Oncoscan: Work package 1

ABSTRACT

Abundance of somatic copy number alterations (SCNA) in human cancer varies according to their size[1–3].

Objectives

Literature review of the definition of "arm-level" and current practices.

1. Percentage of arm to be considered as "arm-level"?
2. Contiguity required?
3. Use of smoothing function?

Literature Review

0.1 Arm-level Alteration

Some of the previous studies have used amplitude base criteria (in copy number space) to distinguish between focal SCNAs and arm-level SCNAs (Figure 1a)[4,5]. However, another study by Beroukhim R et al., shows that SCNA frequency across diverse cancers is inversely proportional to SCNA lengths[2]. This trend was reproduced on a dataset of 178 glioblastoma multiforme (GBM) samples in a TCGA study by Mermel et al.,[1] (Figure 1b).

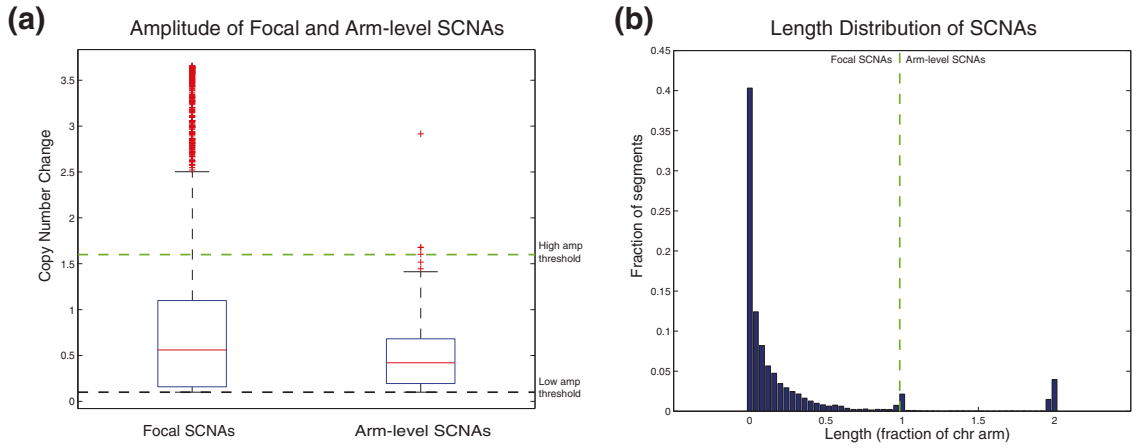

Figure 1. Separation of arm-level and focal SCNA[1]

GISTIC (Genomic Identification of Significant Targets in Cancer) approach developed by Beroukhim R et al., separates SCNAs into arm-level and focal SCNA based on their lengths (focal SCNA: length < 98% of chromosome arm and arm-level SCNA: length >98% of chromosome arm)[1,6]. The above study shows that compared to the amplitude based filtering the length based filtering of SCNA improves the

sensitivity of GESTIC to identify relevant regions of focal SCNA[6]. Anothe study by Roy et al. present a landscape of arm-level SCNA across 33 cancer types and assess its prognostic impact[7]. In this study arm-level SCNAs were defined as a region of amplification or deletion (GISTIC2.0 beta value greater than 0.1 or less than 0.1, respectively) and occupying 70% of the chromosomal arm. This study uses chromosome 9p loss in lower grade glioma (LGG) as a model to understand survival outcomes in LGG. Here, only the deletions more than 5Mb were considered as broad enough and 9p commonly deleted region was defined as the chromosomal start/end site that contained 90% or more of all broad deletions on 9p[7].

References

1. Mermel, C. H. *et al.* GISTIC2.0 facilitates sensitive and confident localization of the targets of focal somatic copy-number alteration in human cancers. *Genome biology* **12**, R41, DOI: 10.1186/gb-2011-12-4-r41 (2011).

2. Beroukhim, R. *et al.* The landscape of somatic copy-number alteration across human cancers. *Nature* **463**, 899–905, DOI: 10.1038/nature08822 (2010).

3. Leach, N. T., Rehder, C., Jensen, K., Holt, S. & Jackson-Cook, C. Human chromosomes with shorter telomeres and large heterochromatin regions have a higher frequency of acquired somatic cell aneuploidy. *Mech. ageing development* **125**, 563–73, DOI: 10.1016/j.mad.2004.06.006 (2004).

4. McLendon, R. *et al.* Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* **455**, 1061–1068, DOI: 10.1038/nature07385 (2008).

5. Pleasance, E. D. *et al.* A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* **463**, 191–196, DOI: 10.1038/nature08658 (2010).

6. Beroukhim, R. *et al.* Assessing the significance of chromosomal aberrations in cancer: Methodology and application to glioma. *Proc. Natl. Acad. Sci.* **104**, 20007–20012, DOI: 10.1073/pnas.0710052104 (2007).

7. Roy, D. M. *et al.* Integrated Genomics for Pinpointing Survival Loci within Arm-Level Somatic Copy Number Alterations. *Cancer Cell* **29**, 737–750, DOI: 10.1016/j.ccell.2016.03.025 (2016).