom based on Korbel and Campbell (Cell, 2013)
Look-Seq: Chromothripsis and micronuclei	Chromothripsis from DNA damage in micronuclei	2015	Nature	Zhang, Pellman	Look-seq: custom analysis of single-cell sequencing data
Renal cell carcinoma	Multilevel genomics-based taxonomy of renal cell carcinoma	2015	Cancer Cell	TCGA	Not specified
Melanoma	Genomic classification of cutaneous melanoma	2016	Cell	TCGA	ShatterSeek (score cut-off value 0.517)
Acute Myeloid Leukemia	Prognosis and *TP53* alterations	2016	Blood	Fontana, Martinelli	CTLP scanner

	Title	Year	Journal	Authors (first, senior)	Algorithm
Prostate cancer	Genomic hallmarks of localized, non-indolent prostate cancer	2017	Nature	Fraser, Boutros	ShatterProof (score cut-off value 0.517)
Pancreatic cancer	A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns	2017	Nature	Notta, Gallinger	Custom (Chrom-AL) based on Korbel and Campbell (Cell, 2013)
Liposarcomas	Recurrent mutation of IGF signalling genes and distinct patterns of genomic rearrangement in osteosarcoma	2017	Nature Communications	Behjati, Campbell	Custom based on Korbel and Campbell (Cell, 2013)
Prostate cancer	Germline *BRCA2* mutations drive prostate cancers with distinct evolutionary trajectories	2017	Nature Communications	Renea, Bristow (including Boutros)	ShatterProof (score cut-off value 0.517)
Leiomyosarcoma	Integrative genomic and transcriptomic analysis of leiomyosarcoma	2018	Nature Communications	Chudasama, Frohling	Custom based on Korbel and Campbell (Cell, 2013)
Pediatric cancers	Pan-cancer genome and transcriptome analyses of 1,699 pediatric leukaemias and solid tumours	2018	Nature	Ma, Zhang	Custom based on Korbel and Campbell (Cell, 2013)
Pediatric cancers	The landscape of genomic alterations across childhood cancers	2018	Nature	Grobner, Pfister	Custom based on Korbel and Campbell (Cell, 2013) and visual inspection
Clear cell renal cell cancer	Timing the landmark events in the evolution of clear cell renal cell cancer: TRACERx Renal	2018	Cell	Mitchell, Campbell	Custom based on Korbel and Campbell (Cell, 2013) and visual inspection

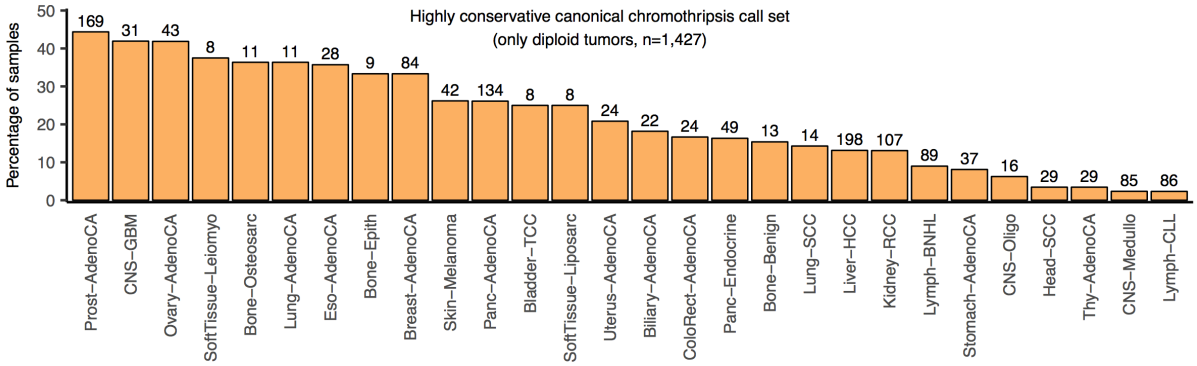
Overall, most of the studies where array or sequencing data was used to detect chromothripsis followed the statistical criteria described by Korbel and Campbell[4]. In addition to these, other metrics to detect simultaneous rearrangements in cancer genomes have been proposed[18–20]. However, these methods are very sensitive to missing SVs, as acknowledged, *e.g.,* in Oesper *et al.* [18], and based on our experience of trying to reconstruct complex regions[21]. In practice, a substantial fraction of the SVs present in a tumor sample are missed in WGS analysis due to intra-tumor heterogeneity, breakpoints in repetitive sequences, low tumor purity, alignment artifacts, etc. Moreover, the PCAWG SV calling pipeline was designed to maximize specificity over sensitivity (by requiring overlap in two or more algorithms). Hence, we believe that our

statistical approach, followed by visual inspection of all calls, represents a more suitable approach for the detection of chromothripsis from our current data. Note that one of the six criteria in the review by Korbel and Campbell includes the “ability to walk the derivative chromosome”, but this criterion is not used in practice (see *e.g.,* Li *et al.*[22]).

CTLPScanner[8,23] is designed to use CN profiles derived from SNP array data as input, and thus lacks sensitivity that comes from WGS data; this makes a comparison between CTLPScanner and our method difficult to interpret. Therefore, we have focused on the comparison of our method with ShatterProof[24], which is the only available package that takes both CN and SV information as input, and with the results provided for Chrom-AL[2].

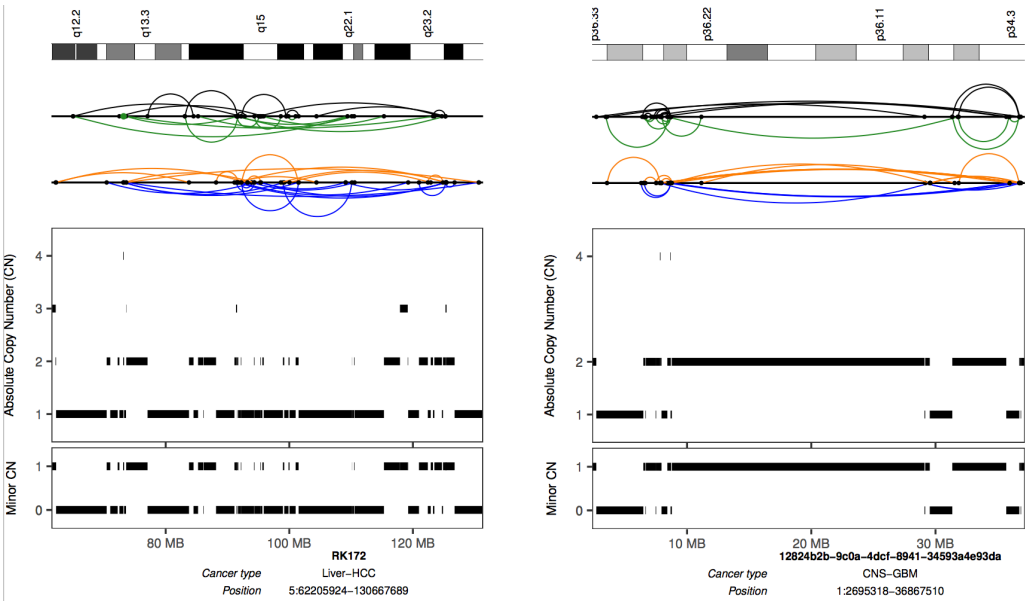
2.2 Validation in diploid tumors

We first carried out an analysis for the ‘canonical’ chromothripsis events in 1,427 diploid tumors, which are much easier to handle, do not generally show secondary events (*e.g.,* high-level amplifications following chromothripsis), and where we could examine all the criteria used for chromothripsis detection (analysis of loss of heterozygosity is not always possible in aneuploid tumors). As can be seen in Supplementary Note Fig. 12, the rates of chromothripsis based only on canonical events are still much higher than previously reported. Three cancer types exhibit chromothripsis rates over 40% (CNS−GBM, Ovary-AdenoCA, and Prost-AdenoCA), and over half of the cancer types examined display rates over 20%.



Supplementary Note Figure 12. Rates of chromothripsis in diploid tumors (ploidy < 2.1). the number on top of the bars indicates the number of tumors analysed.

Our calls in these cases are stringent: as a reminder, we require interleaved SVs, >6 SV breakpoints, 7 contiguous segments oscillating between two states (4 for low-confidence), and equal distribution of SVs types (to remove tandem duplications/deletions, Breakage-Fusion-Bridge (BFB)-only events, etc..). Two examples that appear to be chromothripsis by visual inspection but are not called as canonical chromothripsis cases are shown in Supplementary Note Fig. 13. Therefore, the rates estimated using only diploid cases are likely to be an underestimation of the true chromothripsis rates.

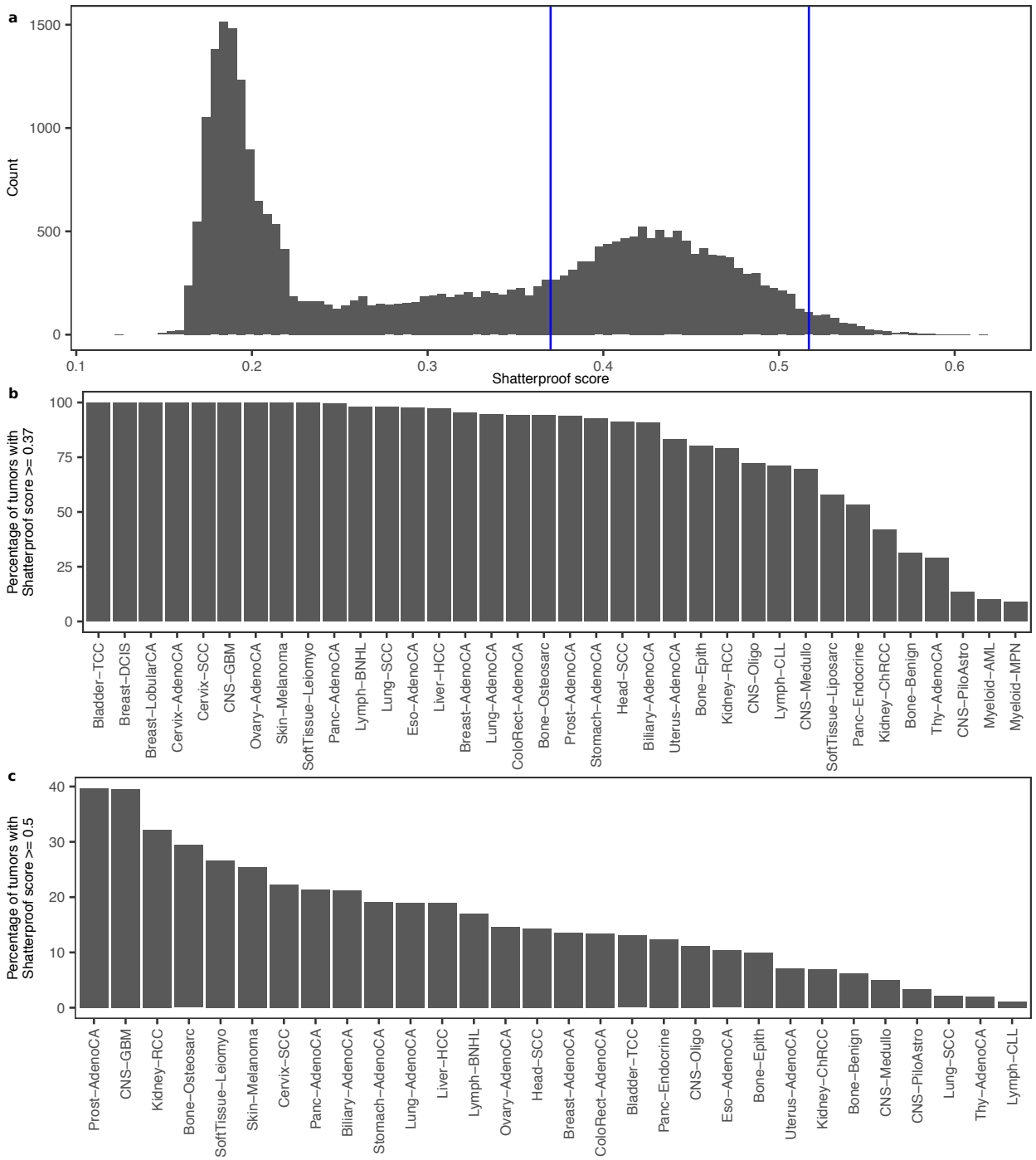


Supplementary Note Figure 13. Example of two events that are not detected as canonical chromothripsis in the diploid analysis but appear to be chromothripsis by visual inspection.

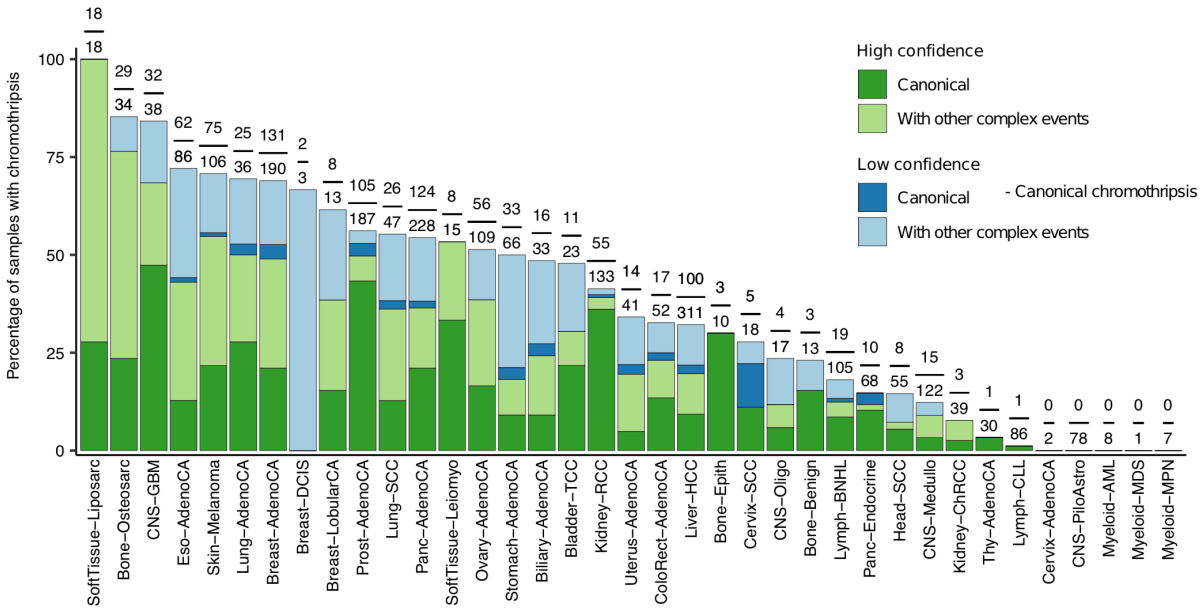
2.3 Comparison with ShatterProof

To benchmark our tool against the state of the art, we used ShatterProof to detect chromothripsis across the entire PCAWG cohort.

We used ShatterProof to detect chromothripsis across the 2,428 tumors that have at least one rearrangement (Supplementary Note Fig. 14). In the ShatterProof publication[24], the authors suggest a cut-off value for the ShatterProof score of 0.37 based on their analysis of 20 whole genomes. In a more recent study[12], the authors used a cut-off value of 0.517. We did not find any justification in that study as to why 0.517 should be used instead of 0.37. Thus, we have used both thresholds for our comparisons. The rates estimated using a cut-off value of 0.37 and 0.517 are shown in Supplementary Note Fig. 14. Overall, the rates of chromothripsis estimated using ShatterProof are substantially higher than ours (Supplementary Note Fig. 15) when using a cut-off value of 0.37 (over 95% of tumors for 12 cancer types). The rates are a bit lower but correlated with ours when using the more stringent cut-off value of 0.517.



Supplementary Note Figure 14. Chromothripsis rates estimated with ShatterProof. (**a**) Distribution of non-zero ShatterProof scores calculated for the PCAWG cohort. The two blue lines indicate the cut-off values used by Govind *et al.* (*i.e.*, 0.37), and by Fraser *et al.* (*i.e.*, 0.517). (**b-c**) Rates of chromothripsis estimated using ShatterProof and a cut-off value of 0.37 (**b**), and 0.517 (**c**), respectively, for the 2,428 tumors we analysed.



Supplementary Note Figure 15. Rates of chromothripsis estimated using ShatterSeek (Fig. 1c in the main text).

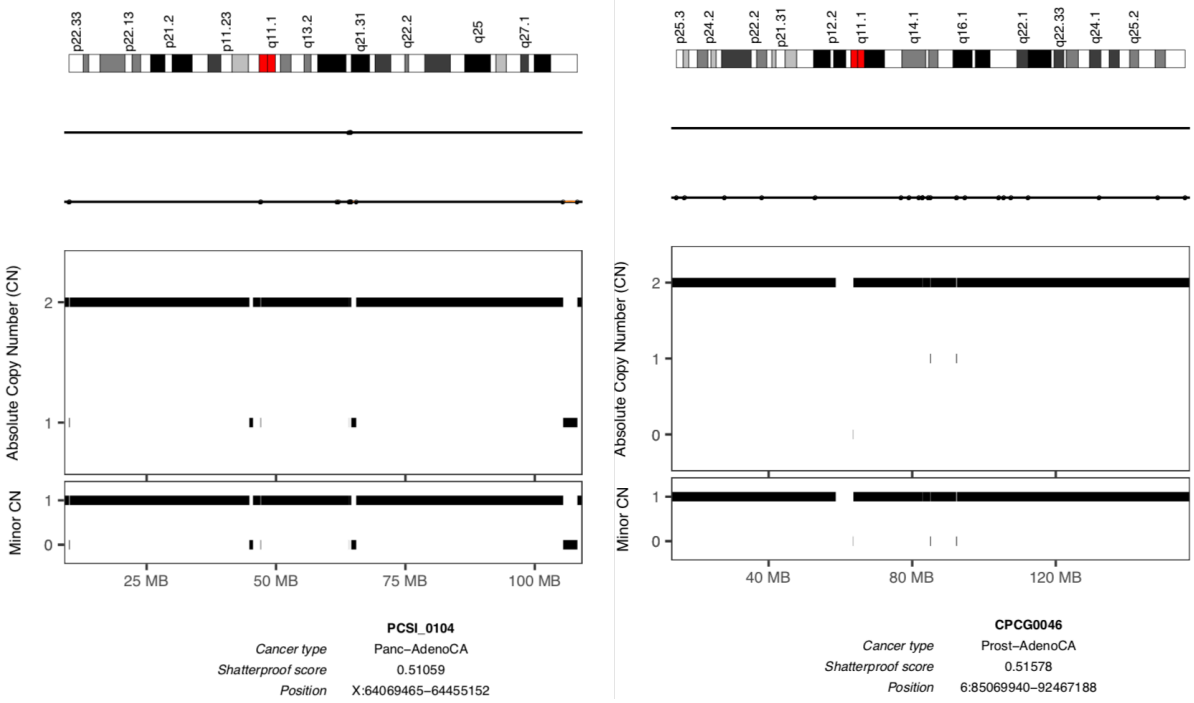
To better understand the differences between ShatterProof and ShatterSeek, we have visually inspected all the chromothripsis regions that were detected by only one approach but not the other.

2.4 Cases missed by ShatterSeek and called by ShatterProof

The regions detected by ShatterProof but not by our method are mostly cases characterized by CN oscillations corresponding to tandem deletions or duplications (two examples are shown in Supplementary Note Fig. 16). For instance, BRCA-deficient breast tumors display many tandem duplications; these should not be called as chromothripsis events, but they are often mistakenly called by ShatterProof. Our method has filtering criteria to avoid calling such events (*i.e.,* the requirement for equal distribution of SV types and the presence of interleaved SVs). In addition, we also removed those cases by visual inspection when necessary.

We note that we do miss to call a small subset of the regions with high ShatterProof scores and are likely to have originated by chromothripsis. These are mostly focal events with less than 6 SVs mapped (the minimum number we require to make a call). We decided to use 6 SVs as a

threshold as this value was used in previous work[2], and because we found through visual inspection of hundreds of cases that requiring less than 6 SVs increased the false positive rate, as clusters of inversions or tandem duplications with overlapping inversions might be included. Another reason to consider at least 6 SVs was to have enough statistical power to assess the even distribution of SV types in order not to call as chromothripsis other mutation types characterized by one SV type (*e.g.,* BFB cycles).

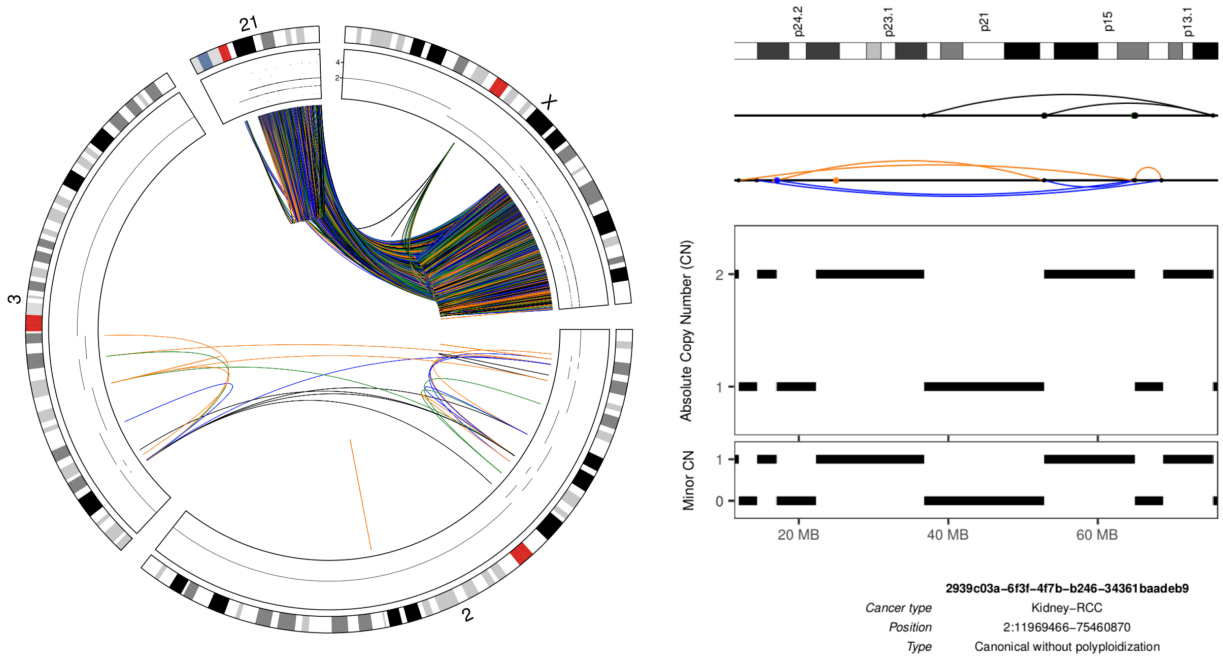


Supplementary Note Figure 16. Examples of regions with a high ShatterProof score and not detected by our method. These two examples show two regions with clusters of tandem deletions (each black dot on the second horizontal line below the chromosome ideogram represents a deletion) that generate CN oscillations. Our method correctly detected that these oscillations are not due to chromothripsis events. However, ShatterProof assigns a score over 0.5 for both, and hence, erroneously calls these two as chromothripsis.

2.5 Cases missed by ShatterProof but detected by ShatterSeek

In numerous cases, ShatterProof misses regions clearly showing the hallmarks of chromothripsis. We suspect that this might be due to the fact that ShatterProof only calculates scores for highly mutated regions (from Govind *et al.*[24]: "*The metrics produced from the sliding window analysis are used to identify highly mutated regions by comparing region-specific SV density to genome-wide density using a z-scale approach*"). In addition, some of the components of the ShatterProof score also depend on the SV density in other chromosomes: for instance, the 'genome localization' score in ShatterProof is only calculated for chromosomes with more SVs than the average number of SVs across all chromosomes. Therefore, ShatterProof will not consider for further analysis regions showing an SV rate lower than the genome-wide SV rate.

An illustrative example of this is shown in Supplementary Note Fig. 17. The two chromothripsis events in chromosomes 21 and X lead to high estimates of genome-wide SV rates, thus not permitting ShatterProof to detect the two chromothripsis regions in chromosomes 2 and 3 involving fewer SVs; the ShatterProof scores for these two chromosomes are 0. This illustrates that methods that rely on increased SV density with respect to the genome-wide rate to detect chromothripsis are likely to miss events in hypermutated tumors (*e.g., BRCA* deficient tumors), or focal events comprising less SVs than the average SV rate in other chromosomes. Based on these observations, we tuned our calling criteria to account for this issue.



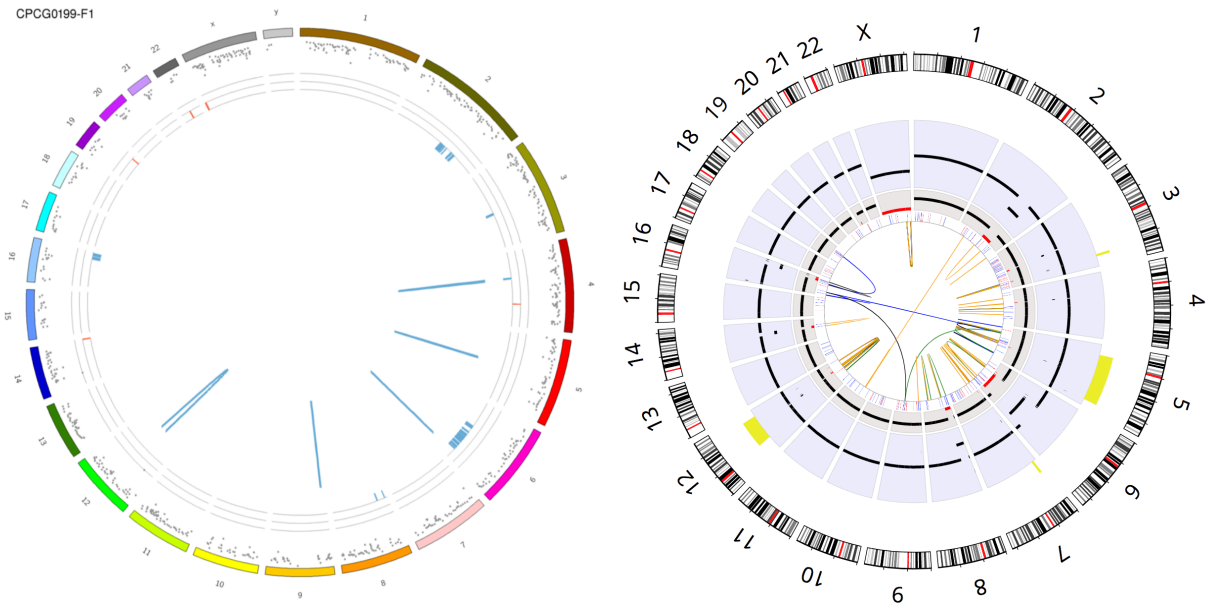
Supplementary Note Figure 17. Circos plot including chromosomes 2, 3, 21 and X for the Kidney-RCC tumor DO17373. The plot on the right-hand side corresponds to the chromothripsis event we detect in chromosome 2.

2.6 Comparing the chromothripsis rates for prostate tumors

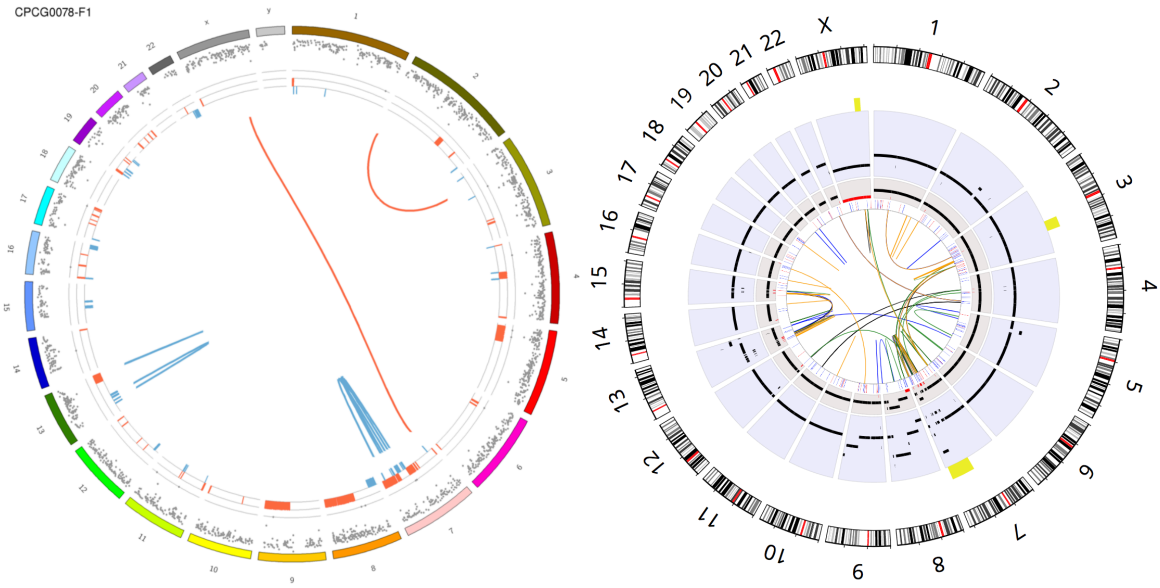
Next, we compared our calls against those previously reported for 109 prostate adenocarcinomas also present in our cohort[12]. Using ShatterProof, the authors detected chromothripsis in 23 prostate tumors (21%). Using our CN and SV calls and ShatterProof version 0.14[24] with default settings we detect chromothripsis in 49 (45%), and in 60 (55%) with our tool, *i.e.,* ShatterSeek. Of the 23 cases reported by Fraser *et al.*[12], we only miss 4, which are focal events involving less than 6 SVs. It is paramount to note that when ShatterProof is run with the default parameter of 0.37 suggested in the original publication, 97% (106/109) of the tumors are annotated as harboring chromothripsis events.

Visual inspection of the cases we detect but are missed by Fraser *et al.*[12] reveals that the lower sensitivity of the SV and CN calls used in that study underlies these differences, as they do not

detect any SVs in some chromosomes where we find clear evidence of chromothripsis. Two examples are shown below in Supplementary Note Figs. 18-19.



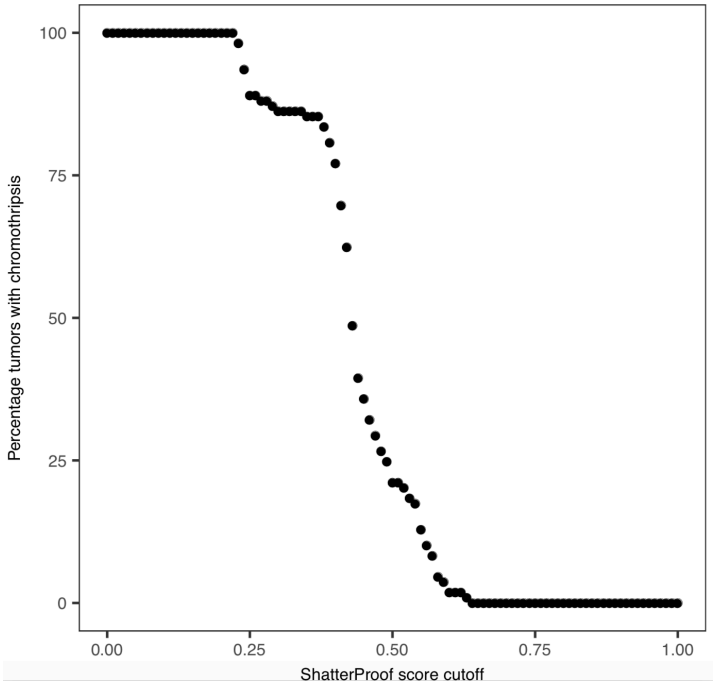
Supplementary Note Figure 18. Example of two focal chromothripsis events missed by ShatterProof in Fraser *et al.* (Circos plot on the left) that we manage to detect (Circos plot on the right) in tumor CPCG0199.



Supplementary Note Figure 19. Example of a chromothripsis case in chromosome 7 in tumor CPCG0078 not reported by Fraser *et al.* (Circos plot on the left).

2.7 Chromothripsis rates as a function of the ShatterProof cut-off value

Finally, we calculated the pan-cancer rate of chromothripsis as a function of the ShatterProof score. As can be seen below (Supplementary Note Fig. 20), the estimated rates vary strongly depending on the cut-off value used and do not converge to a stable value. Hence, we could not determine a reliable cut-off for ShatterProof in our analysis.



Supplementary Note Figure 20. Pan-cancer chromothripsis rates estimated using increasingly higher values for the ShatterProof cut-off score.

2.8 Comparison against Chrom-AL

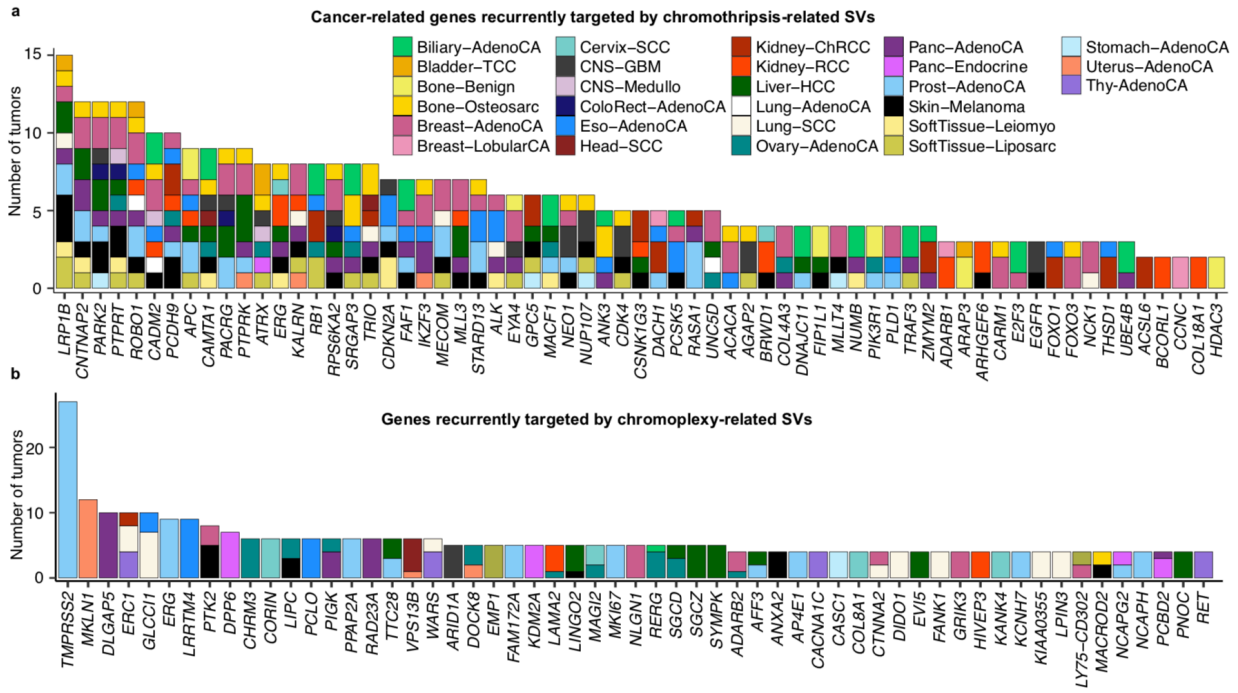
We also compared our method against Chrom-AL[2] for 76 pancreatic tumors also present in our cohort. Both Chrom-AL and our method detect chromothripsis in the same 41 tumors.

2.9 Manual inspection of chromothripsis calls

Finally, we note that none of the statistical criteria proposed and used in the literature can give a definitive result about whether a region is subject to chromothripsis or not. Hence, visual inspection of all cases remains essential (as was done in, *e.g.,* Notta *et al*.[2]). We have visually inspected all our chromothripsis calls, which amounts to analyzing over 55,000 pictures (one picture per chromosome and tumor) of CN and SV profiles.

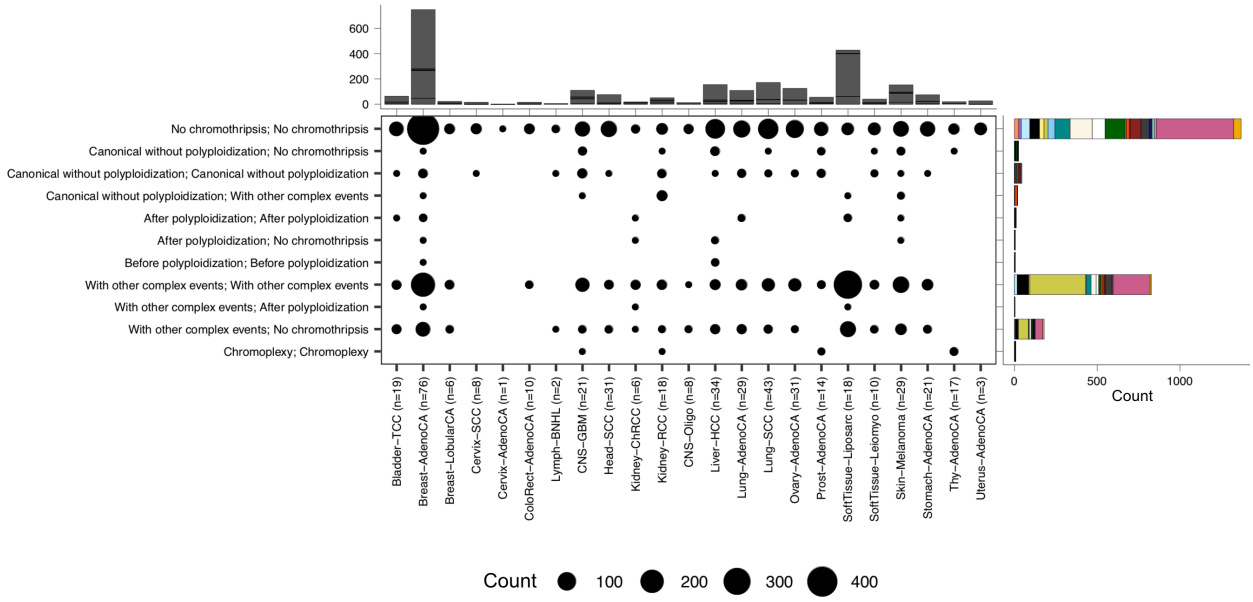
3. Contribution of chromothripsis to gene fusion formation

We also examined those genes targeted by chromothripsis-related SVs. We find that 61% of the breakpoints in high confidence chromothripsis regions map to exonic or intronic regions. This frequency was comparable for canonical events and those co-localized with other complex events. Analysis of these genes reveals that most of them are not recurrently targeted by chromothripsis (*e.g.,* they are targeted in few tumors; Supplementary Note Fig. 21a), in contrast to chromoplexy, as some genes, *e.g., TMPRSS2*, are affected in multiple tumors (Supplementary Note Fig. 21b)[5,14].



Supplementary Note Figure 21. (**a**) Cancer-related genes recurrently targeted by SVs involved in chromothripsis. (**b**) Genes recurrently involved in chromoplexy chains.

The rejoining of DNA fragments in chromothripsis is a potential source of gene fusions[5]. To examine the extent to which chromothripsis contributes to the generation of gene fusions across diverse cancer types, we considered 2,493 gene fusions previously detected using RNA-seq data for the 455 TCGA tumors also present in our cohort that had at least 1 fusion (median=3)[25]. We find that 1,116 fusions (44.8%; Supplementary Figure 22) have at least one gene partner in a chromothripsis region, with the highest frequencies observed for complex events in SoftTissue−Liposarc, Breast-AdenoCA, Skin-Melanoma, and CNS-GBM. Chromoplexy generates gene fusions in CNS-GBM (1 fusion), Kidney-RCC (1), Thy-AdenoCA (4), and, as previously reported[14], in Prost-AdenoCA (2).



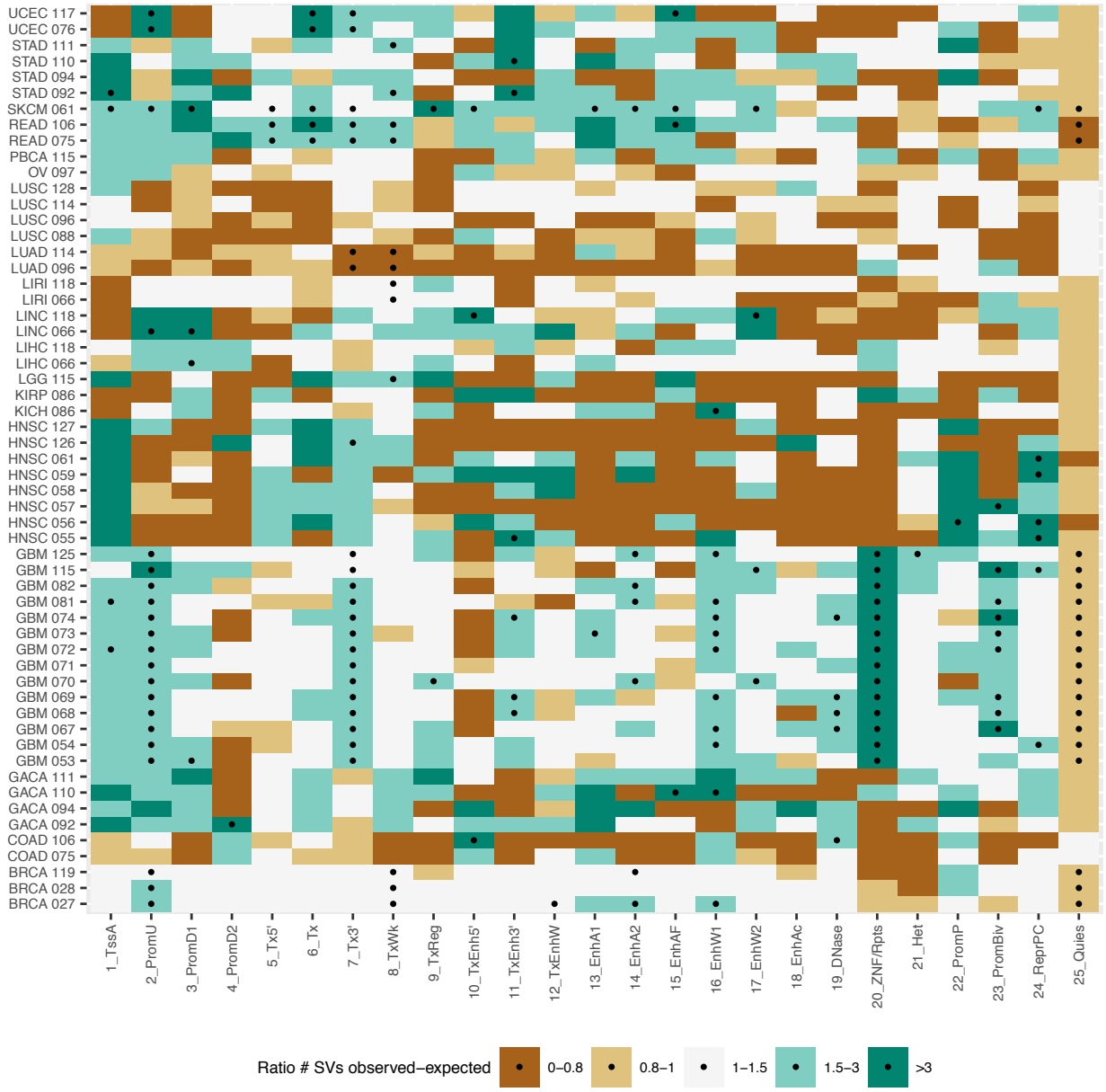
Supplementary Note Figure 22. Gene fusion landscape across 455 tumors. The top barplot shows the number of fusions detected in the tumors corresponding to the cancer type indicated in the *x*-axis. The dot plot represents the number of fusions with breakpoints mapped to regions of the categories indicated on the *y*-axis. The barplot on the right-hand side represents the total count of fusions for each type of event.

4. Analysis of the association between chromothripsis-related breakpoints and epigenetic marks

To examine the association between chromothripsis-related SVs and epigenomic features, we compared the SV density with the 25-state chromatin state maps developed by the Roadmap Epigenomics project[26]. For best estimates, the chromatin state map from the most 'similar' tissue type was used for each tumor type. Specifically, we downloaded the coordinates of the 25-state chromatin state map defined using 12 marks (H3K4me1, H3K4me2, H3K4me3, H3K9ac, H3K27ac, H4K20me1, H3K79me2, H3K36me3, H3K9me3, H3K27me3, H2A.Z and DNase) across 127 reference epigenomes from the Epigenome Roadmap project. The list of chromothripsis-related breakpoints for each cancer type was intersected with the chromatin state maps defined using cell lines from the same anatomical location as the tumor types. We used the chromatin state maps defined using the epigenomes E092, E094, E0110 and E0111 for Stomach-AdenoCA (ICGC projects STAD-US and GACA-CN), E117 and E076 for Uterus-AdenoCA (UCEC-US), E106 and E075 for ColoRect-AdenoCA (COAD-US and READ-US), E086 for Kidney-ChRCC (KICH-US and KIRP-US), E027, E028 and E119 for Breast-AdenoCA, Breast-LobularCA and Breast-DCIS (BRCA-US), E053, E054, E067, E068, E069, E070, E071, E072, E073, E074, E081, E082 and E0125 for CNS-GBM (GBM-US), E097 for Ovary-AdenoCA (OV-US), E088, E096, E114 and E128 for Lung-SCC (LUSC-US), E055, E056, E057, E059, E061, E126, E127 and E058 for Head-SCC (HNSC-US), E086 for Kidney-ChRCC (KICH-US), E115 for CNS-Medullo and CNS-PiloAstro (PBCA-DE), E115 for CNS-Oligo (LGG-US), E066 and E118 for Liver-HCC (LICA-FR, LIHC-US, LINC-JP and LIRI-JP), and E061 for Skin-

Melanoma (SKCM-US). Subsequently, the percentage of chromothripsis SVs detected in all tumors of a given cancer type overlapping each chromatin state was calculated for each matched epigenome, and compared to the fraction of the mappable genome annotated with each chromatin state. The two-tailed Fisher's exact test was used to assess the significance of the enrichment for chromothripsis-related SVs of each chromatin state in each of the cancer genomes. The significance level was set to 0.01 after Bonferroni correction of raw *P* values.

Overall, our analysis indicates that chromothripsis SVs are enriched in actively-transcribed regions, promoters and enhancers in CNS-GBM, ColoRect-AdenoCA, Skin-Melanoma, Uterus-AdenoCA and Stomach-AdenoCA (Supplementary Note Fig. 23), and quiescent chromatin is depleted for chromothripsis SVs in CNS-GBM and Breast-AdenoCA. Together, these results show the over-representation of chromothripsis SVs in functionally important, typically open-chromatin regions, consistent with previous work[27]. Larger patient cohorts will be needed to increase our power to assess whether the lack of enrichment in certain regions is significant.



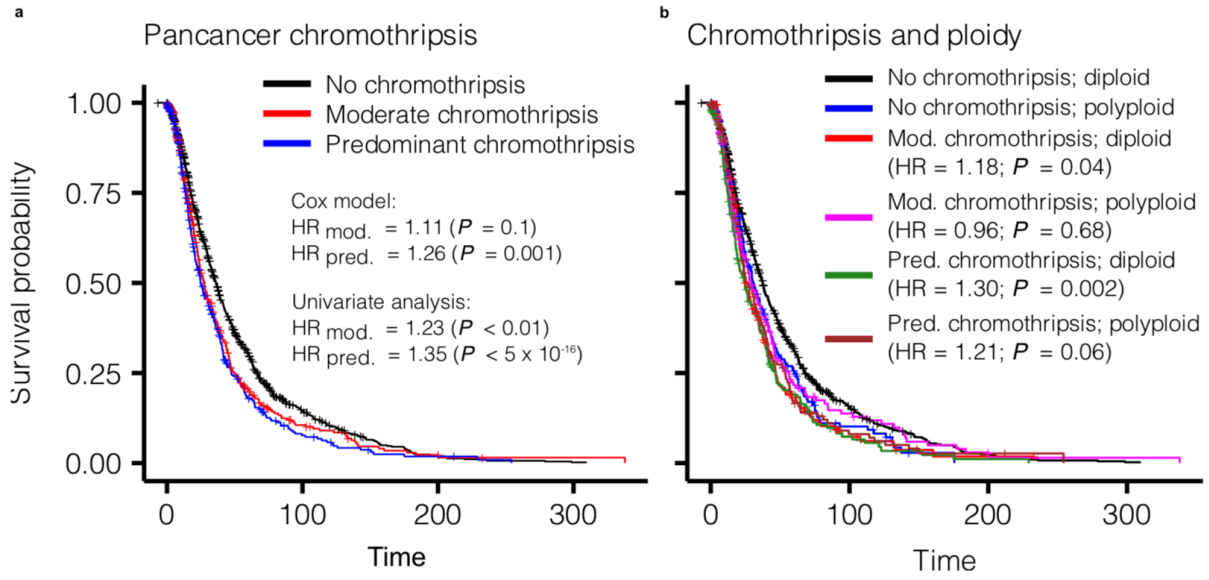
Supplementary Note Figure 23. Enrichment of chromothripsis breakpoints in chromatin states. The colors indicate the ratio between the observed percentage of SVs in each mark and the expected number. Black dots denote statistical significance.

5. Chromothripsis is prognostic of poor patient survival

Chromothripsis has been associated with poor prognosis for several cancer types[2,7,28,29]. Here, the increased sensitivity of our approach and the larger cohort permits us to evaluate the impact of chromothripsis on patient survival in greater detail, and to determine the biological contexts in which chromothripsis leads to more aggressive tumors.

We performed multivariate analysis using the Cox proportional hazards model corrected for

confounding factors known to influence survival rates, namely: age at the time of diagnosis, sex, tumor stage, radiation therapy, the presence of metastasis, and cancer type. Survival analysis was conducted using the *coxph* function from the R package survival version 2.30. Significance was assessed by the likelihood ratio and Wald tests. Tumor stages for all cancer types were manually curated and grouped into four categories. In the pan-cancer analysis, we considered only cancer types with clinical data available for at least 20 patients. The clinical data are listed in Supplementary Table 1. We did not find a significant association between chromothripsis and survival in a multivariate pan-cancer analysis when stratifying the patients into two categories with respect to the presence or absence of chromothripsis (Wald and likelihood ratio tests (LRT)<10^{-15}; hazard ratio (HR): 1.07, *P*=0.24). However, we find a significant association in a stratified analysis when the samples are ordered by the percentage of SVs involved in



Supplementary Note Figure 24. Association between chromothripsis and patient survival. Samples were stratified into three categories based on the fraction of SVs that map to chromothripsis regions: absent (black; no chromothripsis), moderate ("mod."; red; the fraction of chromothripsis-related SVs is smaller than the median within the same cancer type), and predominant ("pred."; blue; the fraction of chromothripsis-related SVs is higher than the median within the same cancer type). Kaplan-Meier plots and estimated Hazard Ratios (HR; 95% confidence intervals) for (**a**) all samples stratified on the basis of chromothripsis. Even after accounting for other variables (Cox model), the predominantly chromothripsis samples have significantly worse survival than those without chromothripsis (HR=1.26, *P*=0.001). (**b**) Chromothripsis and ploidy. For the diploid samples, the negative impact of chromothripsis is stronger, with both predominant and moderate groups reaching statistical significance (*cf*. (**a**))**.**

chromothripsis in each tumor type and classified into three equal-sized groups 'absent', 'moderate', and 'predominant' (Wald and LTR<10^{-15}; Supplementary Note Fig. 24a). The HR for the samples in the predominant and moderate chromothripsis categories are 1.26 (*P*=0.001) and 1.11 (*P*=0.12), respectively. This trend is also observed when also including the low-confidence calls in the analysis, namely 1.26 (*P*<0.001) and 1.12 (*P*=0.10), respectively.

Several factors could influence whether chromothripsis is more prevalent in diploid or polyploid

tumors. In a cancer primarily driven by tumor suppressor loss, the growth-promoting effects should be more penetrant in a diploid tumor relative to a polyploid tumor if chromothripsis happened after the genome doubling. To address the relationship between chromothripsis and polyploidy, we divided the patients into 6 categories depending on the penetrance of chromothripsis (*i.e.,* absent, moderate and predominant) and ploidy, *i.e.,* diploids *vs* polyploids (ploidy ≥ 2.5). We find that the association between chromothripsis and poor prognosis is stronger when it occurs in diploid tumors harboring either moderate ($HR_{diploids}$: 1.18, P=0.04; $HR_{polyploids}$: 0.96, P=0.68) or predominant chromothripsis ($HR_{diploids}$: 1.30, P=0.002; $HR_{polyploids}$: 1.21, P=0.06; Supplementary Note Fig. 24b).

We finally evaluated the association between chromothripsis and the infiltration of immune cell types by regressing the average gene expression of immune gene sets, as well as that of individual genes, on the chromothripsis category and other covariates known to influence the degree of tumor immune cell infiltration [30]. We find that tumors displaying predominant chromothripsis show a significant depletion of cytolytic markers (*PRF1*; $P < 0.05$), natural killer cells, cytolytic T cells (*CD8A*; $P < 0.05$), and tumor antigen presentation (MHC Class I: *B2M* and *TAP1*; $P < 0.05$). This may suggest a non-immunogenic niche for the tumors showing chromothripsis, which warrants clinical considerations and further investigation.

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PCAWG Tumour-specific providers (skin cancer) in Australia

Lauri A Aaltonen[417], Andreas Behren[418], Hazel Burke[419], Jonathan Cebon[418], Rebecca A Dagg[420], Ricardo De Paoli-Iseppi[419], Ken Dutton-Regester[295], Matthew A Field[421], Anna Fitzgerald[422], Sean M Grimmond[348], **Nicholas K Hayward#**[295,419], Peter Hersey[419], Oliver Holmes[295,296], Valerie Jakrot[419], Peter A Johansson[295], Hojabr Kakavand[419], Stephen H Kazakoff[295,296], Richard F Kefford[423], Loretta MS Lau[424], Conrad R Leonard[295,296], Georgina V Long[419], **Graham J Mann#**[393,419,419], Felicity Newell[295,296], Katia Nones[295,296], Ann-Marie Patch[295,296], John V Pearson[295,296], Hilda A Pickett[424], Antonia L Pritchard[295], Gulietta M Pupo[393], Robyn PM Saw[419], Sarah-Jane Schramm[393], **Richard A Scolyer#**[409,413,419], Mark Shackleton[178], Catherine A Shang[422], Ping Shang[419], Andrew J Spillane[419], Jonathan R Stretch[419], Varsha Tembe[393], John F Thompson[419], Ricardo E Vilain[425], Nick M Waddell[296], Nicola Waddell[295,296], James S Wilmott[419], Scott Wood[295,296], Qinying Xu[295,296] and Jean Y Yang[426]

PCAWG Tumour-specific providers (pancreatic cancer) in Canada

John Bartlett[427,428], Prashant Bavi[429], Ivan Borozan[9], Dianne E Chadwick[430], Michelle Chan-Seng-Yue[429], Sean Cleary[429,431], Ashton A Connor[431,432], Karolina Czajka[76], Robert E Denroche[429], Neesha C Dhani[433], Jenna Eagles[76], Vincent Ferretti[44,65], Steven Gallinger[429,431,432], Robert C Grant[429,432], David Hedley[433], Michael A Hollingsworth[434], **Thomas J Hudson#**[75,76], Gun Ho Jang[429], Jeremy Johns[76], Sangeetha Kalimuthu[429], Sheng-Ben Liang[430], Ilinca Lungu[429,435], Xuemei Luo[9], Faridah Mbabaali[76], **John D McPherson#**[76,429,436], Treasa A McPherson[432], Jessica K Miller[76], Malcolm J Moore[433], Faiyaz Notta[429,437], Danielle Pasternack[76], Gloria M Petersen[438], Michael H A Roehrl[125,429,430,439,440,441], Michelle Sam[76], Iris Selander[432], Stefano Serra[394], Sagedeh Shahabi[430], **Lincoln D Stein#**[9,10], Morgan L Taschuk[44], Sarah P Thayer[434], Lee E Timms[76], Gavin W Wilson[9,429], Julie M Wilson[429] and Bradly G Wouters[125]

PCAWG Tumour-specific providers (prostate cancer) in Canada

Timothy A Beck[44,442], Vinayak Bhandari[9], **Paul C Boutros#**[9,125,134,135], **Robert G Bristow#**[125,443,444,445,446], Colin C Collins[142], Shadrielle MG Espiritu[9], Neil E Fleshner[447], Natalie S Fox[9], Michael Fraser[9], Syed Haider[9], Lawrence E Heisler[44], Vincent Huang[9], Emilie Lalonde[9], Julie Livingstone[9], John D McPherson[76,429,436], Alice Meng[448], Veronica Y Sabelnykova[9], Adriana Salcedo[9], Yu-Jia Shiah[9], Theodorus Van der Kwast[441] and Takafumi N Yamaguchi[9]

PCAWG Tumour-specific providers (gastric cancer) in China

Shuai Ding[449], Daiming Fan[450], Yong Hou[38,235], Yi Huang[144,145], Lin Li[38], Siliang Li[38,235], Dongbing Liu[38,235], Xingmin Liu[38,235], **Youyong Lu#**[28,29,30], Yongzhan Nie[450,451], Hong Su[38,235], Jian Wang[38], Kui Wu[38,235], Xiao Xiao[145], Rui Xing[30], **Huanming Yang#**[38], Shanlin Yang[449], Yingyan Yu[452], Xiuqing Zhang[38], Yong Zhou[38] and Shida Zhu[38,235]

PCAWG Tumour-specific providers (renal cancer) in the EU & France

Rosamonde E Banks[453], Guillaume Bourque[454,455], Alvis Brazma[7], Paul Brennan[456], **Mark Lathrop#**[455], Louis Letourneau[457], Yasser Riazalhosseini[455], Ghislaine Scelo[456], **Jörg Tost#**[458], Naveen Vasudev[459] and Juris Viksna[460]

PCAWG Tumour-specific providers (breast cancer) in the EU & United Kingdom

Sung-Min Ahn[461], Ludmil B Alexandrov[1,70,302], Samuel Aparicio[462], Laurent Arnould[463], MR Aure[464], Shriram G Bhosle[1], Ewan Birney[7], Ake Borg[465], Sandrine Boyault[466], Arie B Brinkman[467], Jane E Brock[468], Annegien Broeks[469], Adam P Butler[1], Anne-Lise Børresen-Dale[464,470], Carlos Caldas[278,471], Peter J Campbell[1,2], Suet-Feung Chin[278,471], Helen Davies[1,309,310], Christine Desmedt[472,473], Luc Dirix[474], Serge Serge[1], Anna Ehinger[475], Jorunn E Eyfjord[476], Aquila Fatima[204], John A Foekens[477], P Andrew Futreal[478], Øystein Garred[479,480], Moritz Gerstung[7,8], Dilip D Giri[481], Dominik Glodzik[1], Dorthe Grabau[482], Holmfridur Hilmarsdottir[476], Gerrit K Hooijer[483], Jocelyne Jacquemier[484], Se Jin Jang[485], Jon G Jonasson[476], Jos Jonkers[486], Hyung-Yong Kim[484], Tari A King[487,488,489], Stian Knappskog[1,490], Gu Kong[484], Savitri Krishnamurthy[352,491], Sunil R Lakhani[492], Anita Langerød[464], Denis Larsimont[493], Hee Jin Lee[485], Jeong-Yeon Lee[494], Ming Ta Michael Lee[478], Yilong Li[1], Ole Christian Lingjærde[495], Gaetan MacGrogan[496], John WM Martens[477], Sancha Martin[1,353], Iñigo Martincorena[1], Andrew Menzies[1], Sandro Morganella[1], Ville Mustonen[305,306,307], Serena Nik-Zainal[1,309,310,311], Sarah O'Meara[1], Iris Pauporté[20], Sarah Pinder[497], Xavier Pivot[498], Elena Provenzano[499], Colin A Purdie[500], Keiran M Raine[1], Manasa Ramakrishna[1], Kamna Ramakrishnan[1], Jorge Reis-Filho[481], Andrea L Richardson[204], Markus Ringnér[501], Javier Bartolomé

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PCAWG Tumour-specific providers (malignant lymphoma) in Germany

Ole Ammerpohl[518,519], Sietse Aukema[520,521], Anke K Bergmann[522], Stephan H Bernhart[260,261,264], Hans Binder[260,261], Arndt Borkhardt[523], Christoph Borst[524], Benedikt Brors[79,112,262], Birgit Burkhardt[525], Alexander Claviez[526], Roland Eils[50,52,63,64], Maria Elisabeth Goebler[527], Andrea Haake[518], Siegfried Haas[524], Martin Hansmann[528], Jessica I Hoell[523], Steve Hoffmann[260,261,263,264], Michael Hummel[529], Daniel Hübschmann[52,63,80,81,82], Dennis Karsch[530], Wolfram Klapper[520], Kortine Kleinheinz[50,52], Michael Kneba[530], Jan O Korbel[7,8], Helene Kretzmer[261,264], Markus Kreuz[531], Dieter Kube[532], Ralf Küppers[533], Chris Lawerenz[64], Dido Lenze[529], Peter Lichter[77,386], Markus Loeffler[531], Cristina López[246,518], Luisa Mantovani-Löffler[534], Peter Möller[535], German Ott[536], Bernhard Radlwimmer[386], Julia Richter[518,520], Marius Rohde[537], Philip C Rosenstiel[538], Andreas Rosenwald[539], Markus B Schilhabel[538], Matthias Schlesner[50,102], Stefan Schreiber[540], **Reiner Siebert#**[245,246], Peter F Stadler[260,261,264], Peter Staib[541], Stephan Stilgenbauer[542], Stephanie Sungalee[8], Monika Szczepanowski[520], Umut H Toprak[52,543], Lorenz HP Trümper[532], Rabea Wagener[246,518] and Thorsten Zenz[79]

PCAWG Tumour-specific providers (paediatric brain cancer) in Germany

Ivo Buchhalter[50,51,52], Juergen Eils[63,64], Roland Eils[50,52,63,64], Volker Hovestadt[386], Barbara Hutter[77,78,79], David TW Jones[285,286], Natalie Jäger[50], Christof von Kalle[81], Marcel Kool[93,285], Jan O Korbel[7,8], Andrey Korshunov[93], Pablo Landgraf[544,545], Chris Lawerenz[64], Hans Lehrach[546], **Peter Lichter#**[77,386], Paul A Northcott[547], Stefan M Pfister[93,285,548], Bernhard Radlwimmer[386], Guido Reifenberger[545], Matthias Schlesner[50,102], Hans-Jörg Warnatz[546], Joachim Weischenfeldt[8,107,108], Stephan Wolf[549], Marie-Laure Yaspo[546] and Marc Zapatka[386]

PCAWG Tumour-specific providers (prostate cancer) in Germany

Yassen Assenov[550], Benedikt Brors[79,112,262], Juergen Eils[63,64], Roland Eils[50,52,63,64], Lars Feuerbach[112], Clarissa Gerhauser[268], Jan O Korbel[7,8], Chris Lawerenz[64], Hans Lehrach[546], Sarah Minner[551],

Christoph Plass[268], **Guido Sauter#**[552], Thorsten Schlomm[107,553], Nikos Sidiropoulos[108], Ronald Simon[552], **Holger Sültmann#**[79,554], Hans-Jörg Warnatz[546], Dieter Weichenhan[268], Joachim Weischenfeldt[8,107,108] and Marie-Laure Yaspo[546]

PCAWG Tumour-specific providers (oral cancer) in India

Nidhan K Biswas[555], Luca Landoni[396], Arindam Maitra[555], **Partha P Majumder#**[555] and **Rajiv Sarin#**[556]

PCAWG Tumour-specific providers (pancreatic cancer) in Italy

Davide Antonello[396], Stefano Barbi[403], Claudio Bassi[396], Samantha Bersani[399], Giada Bonizzato[400], Cinzia Cantù[400], Ivana Cataldo[399,400], Sara Cingarlini[36], Vincenzo Corbo[400,403], Maria Vittoria Davi[404], Angelo P Dei Tos[557], Matteo Fassan[558], Sonia Grimaldi[400], Luca Landoni[396], Rita T Lawlor[400], Claudio Luchini[399], Andrea Mafficini[400], Giuseppe Malleo[396], Giovanni Marchegiani[396], Michele Milella[36], Marco Miotto[396], Salvatore Paiella[396], Antonio Pea[396], Paolo Pederzoli[396], Borislav C Rusev[400], Andrea Ruzzenente[396], Roberto Salvia[396], Maria Scardoni[399], **Aldo Scarpa#**[400], Elisabetta Sereni[396], Michele Simbolo[403], Nicola Sperandio[400], Giampaolo Tortora[36,37] and Caterina Vicentini[400]

PCAWG Tumour-specific providers (biliary tract cancer) in Japan

Yasuhito Arai[33], Natsuko Hama[33], Nobuyoshi Hiraoka[559], Fumie Hosoda[33], Mamoru Kato[351], Hiromi Nakamura[33], Hidenori Ojima[560], Takuji Okusaka[561], **Tatsuhiro Shibata#**[33,34], Yasushi Totoki[33] and Tomoko Urushidate[34]

PCAWG Tumour-specific providers (gastric cancer) in Japan

Hiroyuki Aburatani#[256], Yasuhito Arai[33], Masashi Fukayama[562], Natsuko Hama[33], Fumie Hosoda[33], Shumpei Ishikawa[563], Hitoshi Katai[564], Mamoru Kato[351], Hiroto Katoh[563], Daisuke Komura[563], Genta Nagae[256,267], Hiromi Nakamura[33], Hirofumi Rokutan[351], Mihoko Saito-Adachi[351], **Tatsuhiro Shibata#**[33,34], Akihiro Suzuki[256,565], Hirokazu Taniguchi[34], Kenji Tatsuno[256], Yasushi Totoki[33], Tetsuo Ushiku[562], Shinichi Yachida[33,566] and Shogo Yamamoto[256]

PCAWG Tumour-specific providers (liver cancer) in Japan

Hiroyuki Aburatani[256], Hiroshi Aikata[567], Koji Arihiro[567], Shun-ichi Ariizumi[568], Keith A Boroevich[46,47], Kazuaki Chayama[567], Akihiro Fujimoto[47], Masashi Fujita[47], Mayuko Furuta[47], Kunihito Gotoh[569], Natsuko Hama[33], Takanori Hasegawa[83], Shinya Hayami[570], Shuto Hayashi[83], Satoshi Hirano[571], Seiya Imoto[83], Mamoru Kato[351], Yoshiiku Kawakami[567], Kazuhiro Maejima[47],

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PCAWG Tumour-specific providers (biliary tract cancer) in Singapore

Su Pin Choo[573], Ioana Cutcutache[251,304], Narong Khuntikeo[396,574], John R McPherson[251,304], Choon Kiat Ong[575], Chawalit Pairojkul[394], Irinel Popescu[576], **Steven G Rozen#**[251,252,304], **Patrick Tan#**[239,250,251,252] and **Bin Tean Teh#**[250,251,252,253,254]

PCAWG Tumour-specific providers (blood cancer) in South Korea

Keun Soo Ahn[577], Hyung-Lae Kim[27], Youngil Koh[291,292] and **Sung-Soo Yoon#**[292]

PCAWG Tumour-specific providers (chronic lymphocytic leukaemia) in Spain

Marta Aymerich[578], **Elias Campo#**[579,580], Josep L L Gelpi[45,67], Ivo G Gut[127,128], Marta Gut[127,128], Armando Lopez-Guillermo[581], Carlos López-Otín[582], Xose S Puente[582], Romina Royo[45] and David Torrents[45,105]

PCAWG Tumour-specific providers (bone cancer) in the United Kingdom

Fernanda Amary[583], Daniel Baumhoer[584], Sam Behjati[1], Bodil Bjerkehagen[584,585], **Peter J Campbell#**[1,2], **Adrienne M Flanagan#**[586], P Andrew Futreal[478], Ola Myklebost[490], Nischalan Pillay[587], Patrick Tarpey[588], Roberto Tirabosco[589] and Olga Zaikova[590]

PCAWG Tumour-specific providers (chronic myeloid disorders) in the United Kingdom

Jacqueline Boultwood[591], David T Bowen[1], Adam P Butler[1], **Peter J Campbell#**[1,2], Mario Cazzola[592], Carlo Gambacorti-Passerini[177], Anthony R Green[279], Eva Hellstrom-Lindberg[593], Luca Malcovati[592], Sancha Martin[1,353], Jyoti Nangalia[1], Elli Papaemmanuil[2] and Paresh Vyas[295,594]

PCAWG Tumour-specific providers (oesophageal cancer) in the

United Kingdom

Yeng Ang[595], Hugh Barr[596], Duncan Beardsmore[597], Matthew Eldridge[278], **Rebecca C Fitzgerald#**[310], James Gossage[598], Nicola Grehan[310], George B Hanna[599], Stephen J Hayes[600,601], Ted R Hupp[602], David Khoo[603], Jesper Lagergren[593,604], Laurence B Lovat[237], Shona MacRae[375], Maria O'Donovan[310], J Robert O'Neill[605], Simon L Parsons[606], Shaun R Preston[607], Sonia Puig[608], Tom Roques[609], Grant Sanders[234], Sharmila Sothi[610], Simon Tavaré[278], Olga Tucker[611], Richard Turkington[612], Timothy J Underwood[613] and Ian Welch[614]

PCAWG Tumour-specific providers (prostate cancer) in the United Kingdom

Daniel M Berney[615], Johann S De Bono[383], G Steven Bova[316], Daniel S Brewer[381,382], Adam P Butler[1], Declan Cahill[616], Niedzica Camacho[383], **Colin S Cooper#**[382,383,384], Nening M Dennis[616], Tim Dudderidge[616,617], Sandra E Edwards[383], **Rosalind A Eeles#**[383,616], Cyril Fisher[616], Christopher S Foster[618,619], Mohammed Ghori[1], Pelvender Gill[594], Vincent J Gnanapragasam[367,620], Gunes Gundem[187], Freddie C Hamdy[594], Steve Hawkins[278], Steven Hazell[616], William Howat[367], William B Isaacs[621], Katalin Karaszi[594], Jonathan D Kay[237], Vincent Khoo[616], Zsofia Kote-Jarai[383], Barbara Kremeyer[1], Pardeep Kumar[616], Adam Lambert[594], Daniel A Leongamornlert[1,383], Naomi Livni[616], Yong-Jie Lu[615,622], Hayley J Luxton[237], Andy G Lynch[278,279,294], Luke Marsden[594], Charlie E Massie[278], Lucy Matthews[383], Erik Mayer[616,623], Ultan McDermott[1], Sue Merson[383], Thomas J Mitchell[1,279,367], David E Neal[278,367], Anthony Ng[624], David Nicol[616], Christopher Ogden[616], Edward W Rowe[616], Nimish C Shah[367], Jon W Teague[1], Sarah Thomas[616], Alan Thompson[616], Peter Van Loo[60,61], Clare Verrill[594,625], Tapio Visakorpi[316], Anne Y Warren[367,626], David C Wedge[1,340,341], Hayley C Whitaker[237], Jorge Zamora[1,270,271,272], Hongwei Zhang[622] and Nicholas van As[616]

PCAWG Tumour-specific providers (TCGA) in the United States

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