Cytogenetic Analysis of Lymphoid Malignancies Using Mercator and CytoGPS

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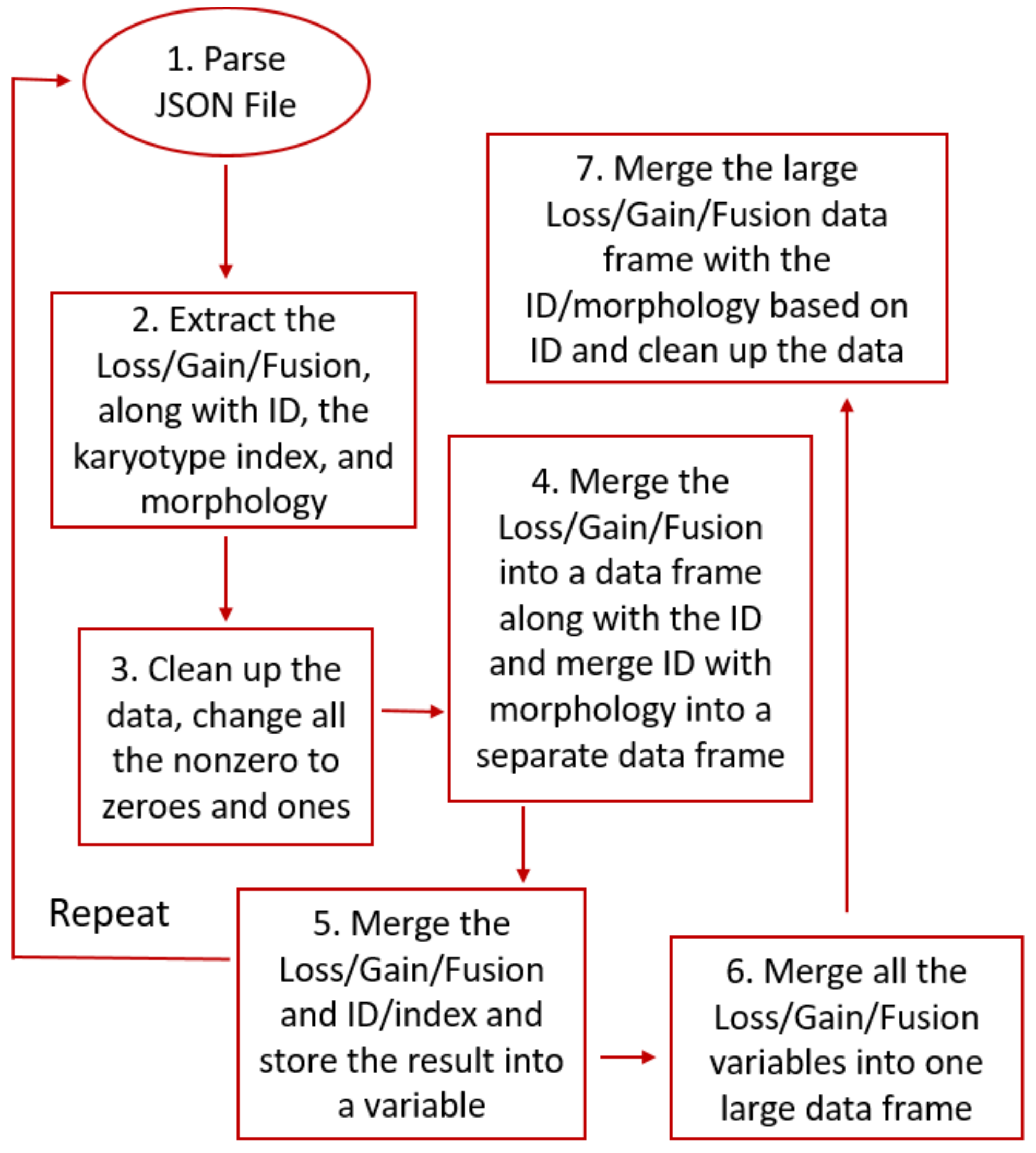
Background

Lymphoid malignancies are commonly classified clinically by location and morphology. However, we hypothesize that useful classifications can be obtained using cytogenetic abnormalities alone. The public Mitelman Database of Chromosomal Aberrations and Gene Fusions in Cancer has curated karyotypes from the literature since 1970. It is the largest database of published cases of cancer karyotypes in general and of lymphoid malignancy karyotypes in particular. We previously developed CytoGPS, a tool that converts text karyotypes into binary vectors using a Loss-Gain-Fusion model. To test our hypothesis, we applied CytoGPS to the lymphoid malignancies in the Mitelman Database. Here, we present an unsupervised analysis using the R-packages Thresher and Mercator.

Methods


1. Parse JSON File

2. Extract the Loss/Gain/Fusion, along with ID, the karyotype index, and morphology

3. Clean up the data, change all the nonzero to zeroes and ones

4. Merge the Loss/Gain/Fusion into a data frame along with the ID and merge ID with morphology into a separate data frame

5. Merge the Loss/Gain/Fusion and ID/index and store the result into a variable

Repeat

6. Merge all the Loss/Gain/Fusion variables into one large data frame

7. Merge the large Loss/Gain/Fusion data frame with the ID/morphology based on ID and clean up the data

Figure 1**:** Workflow for analyzing the Mitelman database obtained from the Cancer Genome Anatomy Project web site. The first step was to extract the data from Mitelman for all 69,174 patients. Then we ran CytoGPS to convert the data to the Loss/Gain/Fusion (LGF) model, stored in 14 JSON files. A total of 22,741 samples were associated with lymphoid malignancies. Afterwards, using Thresher and Mercator, we found that there were 134 clusters; we assigned samples to clusters using Partitioning Around Medoids (PAM). We visualized the results using t-distributed Stochastic Neighbor Embedding (t-SNE). We calculated high-frequency events and displayed them in a heatmap.

Results: t-SNE Plot and Cluster Identities

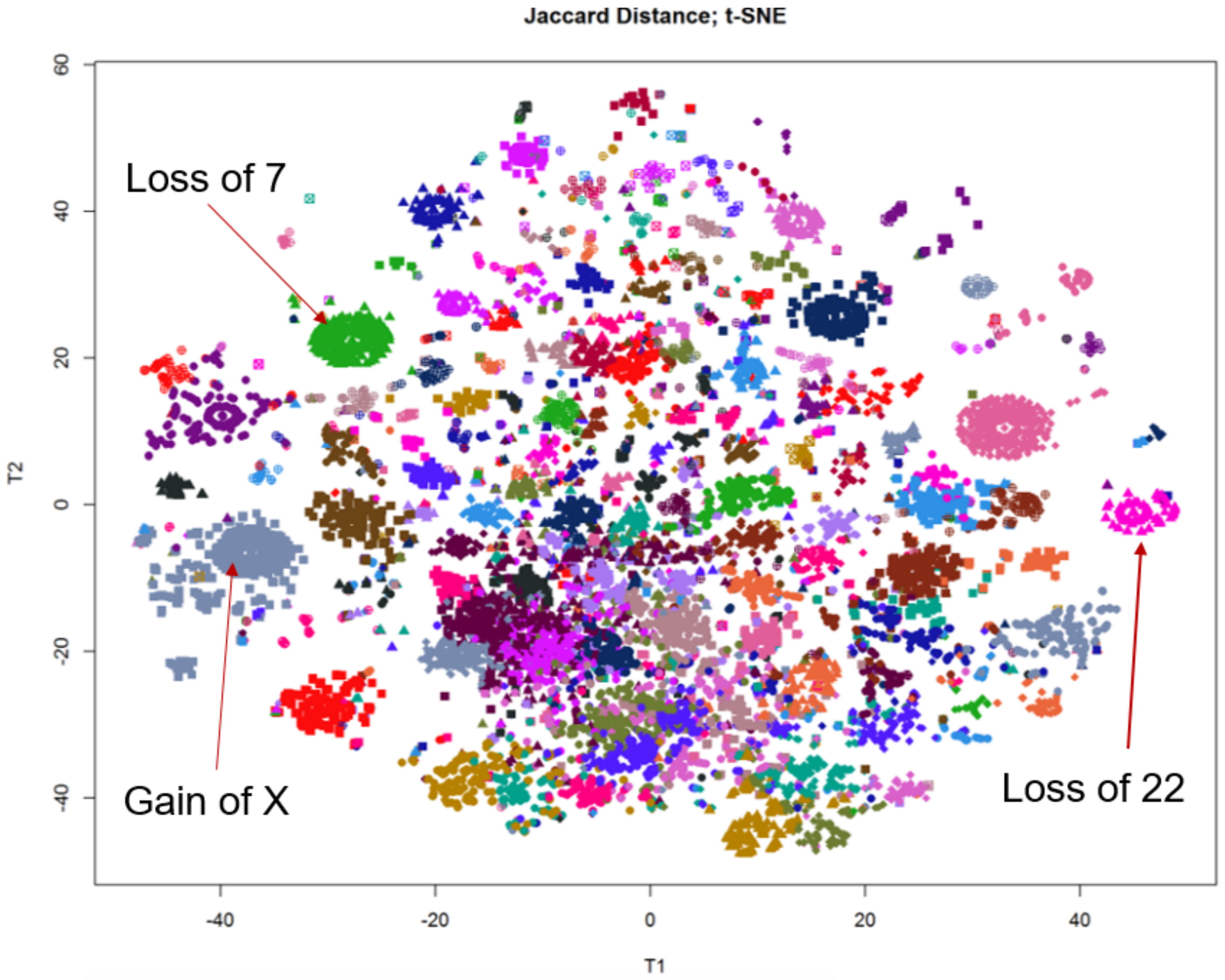


Figure 2**:** t-SNE map of the 134 clusters and related cytogenetic events. The clusters are distinguishable based on the clusters they form and the cytogenetic event. There are numerous clusters that form a sort of gradient that could also separate each cluster. As pointed out in the figure we defined several clusters as a gain or loss of the chromosome including sex chromosome.

Cluster	Symbol	Karyotype	Frequency
ST132	⊠	+Y	100
ST131	⊠	+22	100
ST114	⊕	+20	100
ST101	⊕	t(19q)	100
ST055	▲	+10,+4,+21,+6,+X,+18,-14,+17	100,100,96,87,86,79,74,63
ST053	▲	t(12p;21q)	100
ST047	■	t(8q;14q)	100
ST087	◆	+4,+21,+6,+X,-14	99,92,80,80,63
ST035	■	add(7q),+8,t(7p;18q)	99,96,84
ST060	▲	-Y	99
ST046	■	+8	99
ST081	◆	+X,+21	99,98
ST016	●	+X	99
ST075	◆	+X,-14,+21	99,98,75
ST097	⊕	+16	99
ST095	◆	+15	99
ST041	■	add(7q),t(7p;18q)	99,88
ST008	●	+21	99

Table 1**:** This table displays the top 18 clusters based on frequency of karyotypic event. The frequency represents the percent of cases classified to a cluster that contain the reported karyotype. The findings revealed 49 clusters that include at least 90% of the samples to have the same abnormalities, 70 clusters have a cytogenetic event with at least 80% similarity, and 84 clusters that have 70% similarity. This demonstrate that Mercator generates high fidelity clusters based on cytogenetic patterns.

Results: Heatmap – Abnormalities vs Clusters

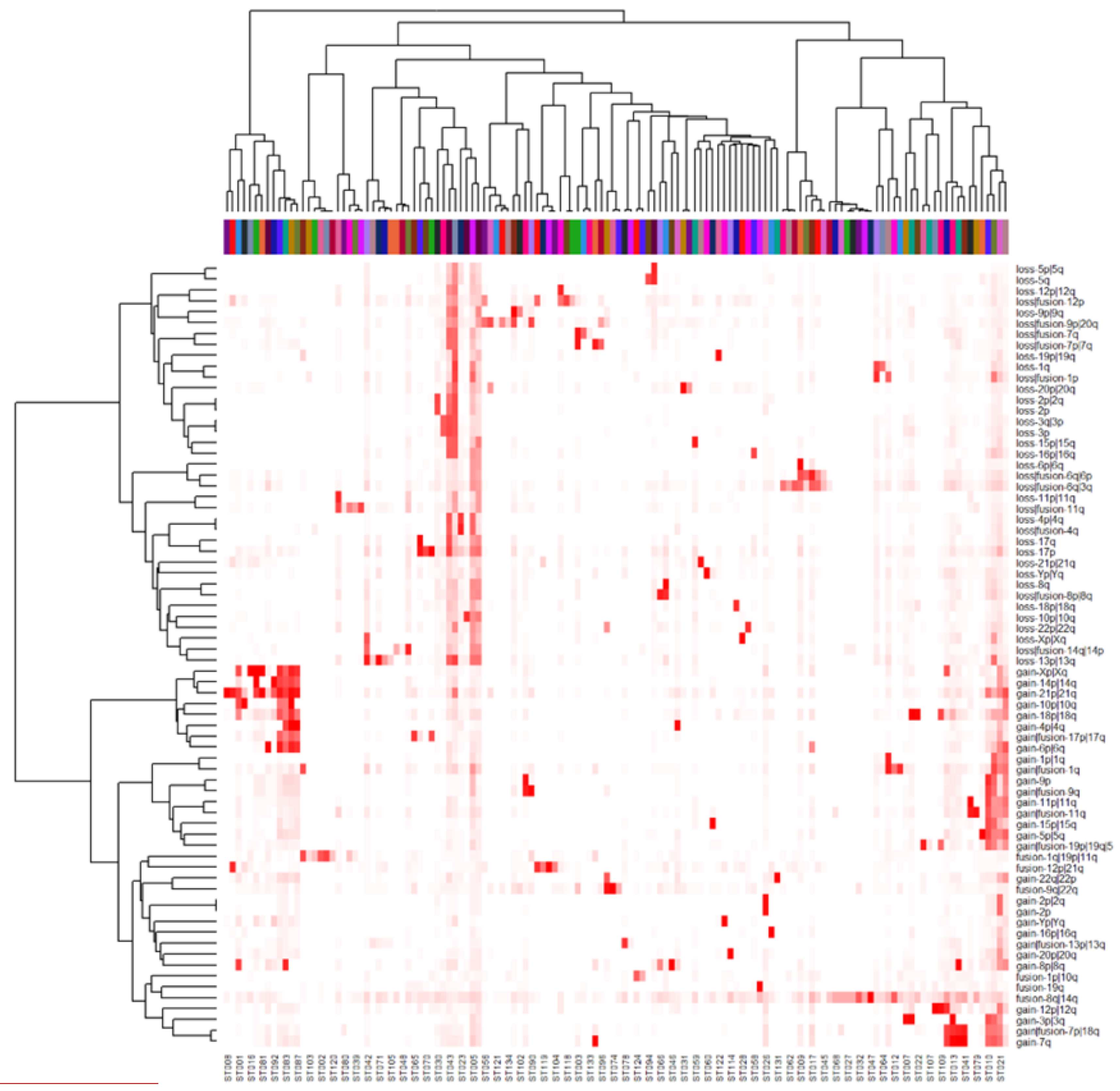


Figure 3**:** This heatmap displays frequent cytogenetic events by clusters. The dendrogram for frequent cytogenetic events clearly shows that the largest separation is based on gains versus losses. The highest level of distinction amongst clusters separates a group of clusters with multiple trisomies, further demonstrating the distinction between cases with monosomies compared to trisomies.

Conclusion

- Comprehensive analysis of karyotype data
  - Enables novel discovery
  - Produce visual models that are easier to process
- Mercator allows comprehensive analysis based on visualizations
- Our method recovers clusters though high fidelity

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