The landscape of somatic copy-number alteration across human cancers

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A powerful way to discover key genes with causal roles in oncogenesis is to identify genomic regions that undergo frequent alteration in human cancers. Here we present high-resolution analyses of somatic copy-number alterations (SCNAs) from 3,131 cancer specimens, belonging largely to 26 histological types. We identify 158 regions of focal SCNA that are altered at significant frequency across several cancer types, of which 122 cannot be explained by the presence of a known cancer target gene located within these regions. Several gene families are enriched among these regions of focal SCNA, including the BCL2 family of apoptosis regulators and the NF-κB pathway. We show that cancer cells containing amplifications surrounding the MCL1 and BCL2L1 anti-apoptotic genes depend on the expression of these genes for survival. Finally, we demonstrate that a large majority of SCNAs identified in individual cancer types are present in several cancer types.

The development of cancer is driven by the acquisition of somatic genetic alterations, including single base substitutions, translocations, infections, and copy-number alterations1–3. Recent advances in genome characterization technologies have enabled increasingly systematic efforts to characterize these alterations in human cancer samples4. Identification of these genome alterations can provide important insights into the cellular defects that cause cancer and suggest potential therapeutic strategies5.

Somatic copy-number alterations (SCNAs, distinguished from germline copy-number variations, CNVs; see Supplementary Note 1a) are extremely common in cancer4–6. Genomic analyses of cancer samples, by cytogenetic studies and more recently by array-based profiling, have identified recurrent alterations associated with particular cancer types4–6. In some cases, focal SCNAs have led to the identification of cancer-causing genes and suggested specific therapeutic approaches3–5.

A critical challenge in the genome-wide analysis of SCNAs is distinguishing the alterations that drive cancer growth from the numerous, apparently random alterations that accumulate during tumorigenesis (see Supplementary Note 1b). By studying a sufficiently large collection of cancer samples, it should ultimately be possible to create a comprehensive, high-resolution catalogue of all SCNAs consistently associated with the development of all major types of cancer. Key open questions include: the extent to which significant SCNAs are associated with known cancer-related genes or indicate the presence of new cancer-related genes in particular cancer types; the extent to which large sample collections can be used to pinpoint the precise ‘targets’ of recurrent amplifications or deletions and thereby to identify cancer-related genes.
(see Supplementary Note 2); and the extent to which SCNAs are restricted to particular types or shared across many cancer types, suggesting common biological pathways.

In this paper, we explore these issues by studying copy-number profiles from 3,131 cancers across more than two dozen cancer types, with the data all derived from a single experimental platform and analysed with a common, rigorous statistical methodology.

A collection of 3,131 copy-number profiles across cancer

The 3,131 cancer copy-number profiles consisted of 2,509 profiles determined by our laboratory (see references in Supplementary Note 3), including more than 800 previously unpublished profiles, and 622 profiles determined by other groups. Most (2,965) come from 26 cancer types, each represented by more than 20 specimens. Seventeen cancer types are represented by at least 40 specimens each (Supplementary Table 1). Most profiles (2,520) were obtained from tissue specimens, with the remainder from cancer cell lines (541) and melanoma short-term cultures.

Copy-number measurements were obtained on the Affymetrix 250 K Sty array, containing probes for 238,270 single nucleotide polymorphisms (SNPs). We compared the signal intensities from each tissue specimen, with the remainder from cancer cell lines (541) and melanoma short-term cultures.

Background rates of focal and arm-level SCNAs

Across the entire genome, the most prevalent SCNAs are either very short (focal) or almost exactly the length of a chromosome arm or whole chromosome (arm-level) (Fig. 1a). The focal SCNAs occur at a...
frequency inversely related to their lengths, with a median length of 1.8 megabases (Mb) (range 0.5 kilobases (kb)–85 Mb).

Arm-level SCNAs occur approximately 30 times more frequently than would be expected by the inverse-length distribution associated with focal SCNAs (Fig. 1a). This observation is seen across all cancer types (Supplementary Fig. 2), and applies to both copy gains and losses (data not shown). As a result, in a typical cancer sample, 25% of the genome is affected by arm-level SCNAs and 10% by focal SCNAs, with 2% overlap. All arm-level (and most focal) SCNAs are of low amplitude (usually single-copy changes), but some focal SCNAs can range to very high amplitude. When analysing SCNAs for evidence of significant alteration in cancer, we accounted for the difference in background rates between arm-level and focal SCNAs by considering them separately.

Several studies have analysed patterns of arm-level SCNAs across large numbers of cancer specimens4–6, and our results are mainly in agreement with theirs. We also observed that the frequency of arm-level SCNAs decreases with the length of chromosome arms. Adjusted for this trend, most chromosome arms show strong evidence of preferential gain or loss, but rarely both, across many cancer lineages (see Fig. 1b and Supplementary Note 4).

The large size of arm-level SCNAs makes it difficult to determine the specific target gene or genes. By contrast, mapping of focal SCNAs has great power to pinpoint the important genes targeted by these events7–14.

**Pooled analysis of focal SCNAs**

We determined the regions in which SCNAs occur at a significantly high frequency. For this purpose, we calculated the genome-average ‘background’ rates for SCNAs in our data set as a function of length and amplitude, and used the GISTIC (genomic identification of significant targets in cancer) algorithm18 with improvements as described in Supplementary Methods.

We identified 158 independent regions of significant focal SCNAs, including 76 amplifications and 82 deletions, in the pooled analysis of all our data (Fig. 1c and Supplementary Table 2). This number was relatively robust to changes in the number of samples (Supplementary Fig. 3a) and removal of individual cancer types from the pooled analysis (Supplementary Fig. 3b). Indeed, a stratified analysis of 680 samples distributed evenly across the 17 most highly represented cancer types identified 76% of these significant SCNAs, similar to the number expected based on the reduced power of this smaller sample set (Supplementary Fig. 3a).

The most frequent of these significant focal SCNAs (MYC amplifications and CDKN2A/B deletions) involve 14% of samples, whereas the least frequent are observed in 2.3% of samples for amplifications and 1.5% for deletions. The frequency of significant arm-level SCNAs is higher (15–29% of samples; Supplementary Fig. 3c). These frequencies are likely to be underestimates, as some SCNAs are not detected owing to contamination of cancer samples with DNA from adjacent normal cells, technical error, and the incomplete spatial resolution afforded by the SNP array platform.

For each of the 158 significant focal SCNAs, we determined a confidence interval (‘peak region’) that has a 95% likelihood of containing the targeted gene (Supplementary Fig. 3d). Our large data set enables more sensitive and high-resolution detection of peak regions than previous copy-number analyses (see Supplementary Note 5 and Supplementary Table 3). An even larger data set would be desirable, on the basis of analyses showing that the increase in resolution with sample size has not reached a plateau (Supplementary Fig. 3e).

The 76 focal amplification peak regions contain a median of 6.5 genes each (range 0–143, including microRNAs). Sixteen regions contain more than 25 genes each; the remaining 60 regions contain in aggregate 364 potential target genes. We found that 25 of the 76 regions (33%) contain functionally validated oncogenes documented to be activated by amplification (Supplementary Table 2), including nine of the top ten regions (MYC, CCND1, ERBB2, CDK4, NKX2-1, MDM2, EGFR, FGFR1 and KRAS; Fig. 1c and Supplementary Table 2).

The 82 focal deletion peaks contain a median of seven genes each (range 1–173). Nineteen regions contain at least 25 genes each; the remaining 63 regions contain in aggregate 474 potential target genes. Nine of the 82 regions (11%) contain functionally validated tumour suppressor genes documented to be inactivated by deletion (Supplementary Table 2). Two other deletions (involving ETV6 and the span from TMPRSS2 to ERG) are associated with translocation events that create oncogenes. Another deletion adjacent to the T-cell-receptor-β locus occurs in acute lymphoblastic leukaemia and likely is not associated with cancer, as it occurs during normal T-cell development.

The remaining 70 deletion peaks do not contain known tumour suppressor genes, translocation sites, or somatic rearrangements. More than one-third (26) contain large genes, the genomic loci of which span more than 750 kilobases (kb); none of these genes has been convincingly demonstrated to be a tumour suppressor gene. Conversely, 19 of the 40 largest genes in the genome occur in deletion peaks (Fig. 2a; \( P = 3 \times 10^{-5} \)). This association between deletions and large genes could be due to a propensity for both to occur in regions of low gene density. Indeed, large genes tend to occur in gene-poor regions (Fig. 2a, bottom), and an analysis of all SCNAs in the data set shows that deletions (but not amplifications) show a bias towards regions of low gene density (up to 30% below the genome average; Fig. 2b). Even after removing the 26 SCNAs containing large genes, the gene density among the remaining deletions is still 25% below the genome average. These observations suggest that some of the deletions may not be related to cancer aetiology, but rather may reflect a high frequency of deletion or low levels of selection against deletion in these regions.
Most known amplified oncogenes reside within the 76 amplified regions, although there are exceptions. For example, MITF is probably undetected because it is a lineage-specific oncogene restricted to melanoma. At least ten known deleted tumour suppressor genes do not reside in the deleted regions in the pooled analysis (BRCA2, FBXW7, NF2, PTC11, SMARCBI, STK11, SUFU, VHL, WT1 and WTX (also known as FAM123B)). Some of these are specific to cancer types not represented in our data set (for example, NF2, WT1 and WTX), whereas others (for example, BRCA2, FBXW7, STK11 and VHL) primarily suffer arm-level deletions (with possible further deletions beyond the resolution of the array platform). Other tumour suppressor genes may be missed if they lie within regions in which the background deletion rates are lower than the genome-wide average, or if they are adjacent to genes in which deletion is poorly tolerated (which would be expected to occur more readily in regions of high gene density; see Supplementary Note 1b). Such tumour suppressors might be inactivated by point mutations more often than SCNAS.

**Over-represented gene families and pathways**

We assessed potential cancer-causing genes in the SCNAS using GRAIL (gene relationships among implicated loci), an algorithm that searches for functional relationships among genomic regions. GRAIL scores each gene in a collection of genomic regions for its ‘relatedness’ to genes in other regions based on textual similarity published abstracts for all papers citing the genes, on the ‘relatedness’ to genes in other regions based on textual similarity that searches for functional relationships among genomic regions. Other tumour suppressor genes may be missed if they lie within regions in which the background deletion rates are lower than the genome-wide average, or if they are adjacent to genes in which deletion is poorly tolerated (which would be expected to occur more readily in regions of high gene density; see Supplementary Note 1b). Such tumour suppressors might be inactivated by point mutations more often than SCNAS.

**Figure 3** | Dependency of cancer cell lines on the amplified BCL2 family members, MCL1 and BCL2L1. **a**. Enrichment of pro- and anti-apoptotic BCL2 family members deletion and amplification peaks. **b**, Copy-number profiles among 50 cancer samples around MCL1 (lineages are across the top; genomics locations are on the left). **c**, Changes in cell number after MCL1 knockdown relative to controls. **d**, Proliferation rates in NCI-H2110 cells after siRNA transfection against the listed genes. **e**, Effect of MCL1 knockdown on growth of NCI-H2110 xenografts. **f**, Changes in cell number after BCL2L1 knockdown relative to controls. Error bars represent s.e.m. across three experiments.
of this pathway (TRAF6, IKKBK, IKBKG, IRAK1 and RIPK1; \(P = 0.001\) for pathway enrichment\(^{27}\)) and consistent with an emerging recognition of its importance in several cancer types\(^{26–30}\).

Because some gene families may have been missed by GRAIL, we separately analysed gene ontology (GO) terms for association with amplification peaks (data not shown). We identified significant enrichment of genes associated with ‘molecular adaptor activity’ (GO: 0060090, \(P = 4 \times 10^{-10}\)), including IRS2, GRB2, GRB7, GAB2, GRAP, TRAF2, TRAF6 and CRKL. IRS2 and GAB2 are known to be transforming when overexpressed\(^{31,32}\), and CRKL has been reported as an essential gene among cells in which it is amplified\(^{33}\).

**Amplifications of MCL1 and BCL2L1**

MCL1 is one of nine genes in an amplification peak in cytoband 1q21.2 (Fig. 3b and Supplementary Table 2) with focal amplifications observed in 10.9% of cancers across multiple tissue types. Fluorescence in situ hybridization (FISH) of the MCL1 region in lung and breast cancers showed much higher rates of focal amplification (Supplementary Fig. 4a–b). Amplifications of 1q21.2 were previously reported in two studies of lung adenocarcinoma\(^{34,35}\), and one of melanoma\(^{36}\), but the peak regions in these studies contained 86, 36 and 53 genes respectively.

We examined whether cell growth depends on MCL1 in the presence of gene amplification by measuring the rate of change in cell number after activating an inducible short hairpin RNA (shRNA) against MCL1 in cells with and without 1q21.2 amplification. We observed a more pronounced reduction in proliferation rates among four MCL1-amplified cell lines, compared to three MCL1-unamplified control cell lines (\(P = 0.05\); Fig. 3c) (all achieved >70% knockdown; Supplementary Fig. 4c). Reducing the expression of six of the other genes (all by >70%; Supplementary Fig. 4d) within the 1q21.2 amplicon in NCI-H2110 cells produced no significant effects (Fig. 3d). Similar effects were observed after MCL1 depletion with many shRNAs and short interfering RNAs (siRNAs) (Supplementary Fig. 4e). Growth of NCI-H2110 xenografts were also inhibited by induction of anti-MCL1 shRNA (Fig. 3e).

BCL2L1 is one of five genes in a peak region of amplification on 20q11.21 (Supplementary Fig. 5a). Amplifications of this region have been previously noted in lung cancer\(^{37}\), giant-cell tumour of bone\(^{38}\), and embryonic stem cell lines (the latter also amplifying a region including BCL2)\(^{39,40}\), but functional validation of BCL2L1 as a gene targeted by these amplifications has not been reported. We examined BCL2L1 dependency using shRNA against BCL2L1 in cells with and without 20q11.21 amplification. We observed a more pronounced reduction in proliferation rates among six BCL2L1-amplified lines (including SKL1, which was MCL1-independent), compared to seven BCL2L1-unamplified lines (\(P = 0.006\); Fig. 3f). These decreased proliferative rates were associated with increased apoptosis (Supplementary Fig. 5b).

We then sought to explore how amplification of these BCL2 family members might act in cancer by examining other SCNAs found in cancers carrying MCL1 or BCL2L1 amplifications. The most frequent other focal SCNA in these cancers was amplification of the region carrying MYC (observed in approximately two-thirds of these cases). BCL2 has previously been shown to reduce MYC-induced apoptosis in lymphoid cells\(^{41}\). We found that overexpression of MCL1 and BCL2L1 in immortalized bronchial epithelial cells also reduces MYC-induced apoptosis (Supplementary Fig. 5c, d). Oncogenic roles for MCL1 and BCL2L1 have been previously suggested by reports of increased rates of lymphoma and leukemia in transgenic mice\(^{41,42}\). Somatic amplification of MCL1 and BCL2L1 may therefore be a common mechanism for cancers, including carcinomas, to increase cell survival.

**Sharing of focal SCNAs across cancer types**

Our analysis of a large number of cancer types with a high-resolution platform afforded an opportunity to quantify the degree to which significant focal SCNAs are shared across cancer types. We performed separate analyses of each of the 17 cancer types represented by at least 40 samples and compared the significant SCNAs to those from a pooled analysis of the remaining samples, excluding the cancer type in question.

Most focal SCNAs identified in any one of these 17 cancer types are also found in the pooled analysis excluding that cancer type (median 79% overlap, versus 10% for randomly permuted regions, \(P < 0.001\); Fig. 4) and, indeed, in the 158 regions from the overall pool. Nonetheless, cancer-type-restricted analyses identified a further 199 significant SCNAs (145 regions of amplification, 54 regions of deletion; Supplementary Table 5). (These exclude 79 regions of amplification on chromosome 12 found only in dedifferentiated liposarcomas that are probably related to the ring chromosomes in that disease\(^{43}\).) However, many of these regions were even found to occur in more than one cancer type (median two). As would be expected, the 158 regions in the pooled analysis were found in more cancer types (median five) and were better localized (median size 1.5 Mb versus 11 Mb in the lineage-restricted analyses).

Arm-level alterations, like focal SCNAs, tend to be shared among several cancer types (Supplementary Note 4). Previous studies have demonstrated a tendency for cancers of similar developmental lineages to exhibit similar recurrent arm-level SCNAs\(^{44}\). We found that this tendency was much more apparent for arm-level than focal SCNAs (see Supplementary Note 6), suggesting that arm-level SCNAs are shaped to a greater extent by developmental context.

**Portal for cancer genomics**

The raw data and analyses from this study are available at http://www.broadinstitute.org/tumorscape, including segmented copy-number data (viewable using the Integrative Genomics Viewer; J. Robinson et al., manuscript in preparation) and profiles describing the significance of copy-number changes. The portal also supports gene copy-number queries across and within individual cancer types (instructions are in Supplementary Note 7).

**Figure 4 | Most significant focal SCNA peaks identified in any one cancer type are also identified in the rest of the data set (its complement).** The top Venn diagram represents median results across the 17 cancer types represented by >40 samples. Venn diagrams representing the specific examples of non-small cell lung cancer, oesophageal adenocarcinoma, and acute lymphoblastic leukaemia are shown along the bottom. The three dots indicate similar analyses were performed on the remaining 14 cancer types. Diagrams are not drawn to scale.
Discussion

This study represents the largest analysis so far of high-resolution copy-number profiles of cancer specimens. Several features of the copy-number landscape apply to the vast majority of cancer types. There is a notably high prevalence of arm-level SCNAs4–6, which probably reflects the ease with which such mutational events occur compared to focal events7,8. The analysis also shows a strong tendency for significant focal SCNAs in one cancer type to be also found in several others.

We identified a total of 357 significant regions of focal SCNA, including 158 regions in the pooled analysis and 199 regions in analyses of individual cancer types. These are surely underestimates of the number of regions that are significantly altered in cancer. Many cancer types were represented by relatively few samples; others were not represented at all. Some SCNAs were missed owing to the resolution limit of the array platform. Further efforts will be needed to characterize larger numbers of cancer genomes at higher resolution to create a comprehensive catalogue of the significant SCNAs and define their occurrence in difference cancer types.

An important challenge is to identify the cancer gene targets of each of these SCNAs. Less than one-quarter of the 158 common peak regions are associated with previously validated targets of SCNAs in human cancer. Although a subset of the SCNA may represent deletion events that are tolerated but not causally involved in cancer (as suggested by the correlation with gene-poor regions) or frequent owing to mechanistic bias (for example, associated with fragile sites)9,10, many more cancer-causing genes are likely to be found through analysis of SCNA. The GRAIL analysis of our peak regions points to more than a dozen probable candidates, and the functional analysis of MCI and BCL2L1 strongly implicates these genes as amplification targets. Moreover, some SCNAs may contain several functional targets11.

Identification of the target genes will require both genomic and functional studies. For focal events, the copy-number profiles of further samples at higher resolution can help narrow the lists of candidates. Nucleotide sequencing may identify point mutations, and further samples at higher resolution can help narrow the lists of functional studies. For focal events, the copy-number profiles of cancer specimens. Several features of the copy-number landscape apply to the vast majority of cancer types. There is a notably high prevalence of arm-level SCNAs4–6, which probably reflects the ease with which such mutational events occur compared to focal events7,8. The analysis also shows a strong tendency for significant focal SCNAs in one cancer type to be also found in several others.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Information The SNP array data have been deposited to the Gene Expression Omnibus (GEO) under accession number GSE19399. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to E.S.L. (lander@broadinstitute.org), G.G. (gadgetz@broadinstitute.org), W.R.S. (william.sellers@novartis.com) or M.M. (matthew.meyerson@dfci.harvard.edu).