Supplementary Methods S5: Copy Number Analysis

Segmented copy number profiles for ovarian carcinoma and matched control DNAs (489 Agilent 1M arrays for tumor and for normal, or 978 total – see Table 1) were analyzed using *Ziggurat Deconstruction*, an algorithm that parsimoniously assigns a length and amplitude to the set of inferred copy number changes underlying each segmented copy number profile (for details, see Beroukhim *et al.*[1] and Mermel et al, submitted). As has been previously reported for multiple cancer types[1], across all samples the copy number events can be clearly divided into at least two classes on the basis of their observed frequency: focal copy number events much smaller than a chromosome arm, and broad copy number events that span a chromosome arm or entire chromosome (see **Figure S3.1**). As broad and focal copy number changes appear to have markedly different rates of occurrence, and may have distinct biological consequences, we analyzed them separately. A length threshold of 50% of a chromosome arm was used to distinguish between broad and focal events (see **Figures S3.2** and **S3.3**). To remove false positive segments resulting from hyper-segmentation, we further filtered segments using an amplitude threshold at a copy-difference of 0.1 (data not shown).

For broad copy number changes, the frequency with which chromosomal arms are measured to undergo gain or loss is negatively correlated with the size of that arm (**Figure S3.4**). To determine which arms were significantly enriched/depleted among copy gains and losses after accounting for this trend, we compared the expected frequency of gain and loss for each arm, determined by linear regression, with the actual frequency observed over the entire dataset. Since samples with gain of a chromosome arm cannot have loss of the same arm, we computed the frequency of gains and loss among the undeleted and unamplified samples, respectively. By decoupling the gains and losses in this way, the frequency metric follows a binomial distribution; z-scores for each arm were calculated using the normal approximation to the binomial (**Table S5.1**), and the resulting one-sided p-values were corrected for multiple hypotheses testing using the Benjamini-Hochberg FDR method. The frequency of samples that have segments whose length is at least 50% of a chromosome arm, displaying gains (relative copy number >2.1) and losses (relative copy number <1.1) is shown for each chromosome arm (**Table S5.1**).

Focal copy number changes in the 489 ovarian carcinoma DNA samples were analyzed using the GISTIC methodology[2] with modifications as described in further detail in (Mermel et al, submitted). Briefly, each marker was scored according to the mean amplitude and frequency of focal amplification across the dataset, and significance values were computed by comparing to the distribution of scores obtained by random permutation of the markers across the genome. Significant peak regions of amplification (or deletion) are identified using an iterative peel-off procedure that distributes the score associated with amplified (or deleted) segments among all peaks that overlap them (weighted according to each peak's score) until no new region crosses the significance threshold of q-value ≤0 .25 on each chromosome. Finally, by taking into account the auto-correlation within the GISTIC score profiles, we compute for each peak region a confidence interval that is predicted to contain the true driver gene or genes with at least 99% probability (see Supplementary methods of Beroukhim et al. [1], Mermel et al, submitted). The output of focal GISTIC, defining the key peaks of amplification and deletion in the 489 ovarian carcinoma DNA samples, appears in **Table S5.2**.

Regions are defined as possessing deep deletions, shallow deletions, neutral copy number, low gain, and high gain in each sample using sample-specific thresholds as previously described[3]. In brief, high gains are segments with copy number that exceed the maximum median chromosomal arm copy number for that sample by at least 0.1; low gains are segments with copy numbers from 2.1 to the high gain threshold; neutral segments have copy numbers between 1.9 and 2.1; shallow losses have copy numbers between 1.9 and the deep deletion threshold; and deep deletions have copy numbers that are below the minimum median chromosomal arm copy number for that sample by at least 0.1. Frequencies of all these events are tallied across the 489 ovarian carcinoma samples (**Table S5.2**).

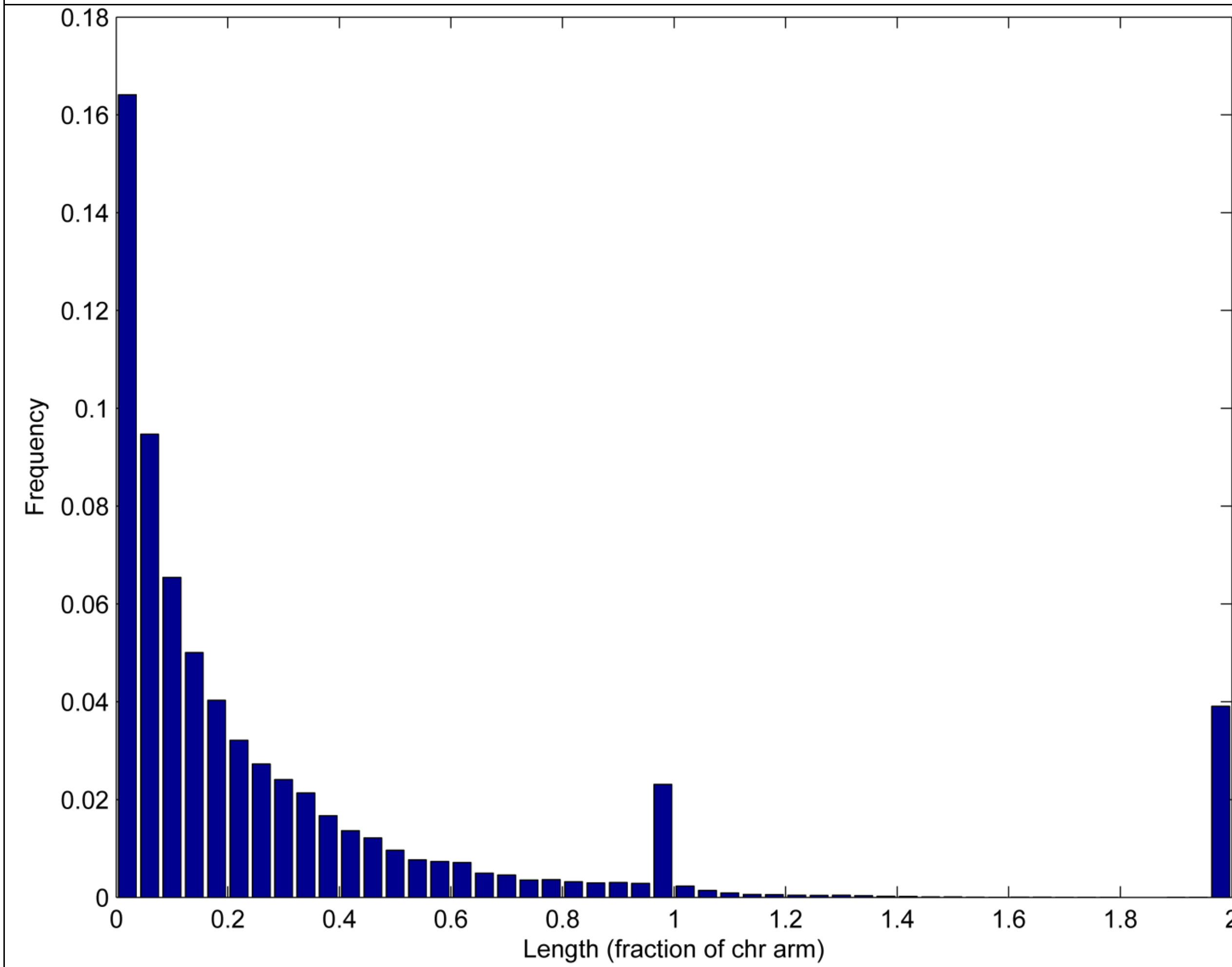
A subset of genes located in the 63 recurrent focal amplification regions were selected based on an Ingenuity database search and visual scanning genes of interest. We searched the subset of genes against information obtained from DrugBank (http://www.drugbank.ca)[4,5], including drug and associated target information on 1589 genes and 2010 drug entries. Since we are searching for inhibitors target the frequently amplified and actively expressed genes, we retained only inhibitors from the resulting list. The list was further manually curated using http://clinicaltrials.gov and the literature. The final list of 22 genes and their corresponding therapeutic compounds is in **Table S5.3**.

References

1. Beroukhim, R. et al. The landscape of somatic copy-number alteration across human cancers. *Nature* **463**, 899-905.
2. Beroukhim, R. et al. Assessing the significance of chromosomal aberrations in cancer: methodology and application to glioma. *Proc Natl Acad Sci U S A* **104**, 20007-12 (2007).
3. TCGA Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* **455**, 1061-8 (2008).
4. Wishart, D.S., et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2008 Jan;36(Database issue):D901-6.
5. Wishart, D.S., et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 Jan 1;34(Database issue):D668-72.

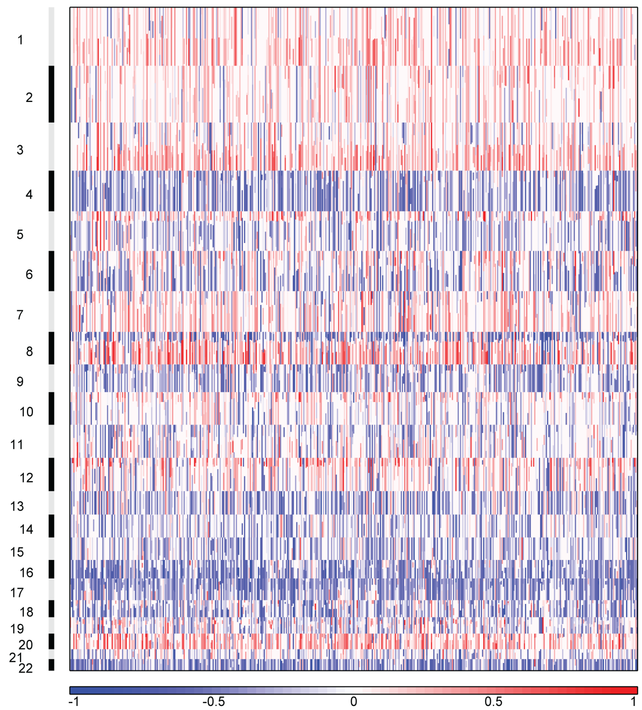
Supplementary Figures

Figure S5.1 Histogram distribution of copy number change frequency scaled by chromosome arm length. Note peaks at 1 and 2 indicating arm or chromosome gains.



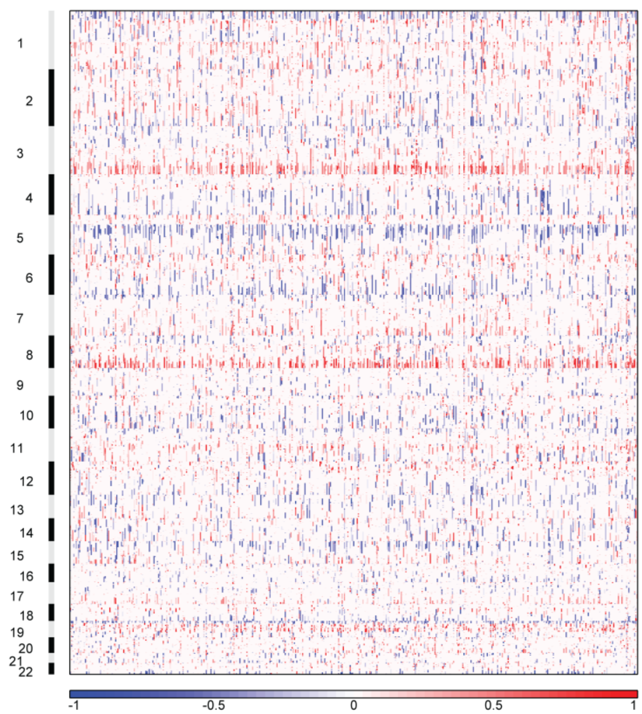
Supplementary Figure S5.1

Figure S5.2. Arm events found in ovarian serous carcinoma.



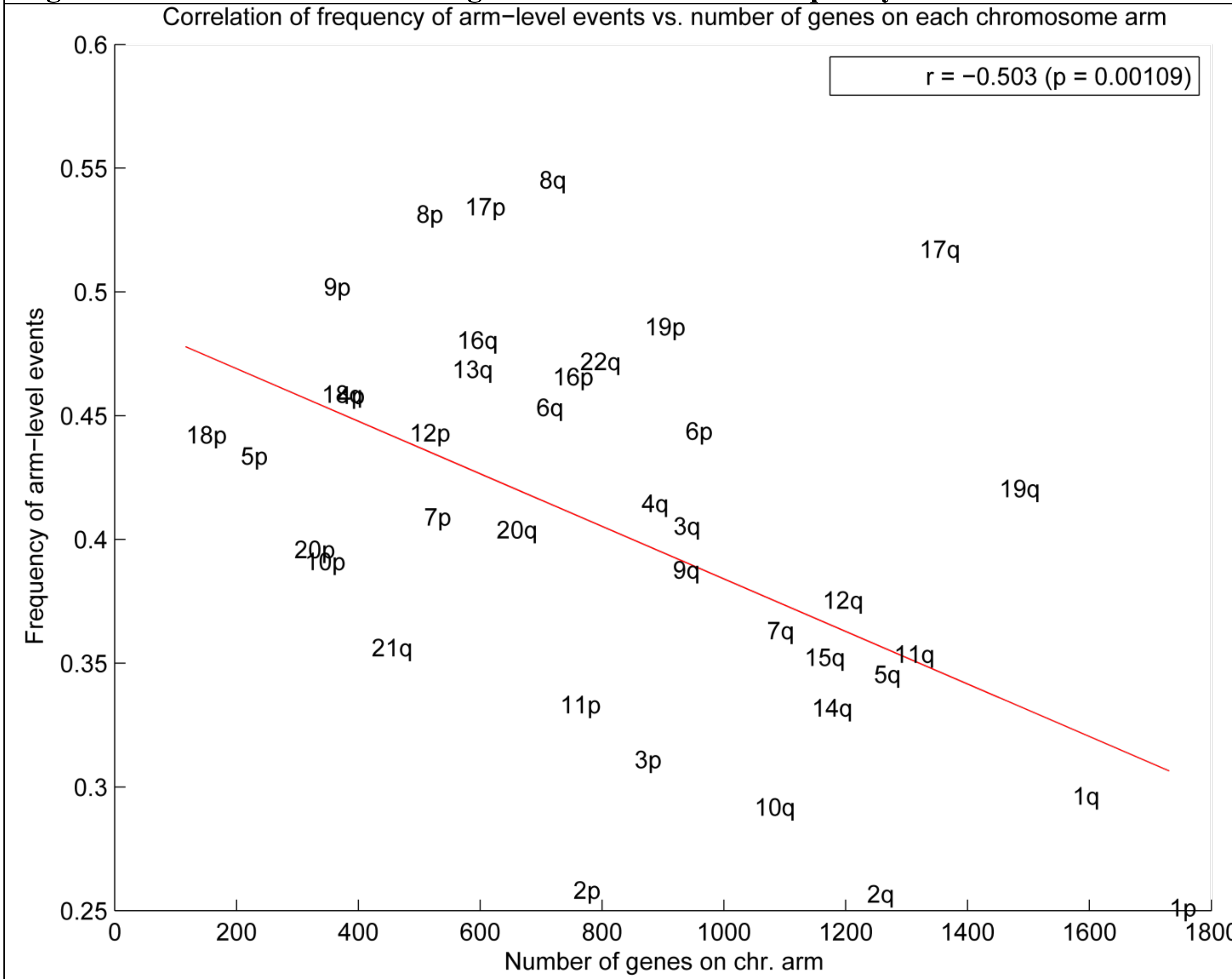
Supplementary Figure S5.2

Figure S5.3. Focal copy number changes plotted alone.



Supplementary Figure S5.3

Figure S5.4. Correlation between gene number and loss frequency.



Supplementary Figure S5.4