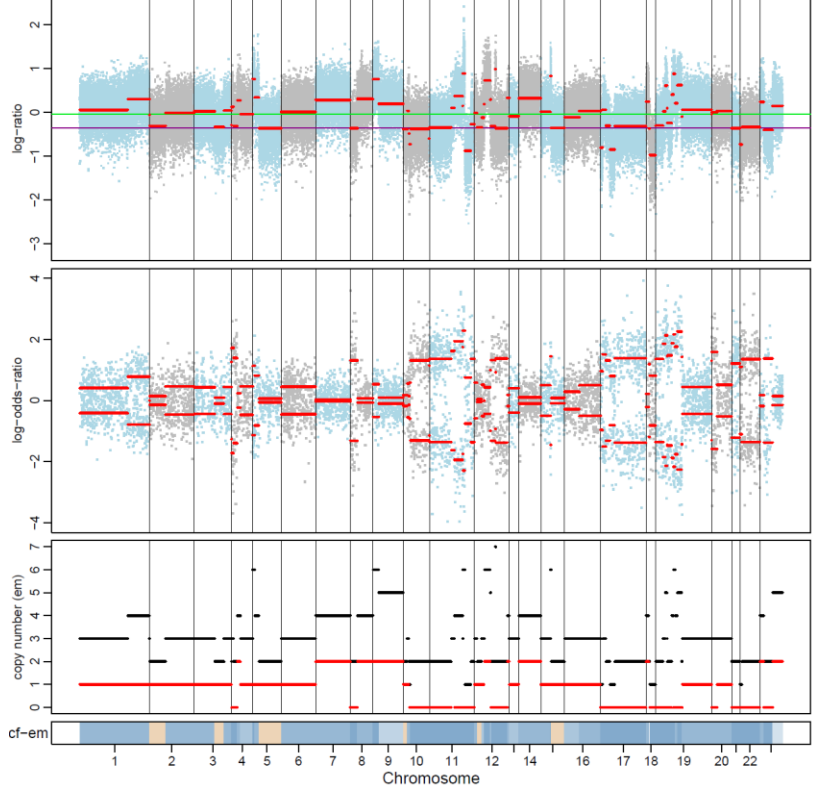


**Supplementary Figures**

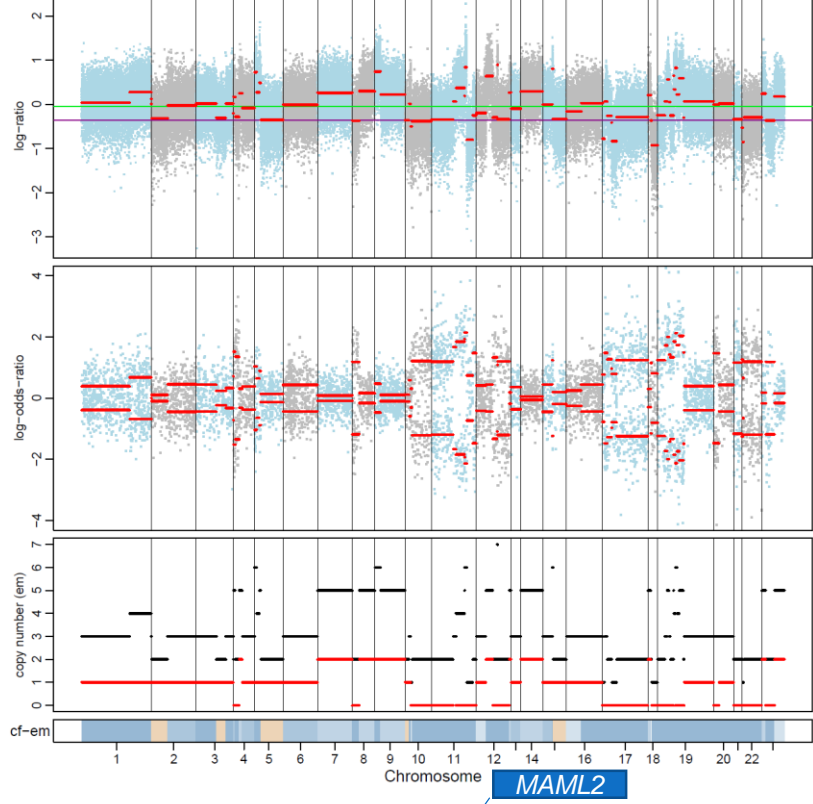
**Figure S1:** Raw copy number plots using Facets. Tumour-specific (either primary or metastasis) driver copy-number events, including deleted tumour suppressor genes and amplified oncogenes, have also been indicated where relevant.



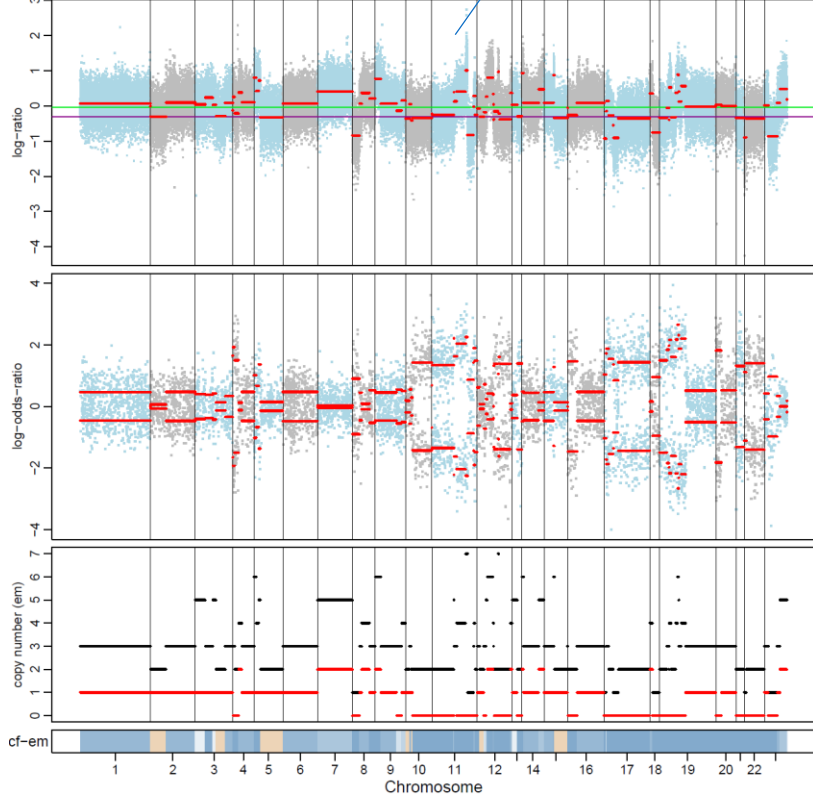
083-03-P



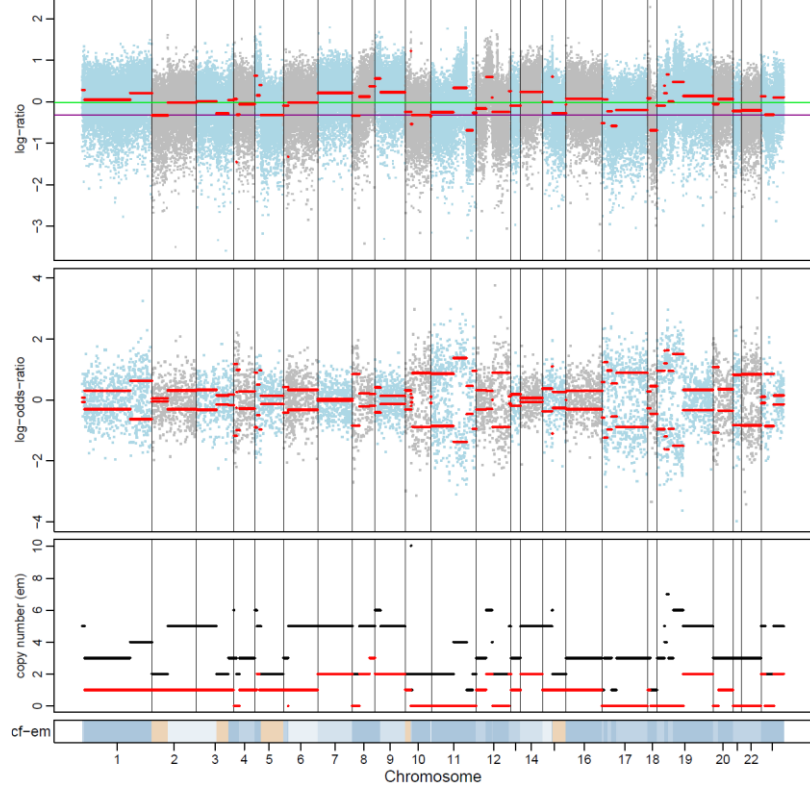
083-03-P2



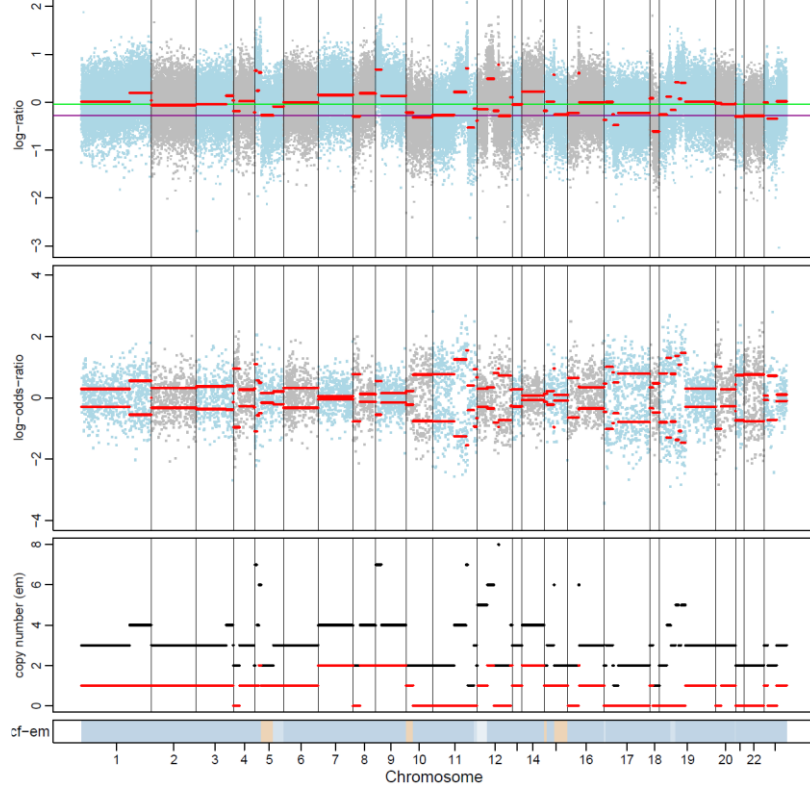
083-03-M



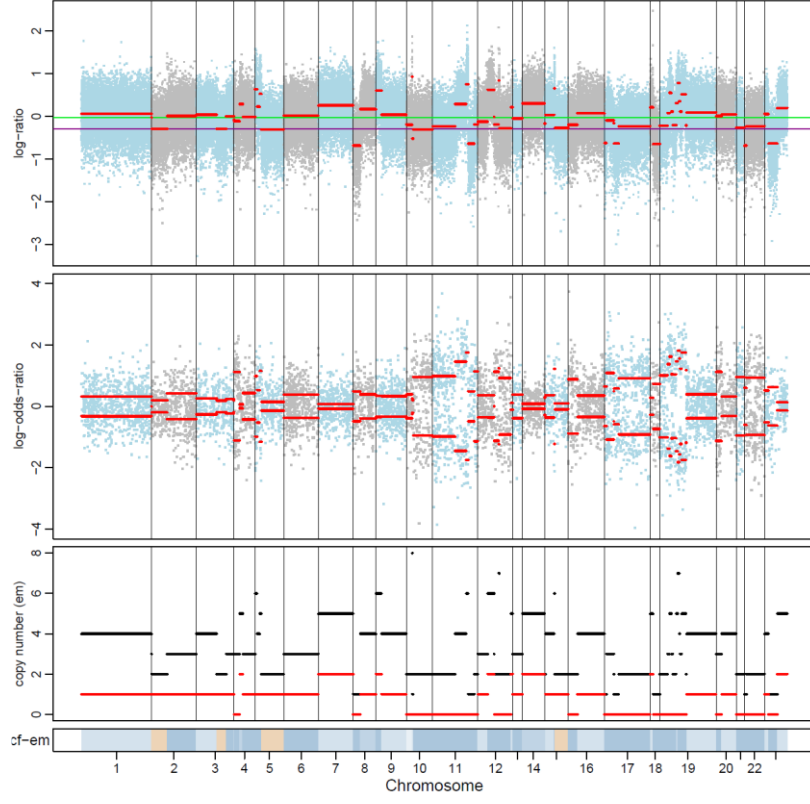
083-03-P1



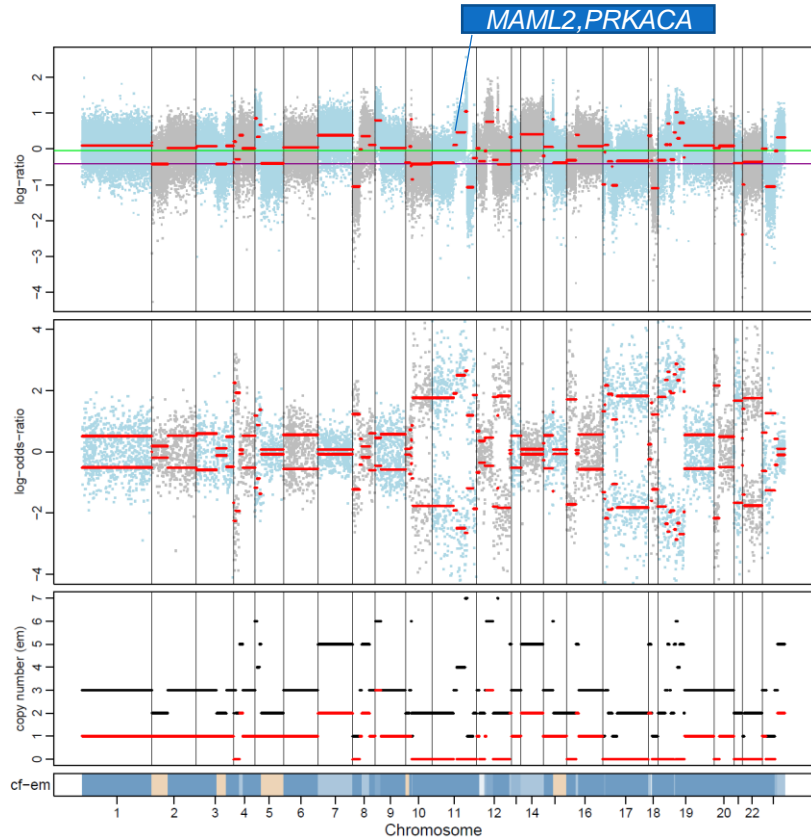
083-03-P3



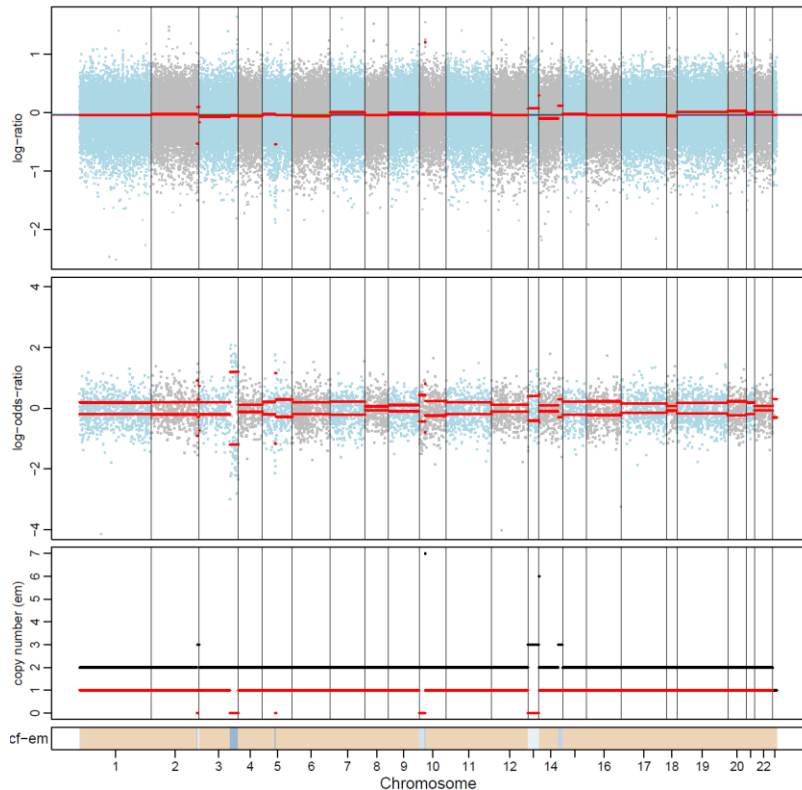
083-03-M1



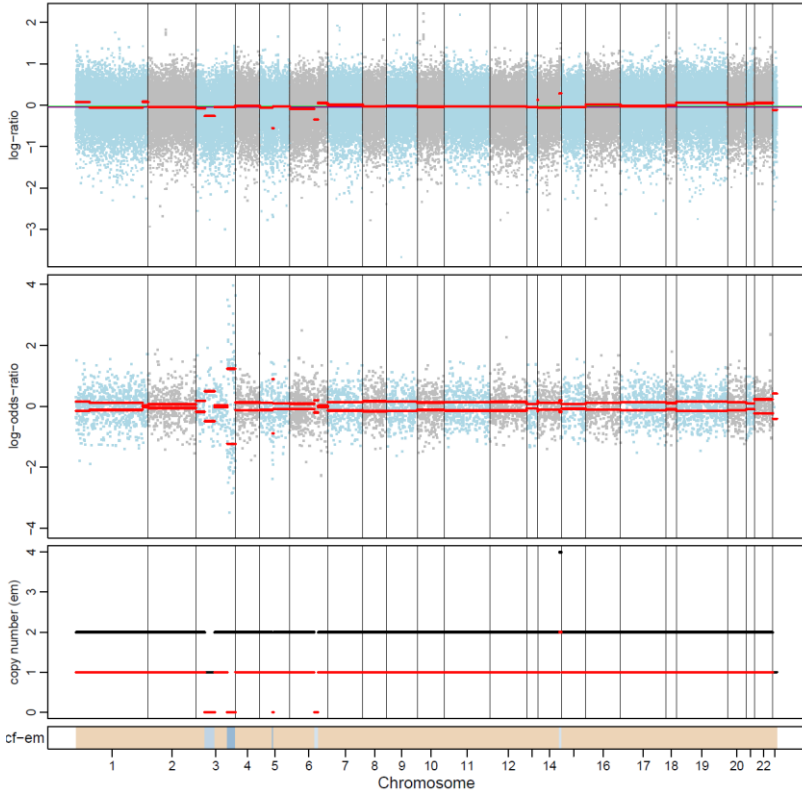
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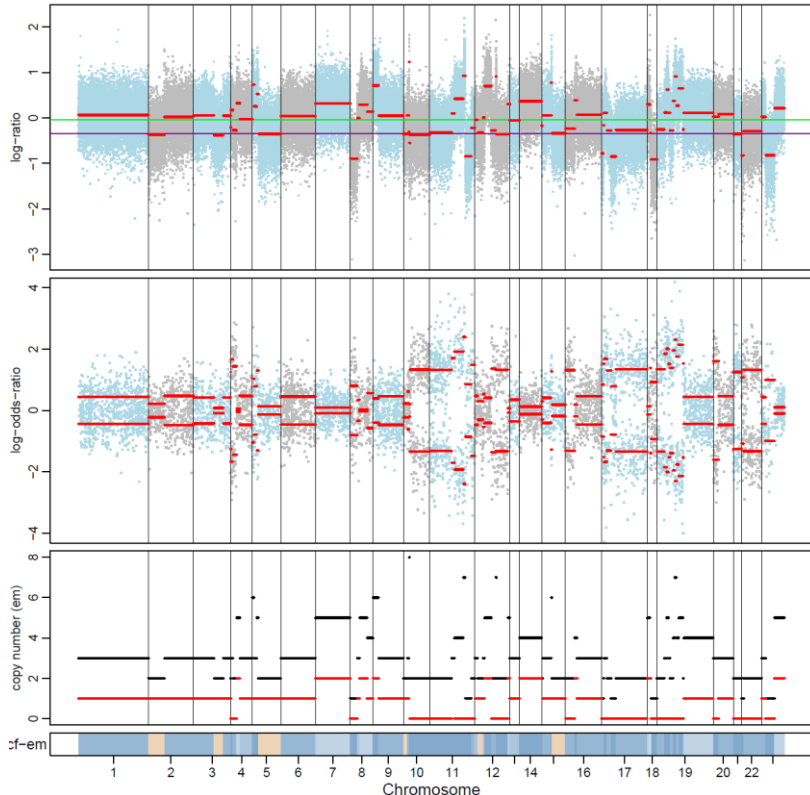
083-32-P



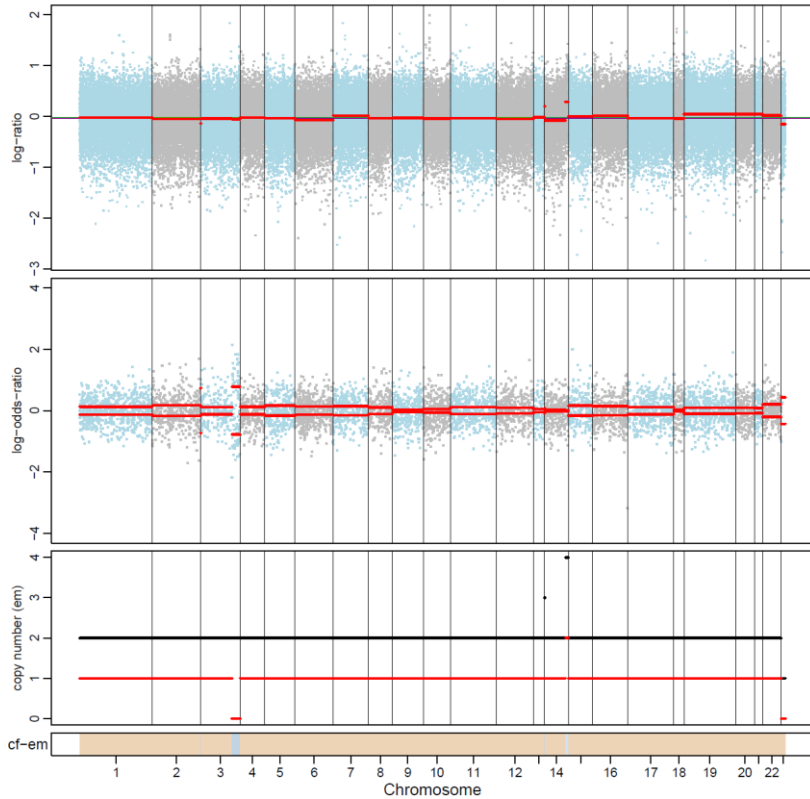
083-32-P2



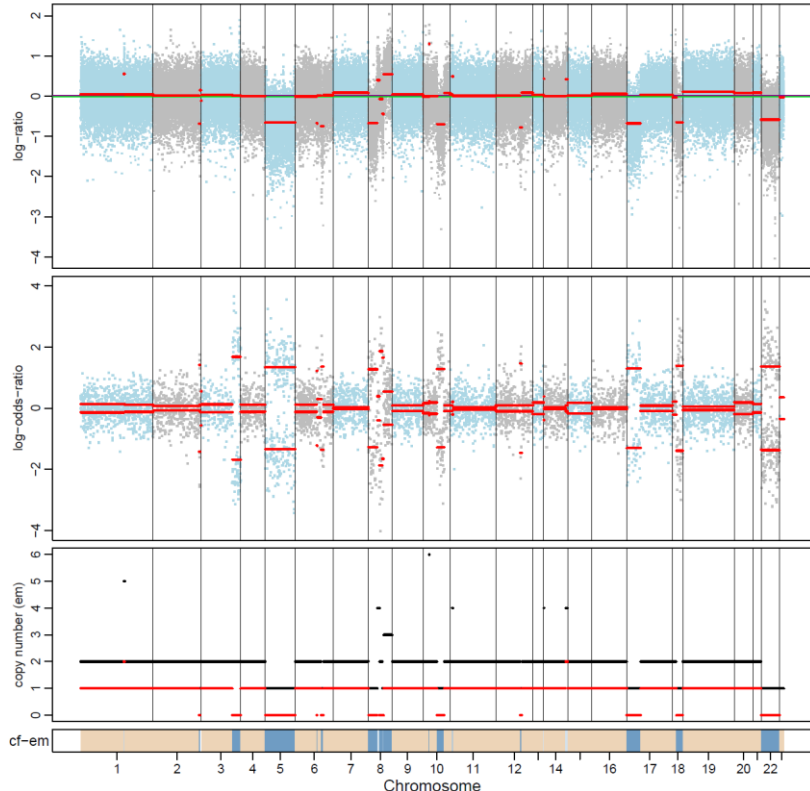
083-03-M3



083-32-P1

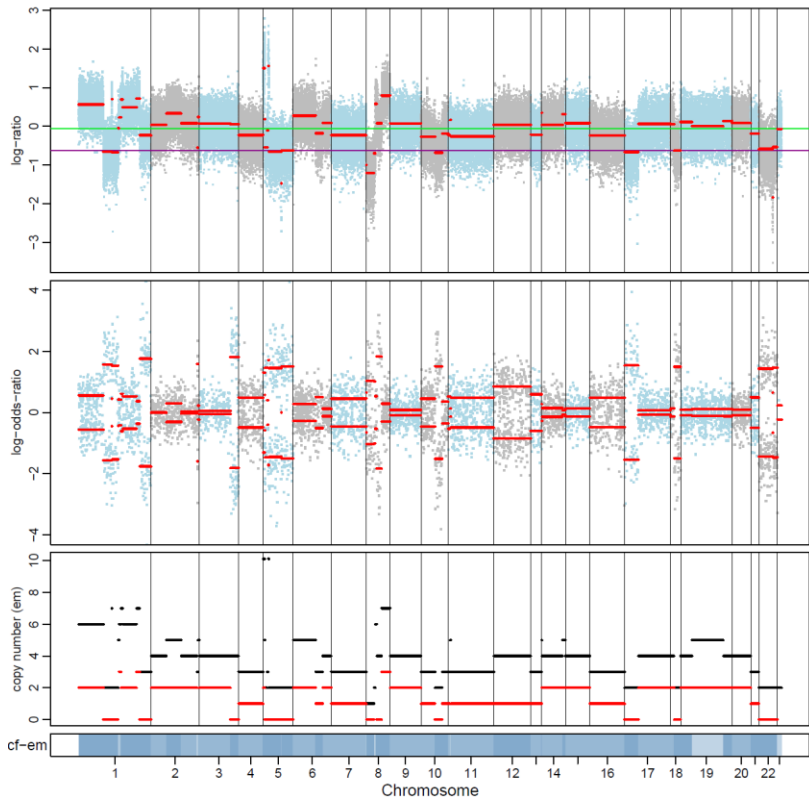


083-32-P3

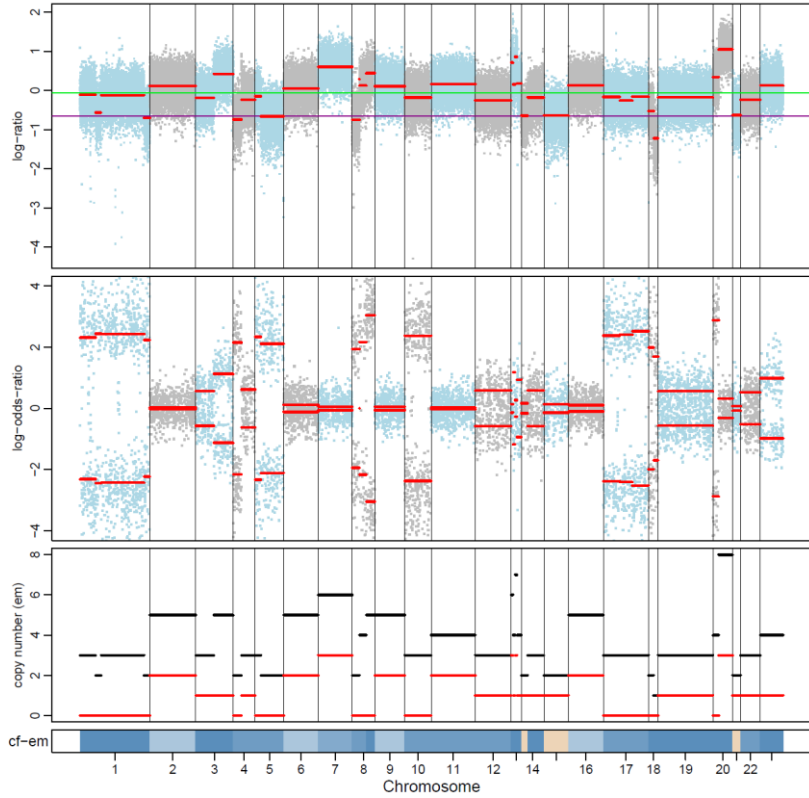




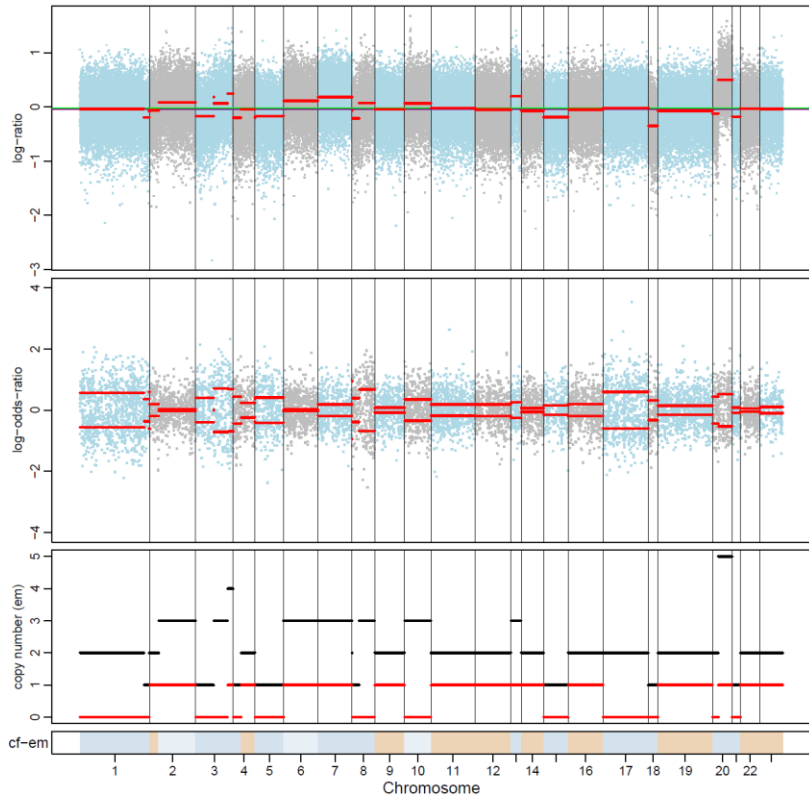
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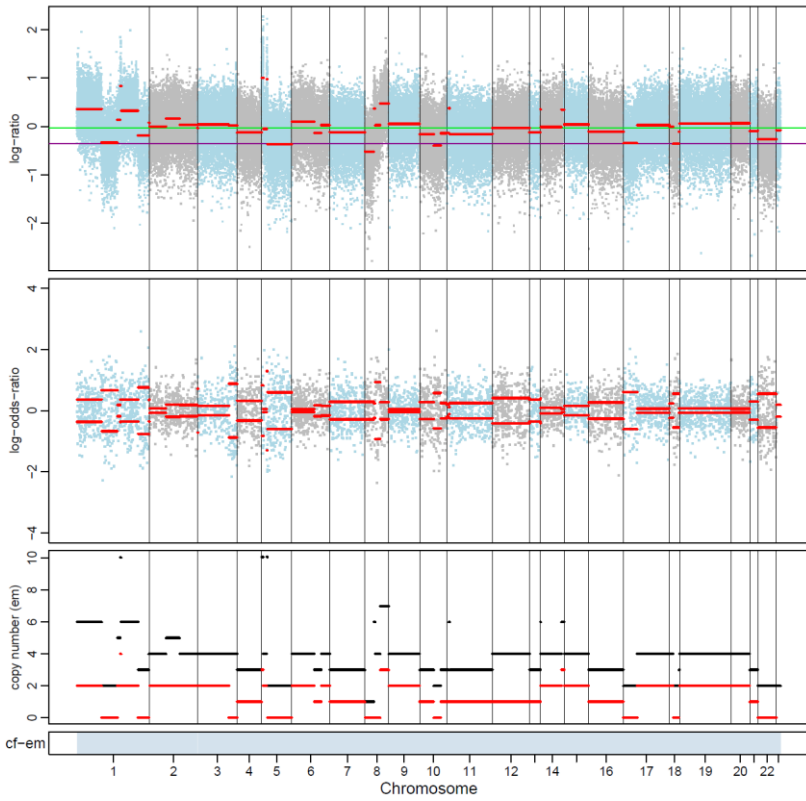
112-038-P



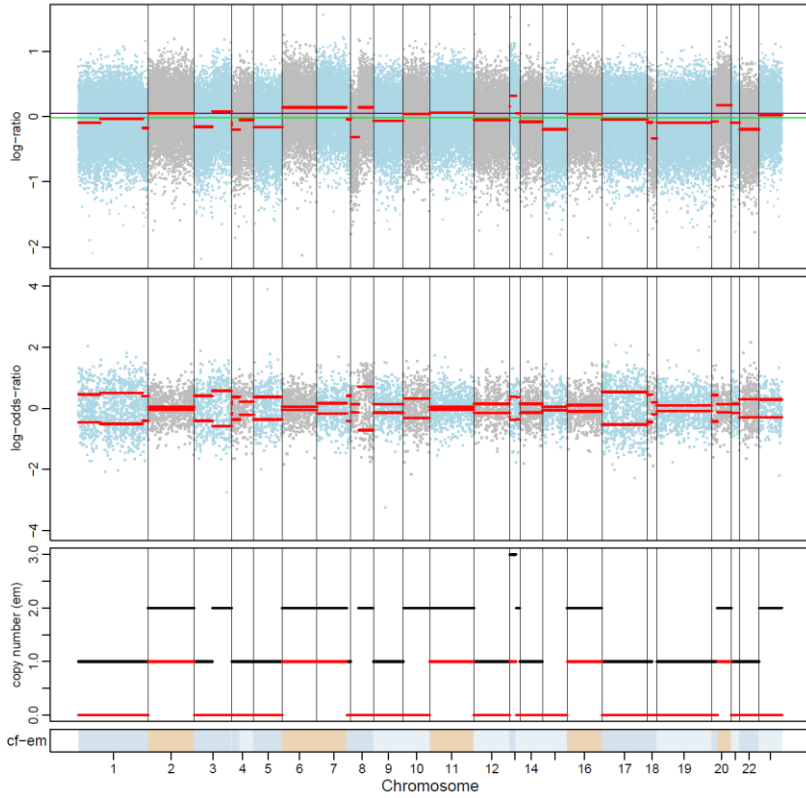
112-038-P2



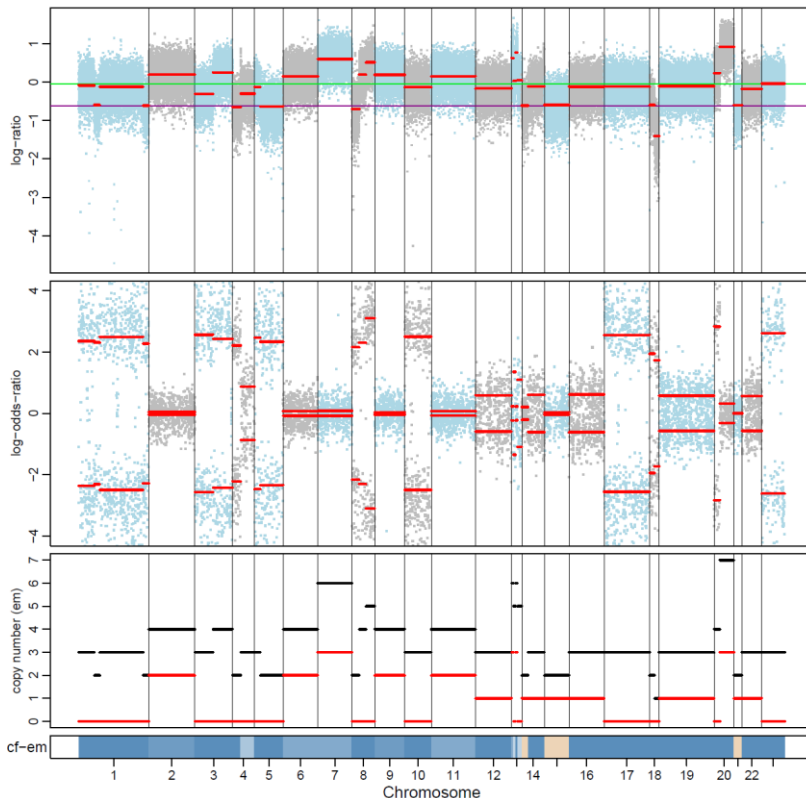
083-32-M1



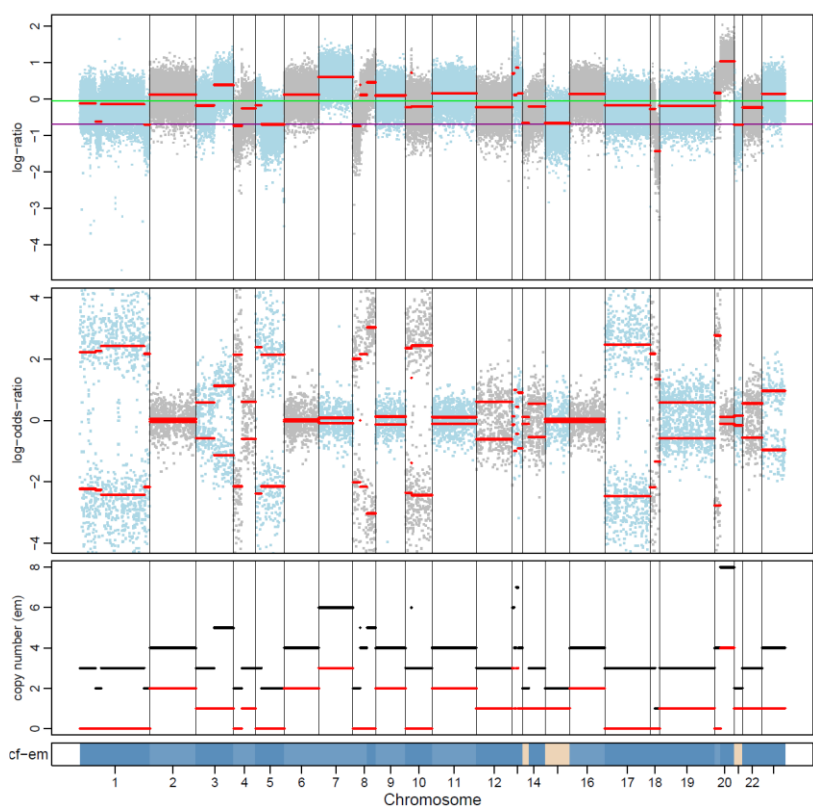
112-038-P1



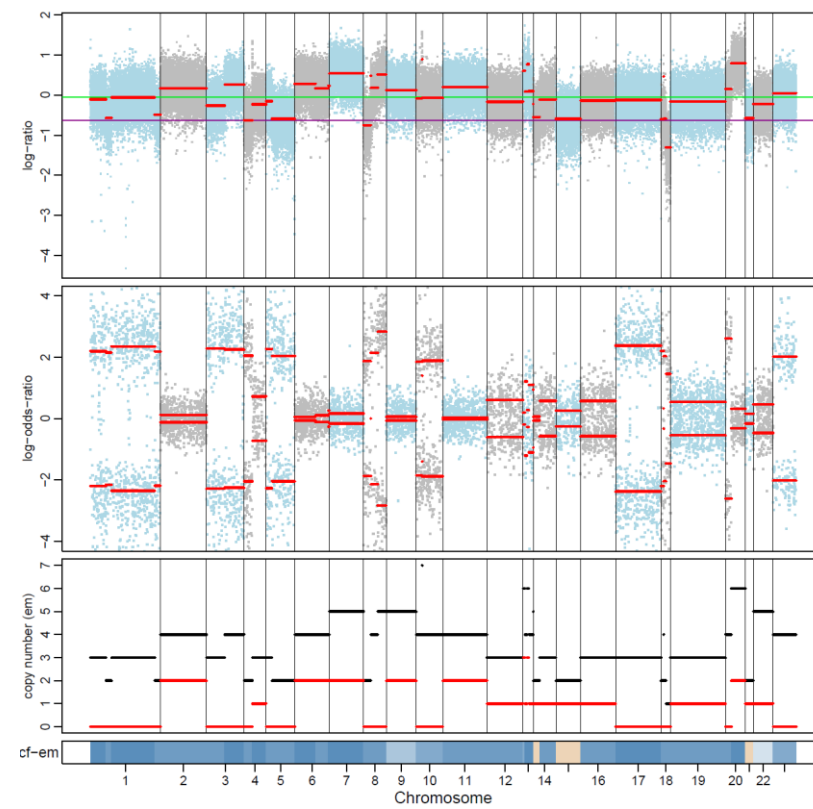
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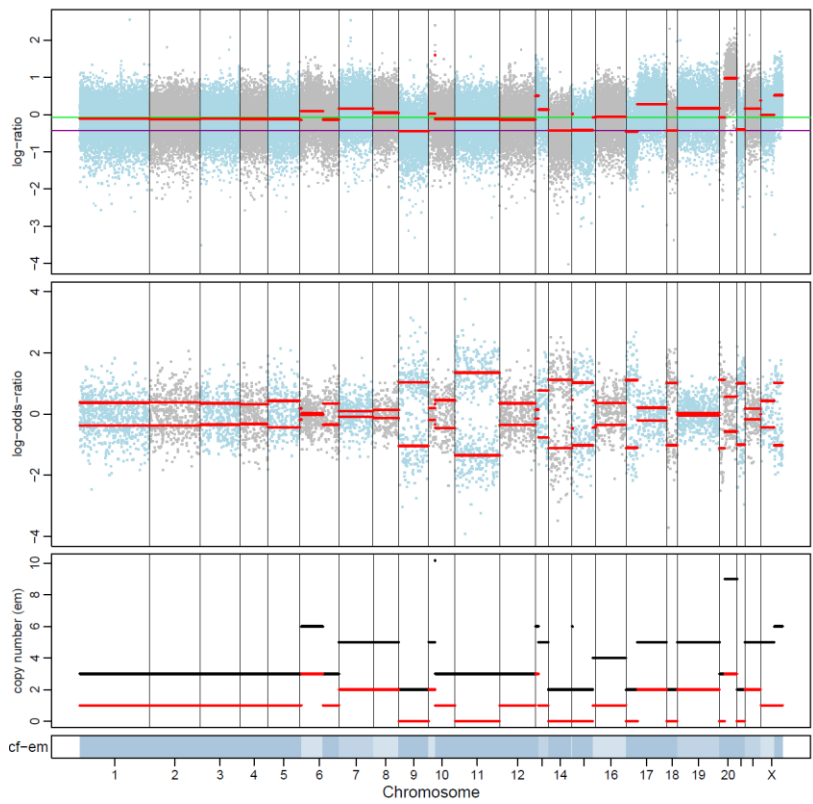
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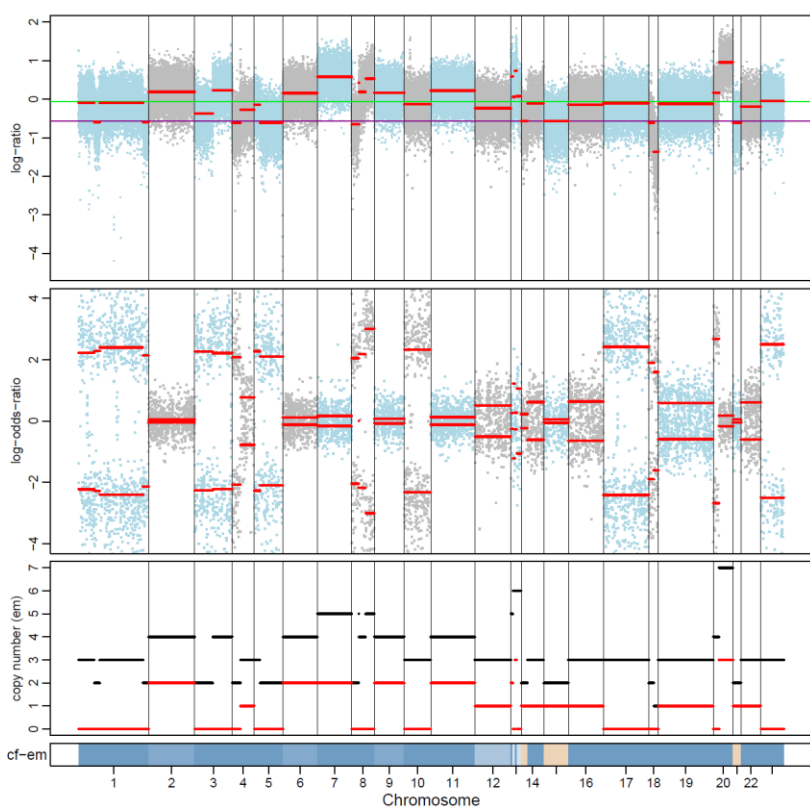
112-038-M3



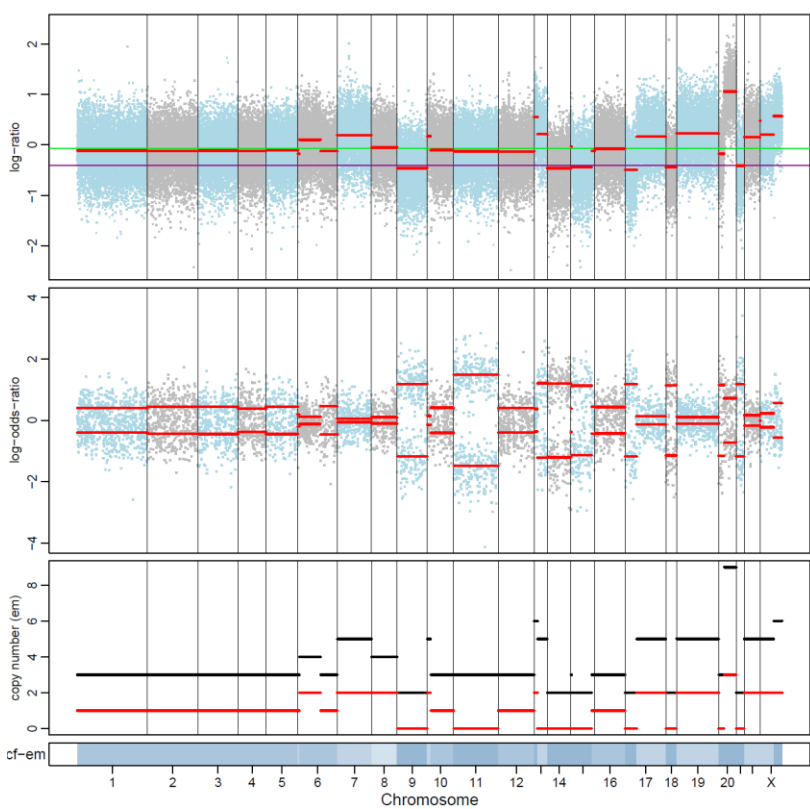
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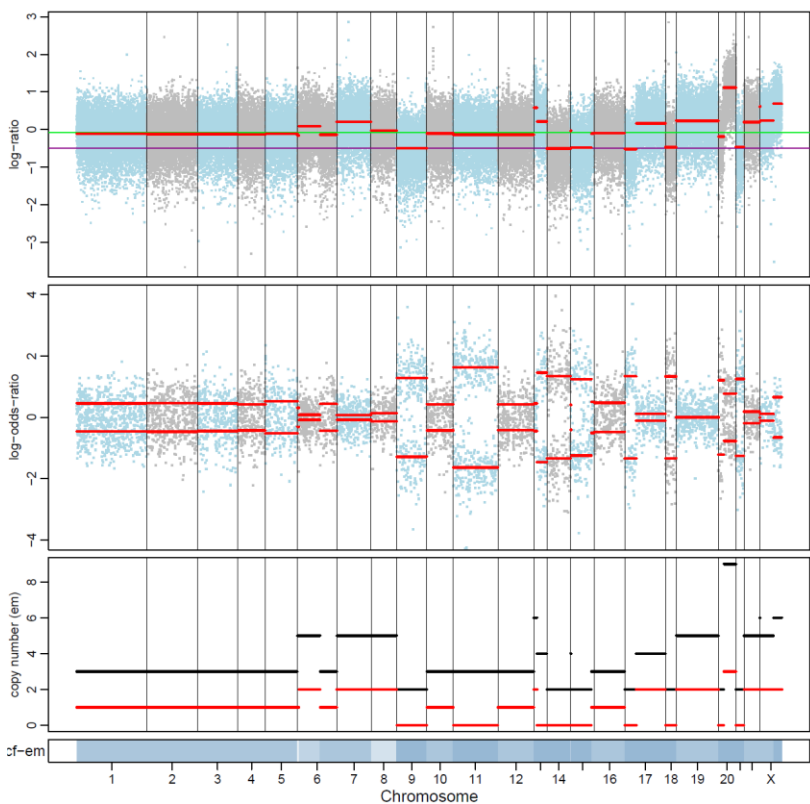
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112-058-P

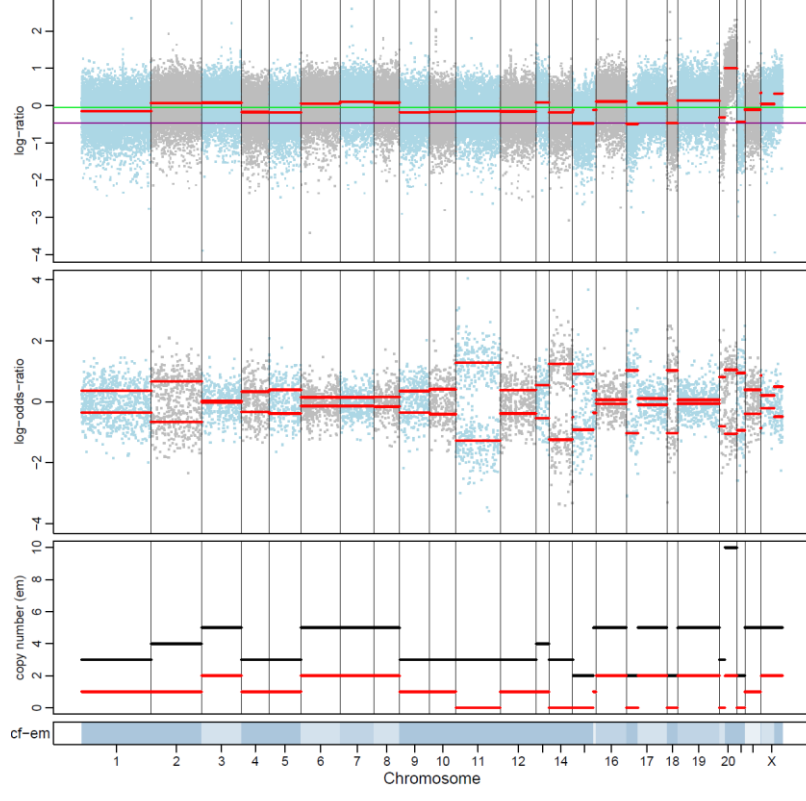


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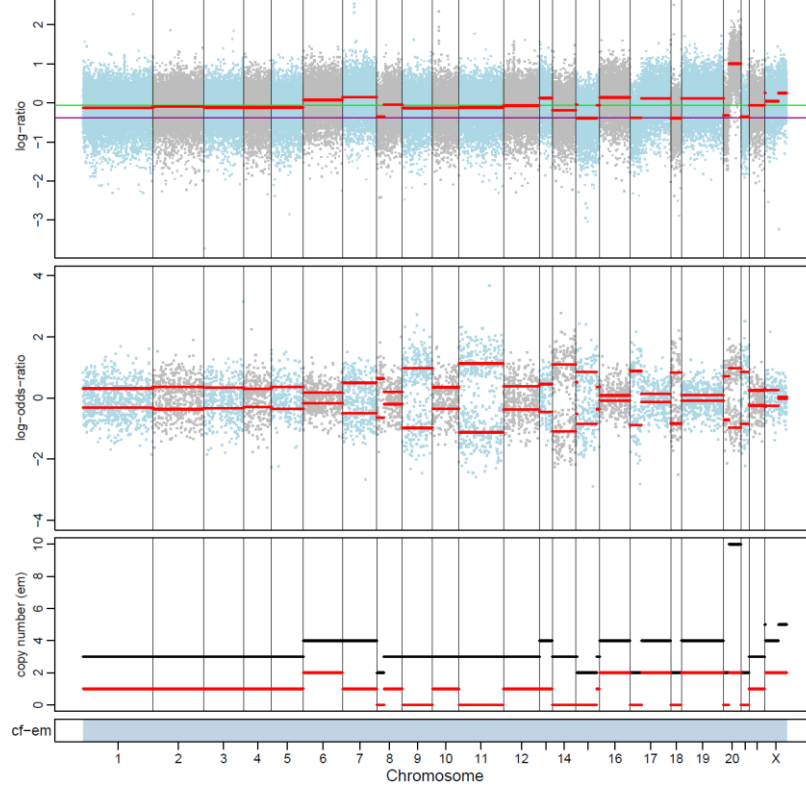




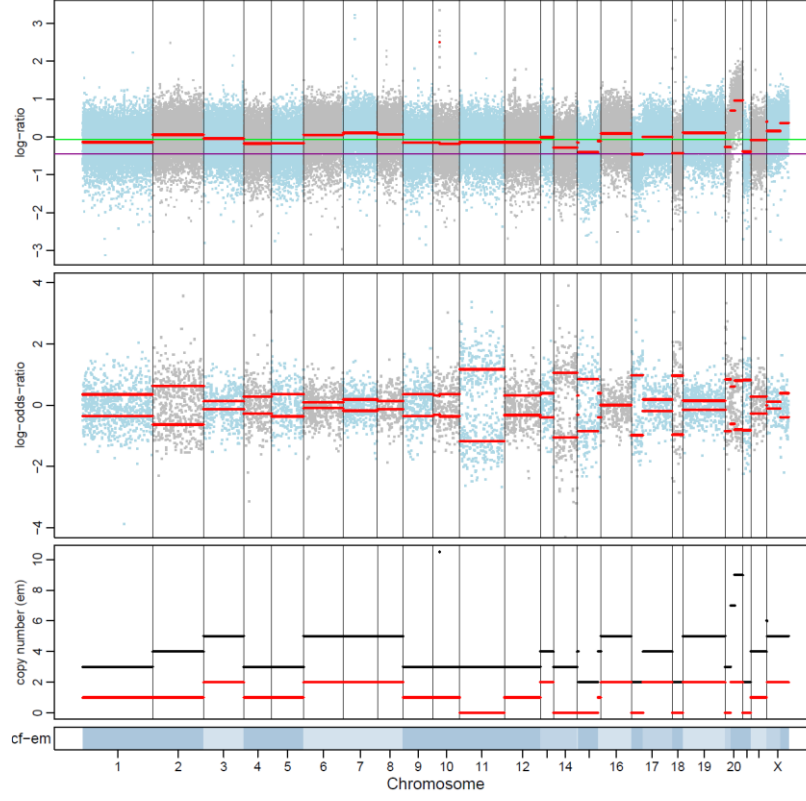
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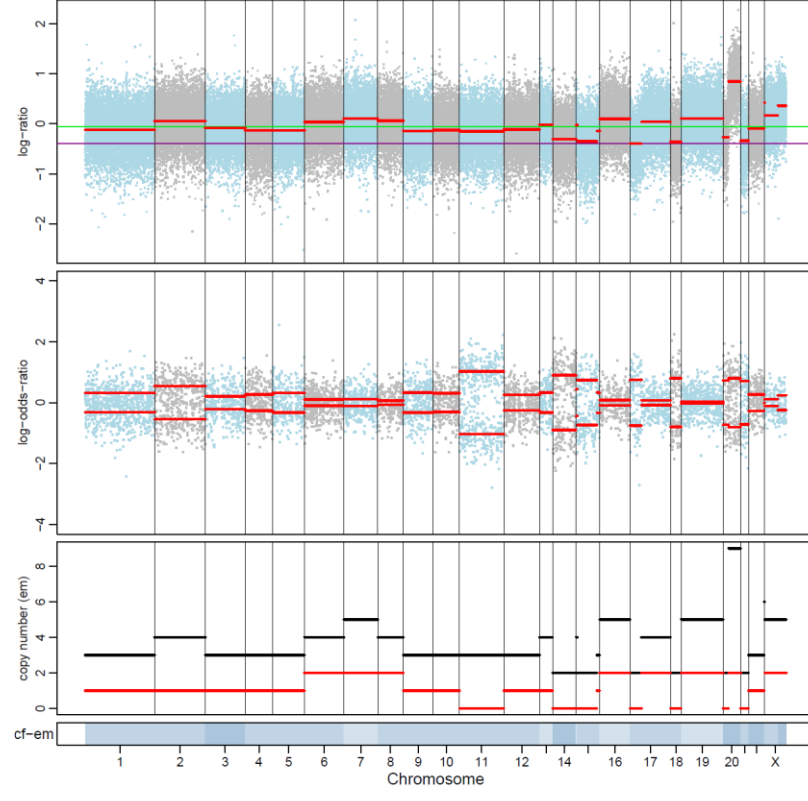
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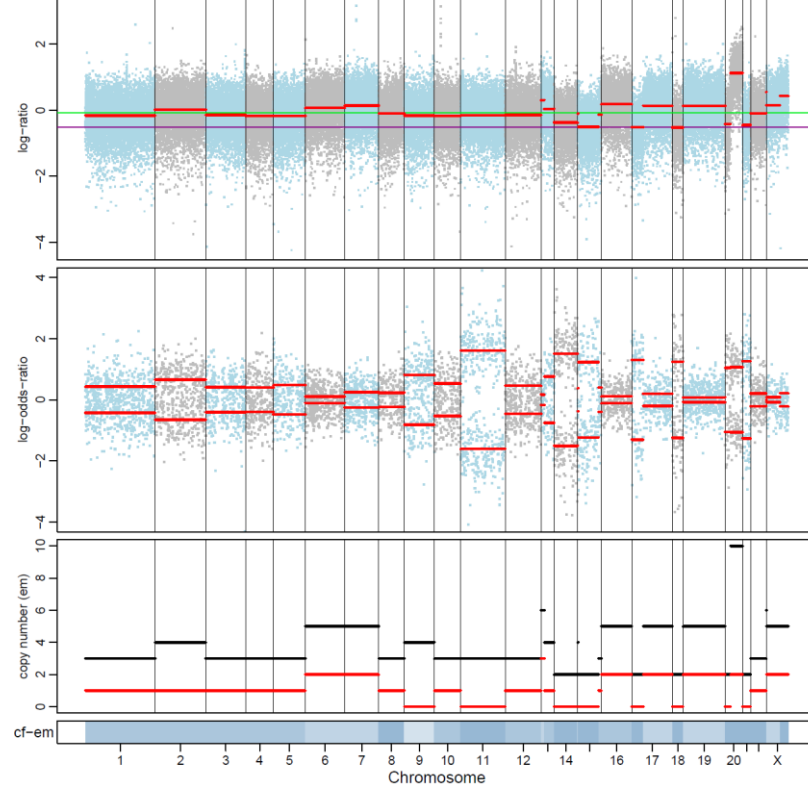
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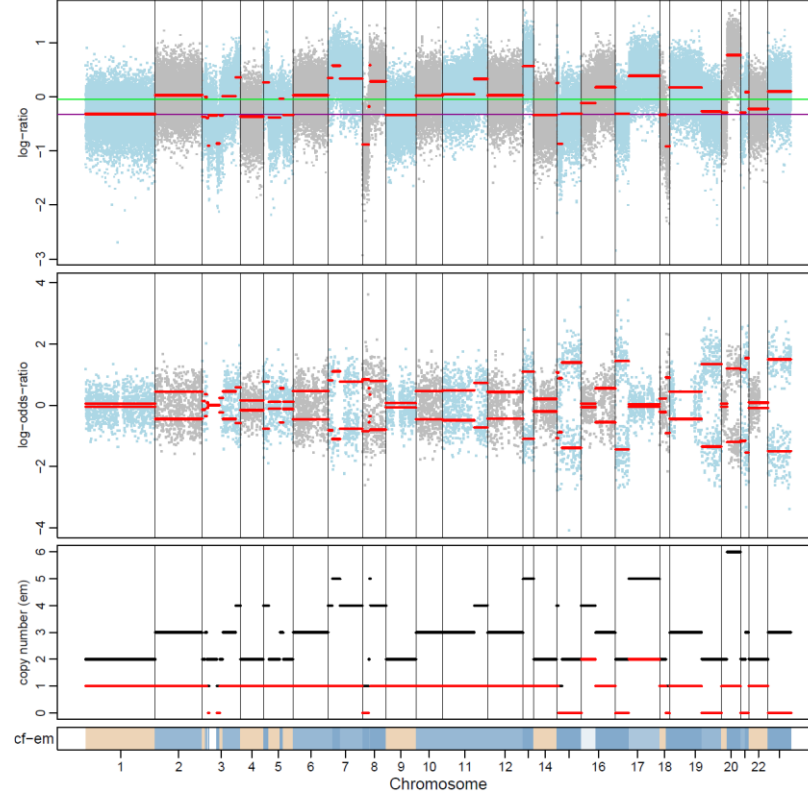
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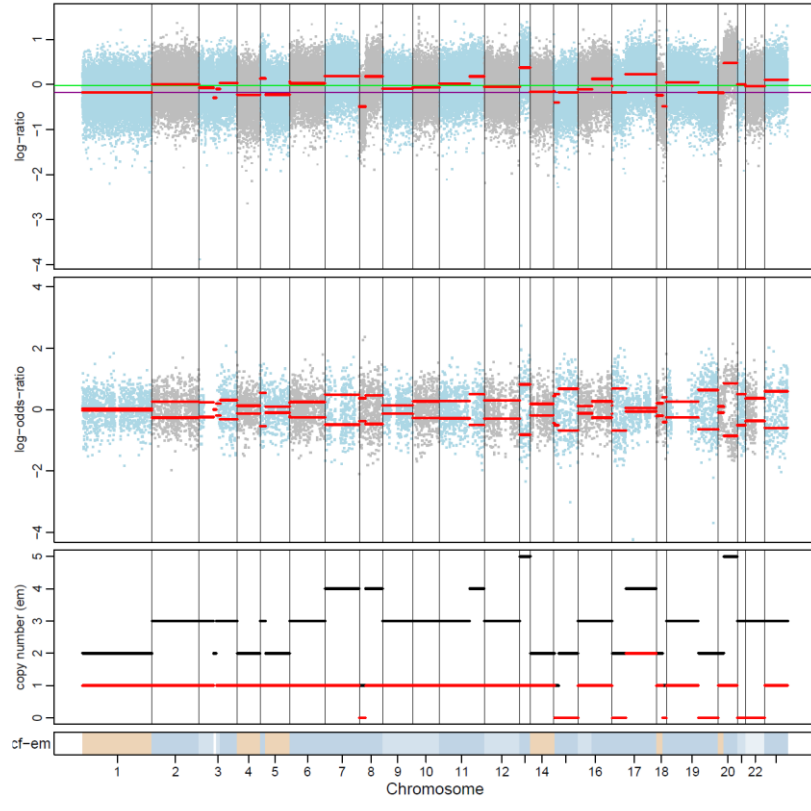
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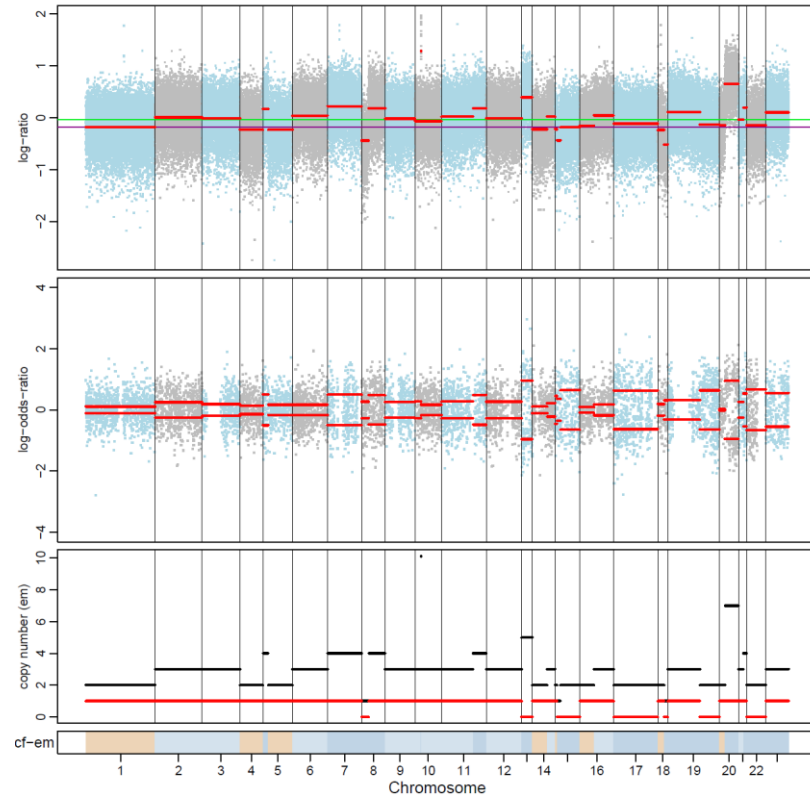
112-091-P



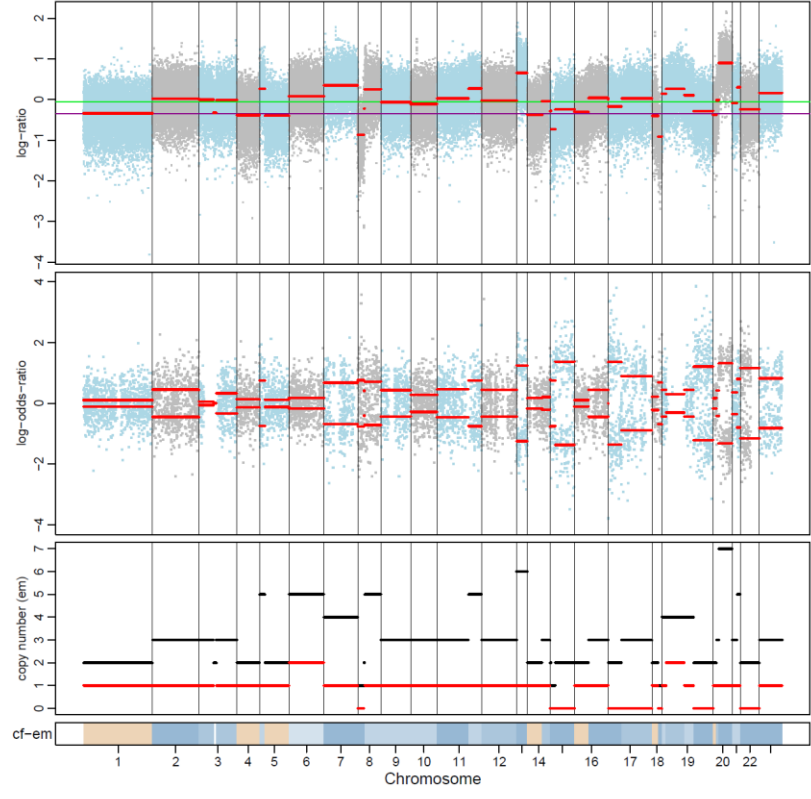
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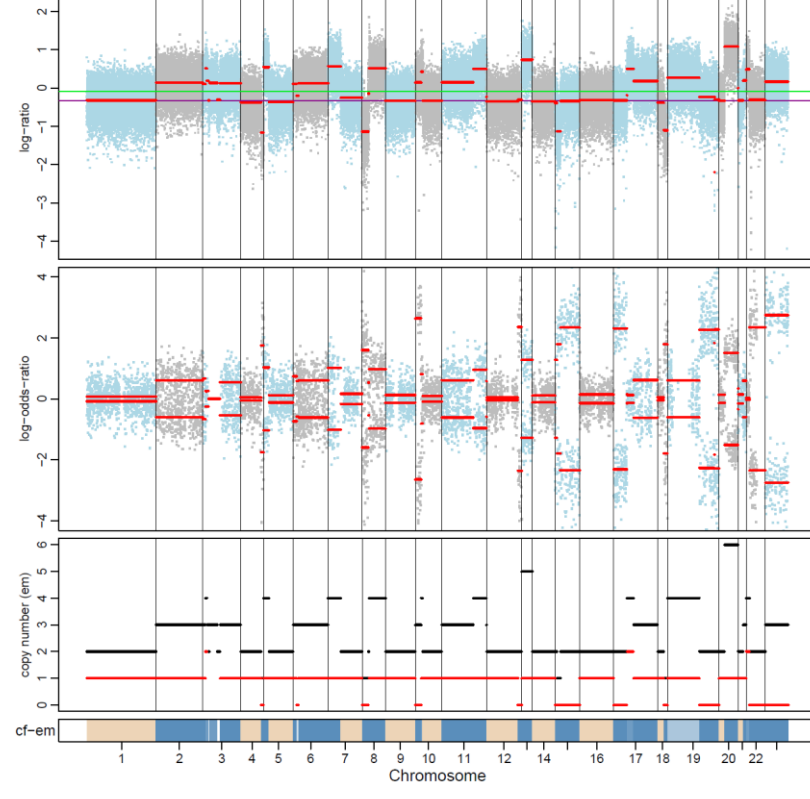
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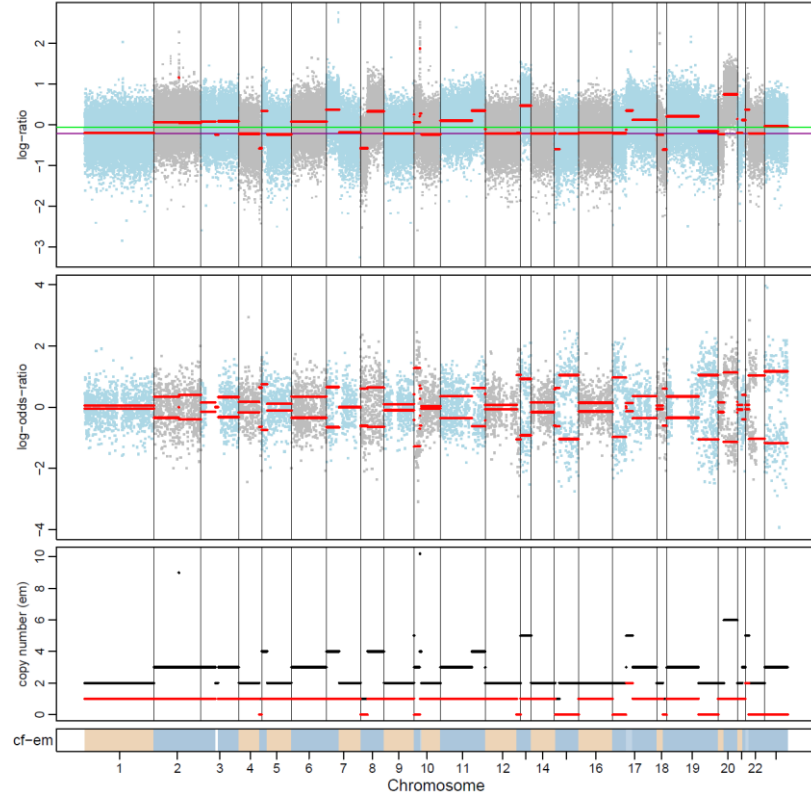
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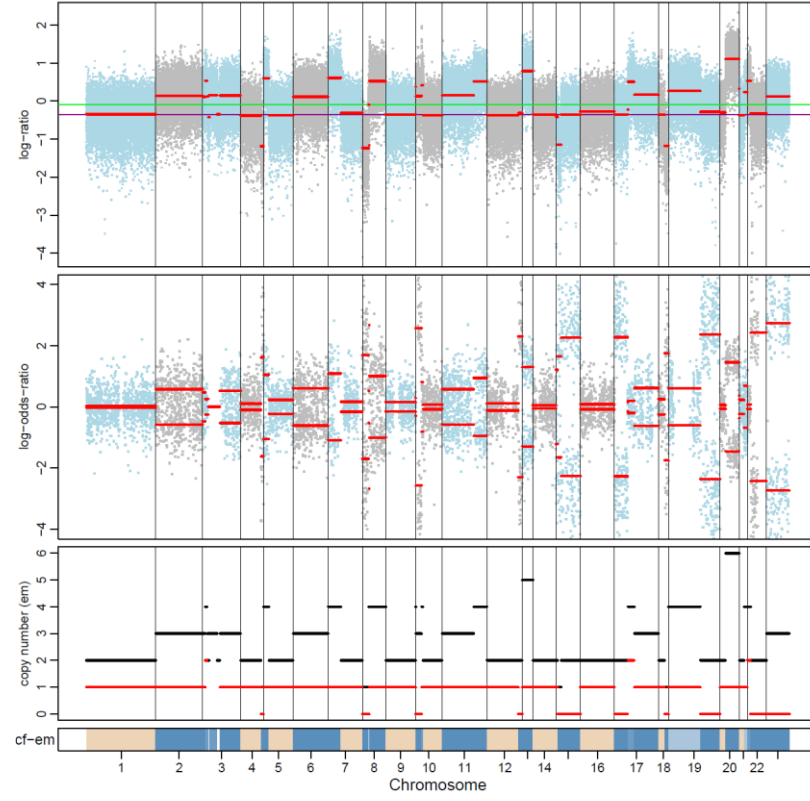
112-091-M



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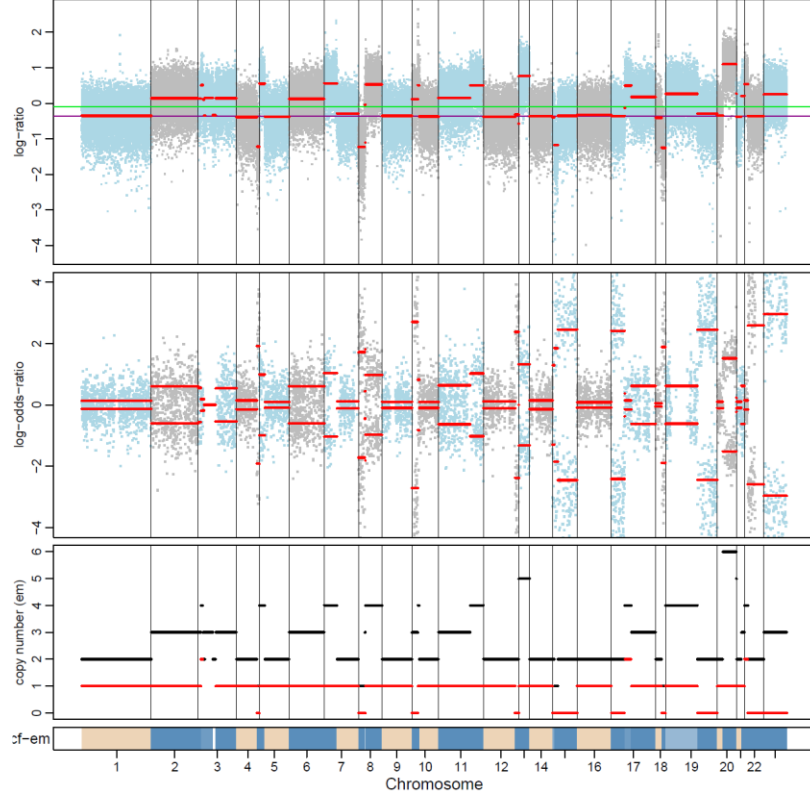


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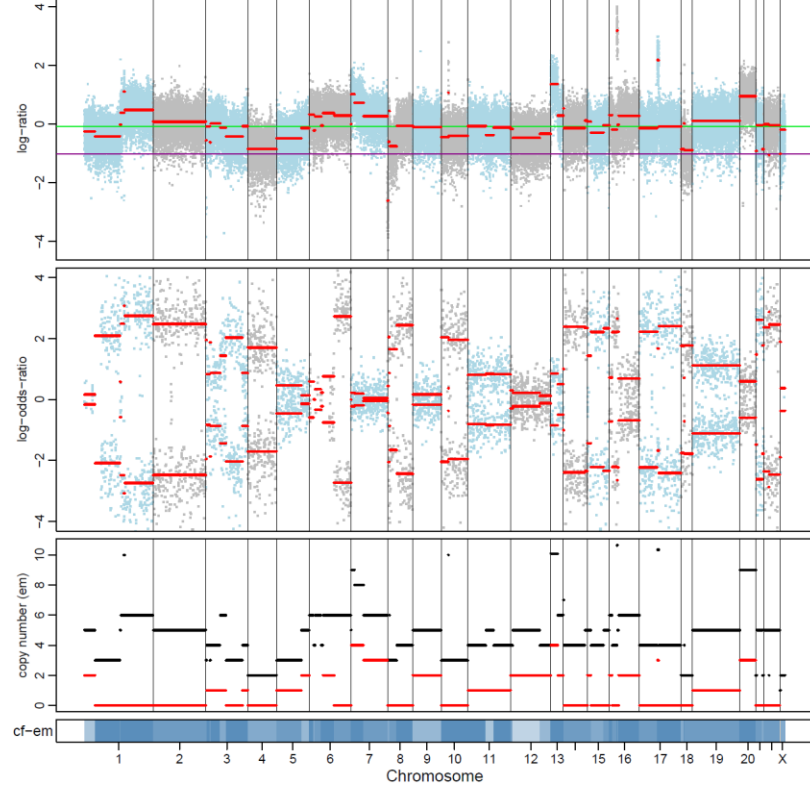




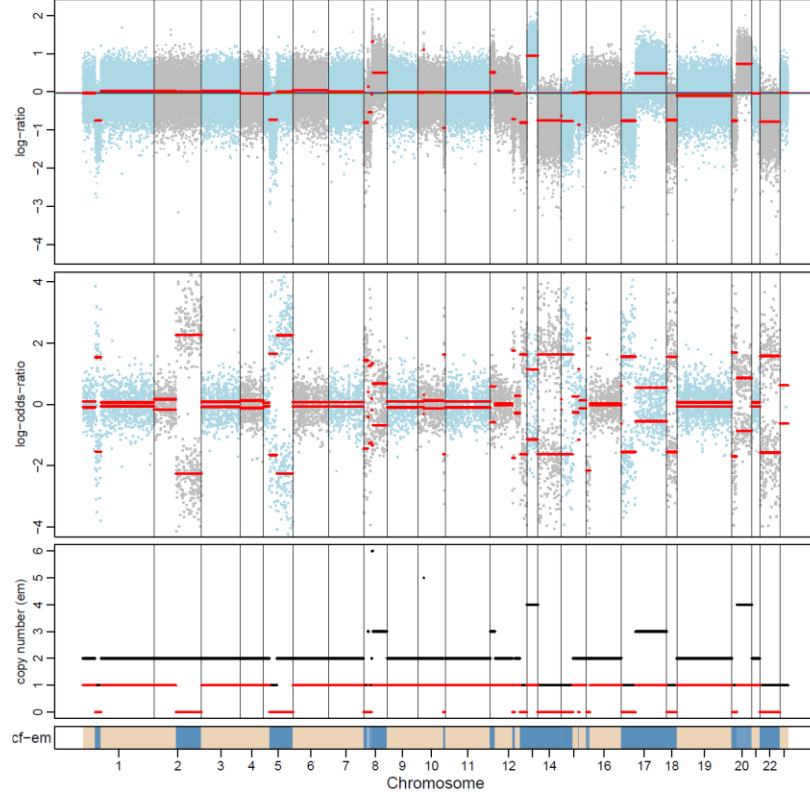
112-091-M3



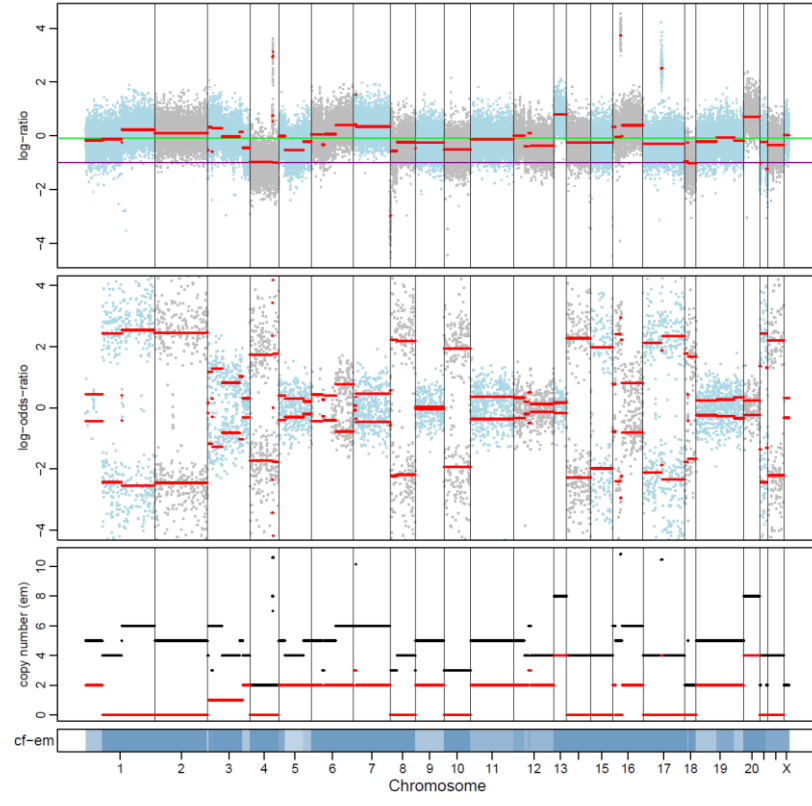
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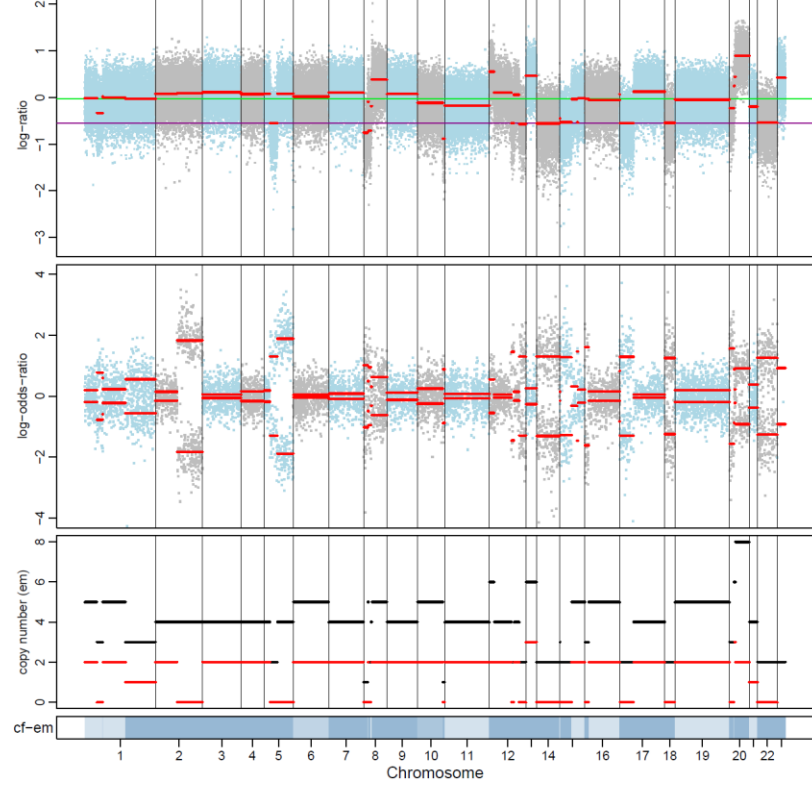
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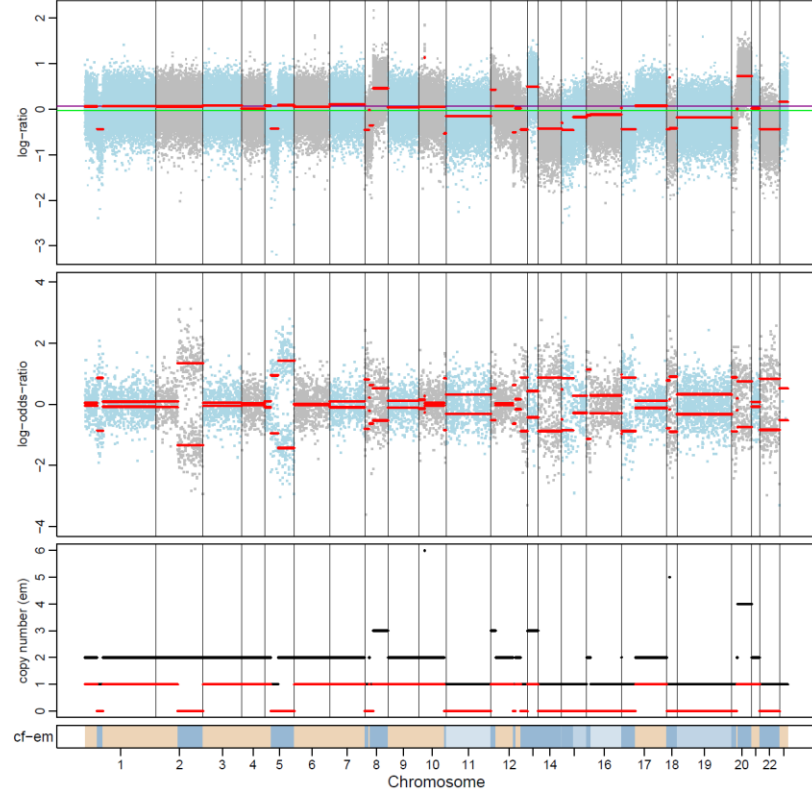
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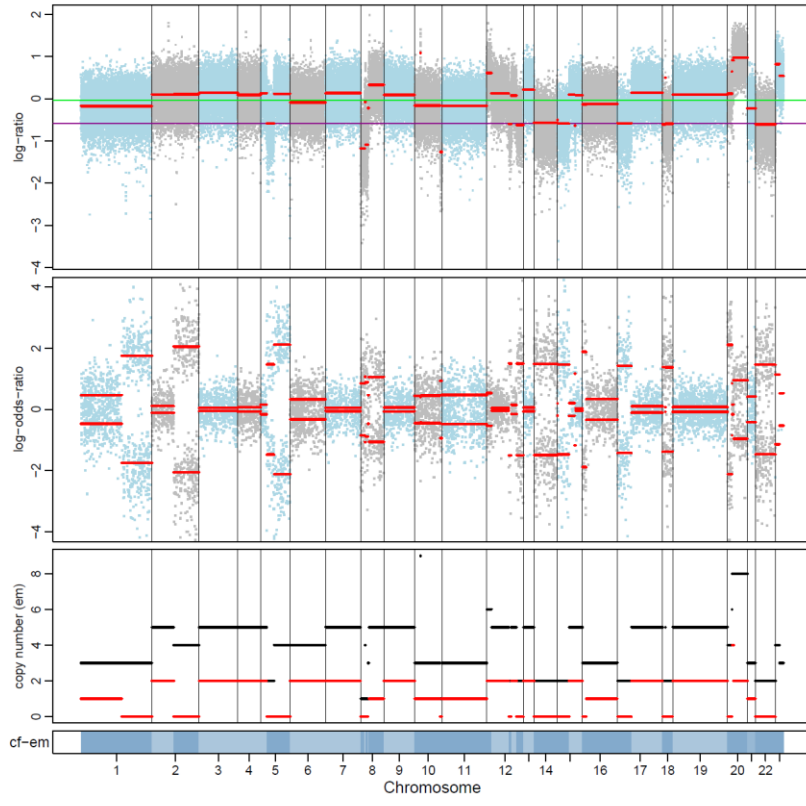
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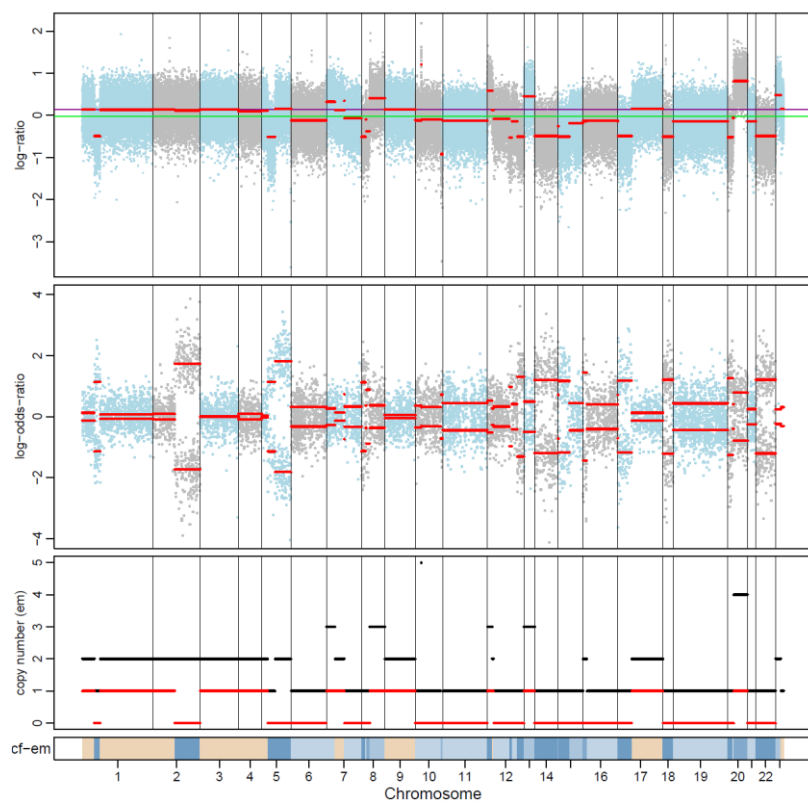
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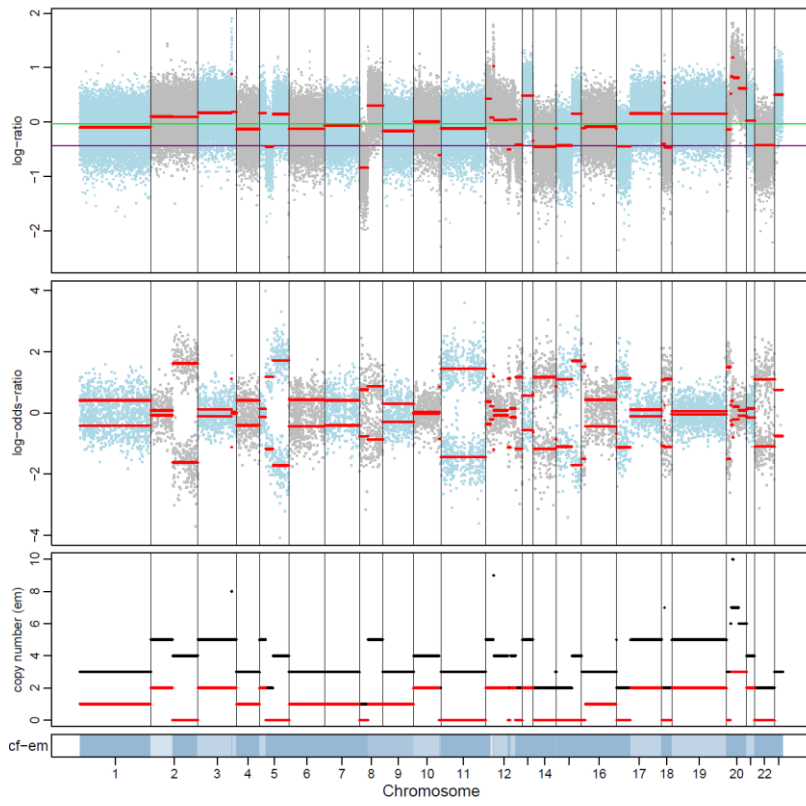
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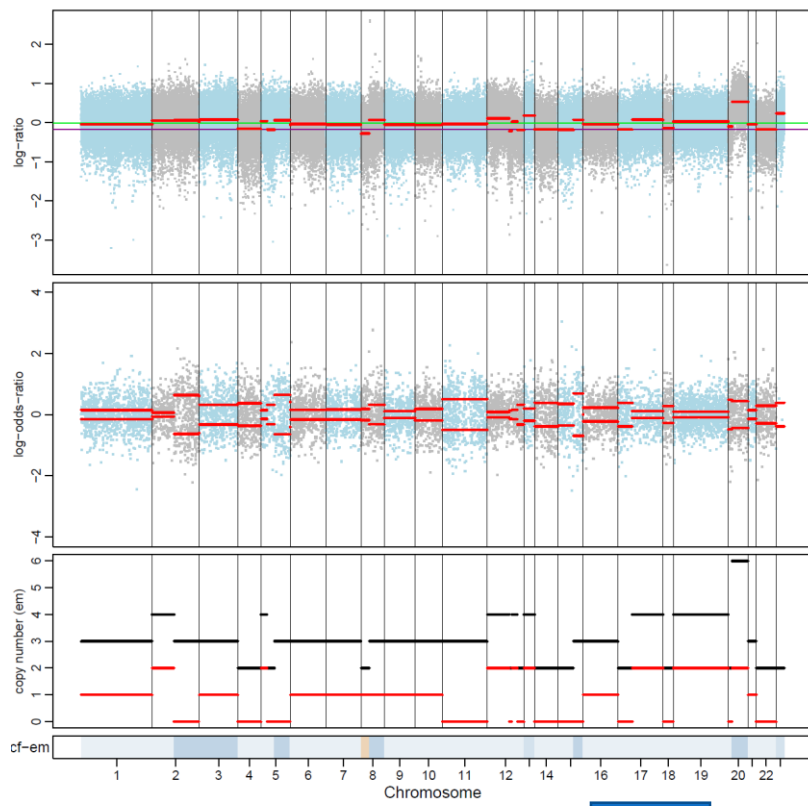
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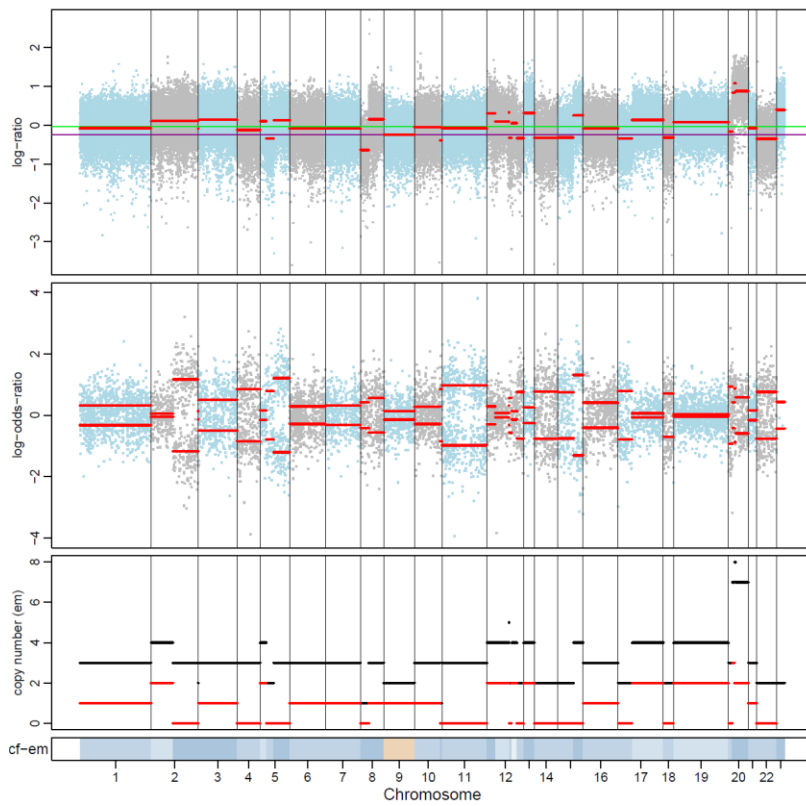
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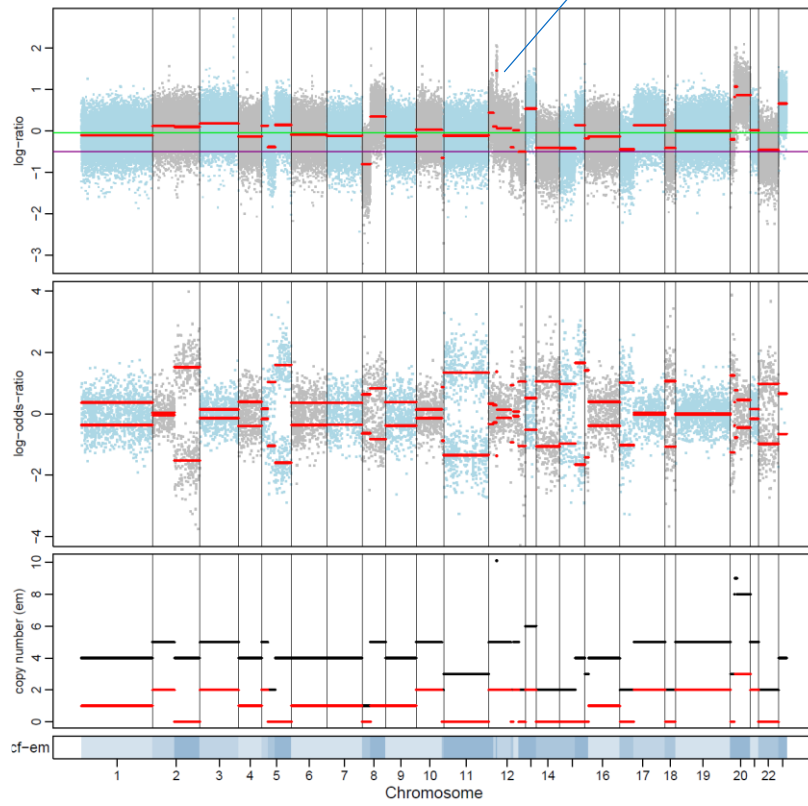
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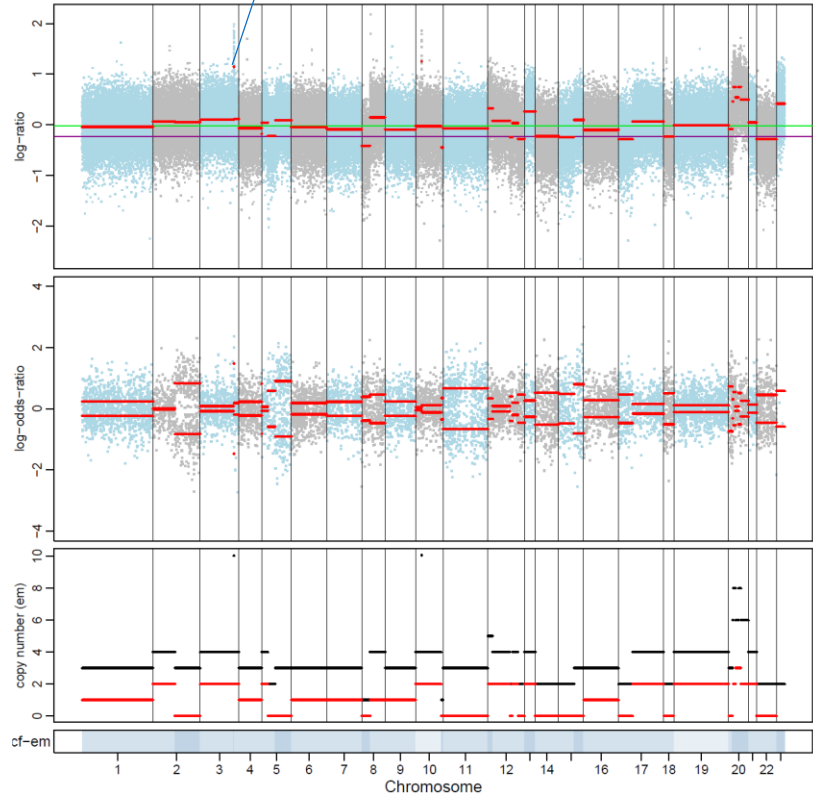


197-064-M3

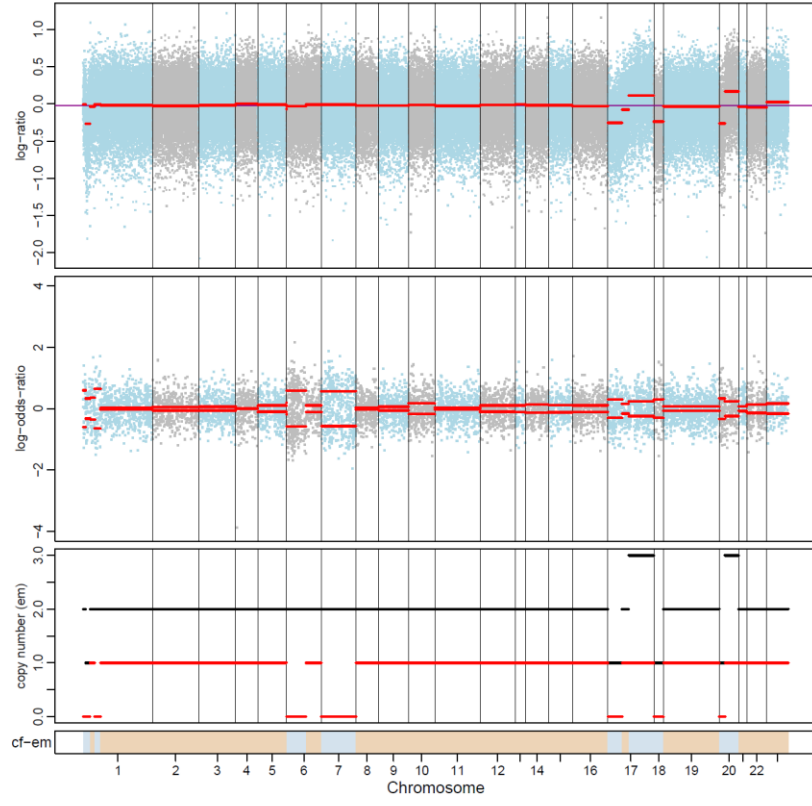




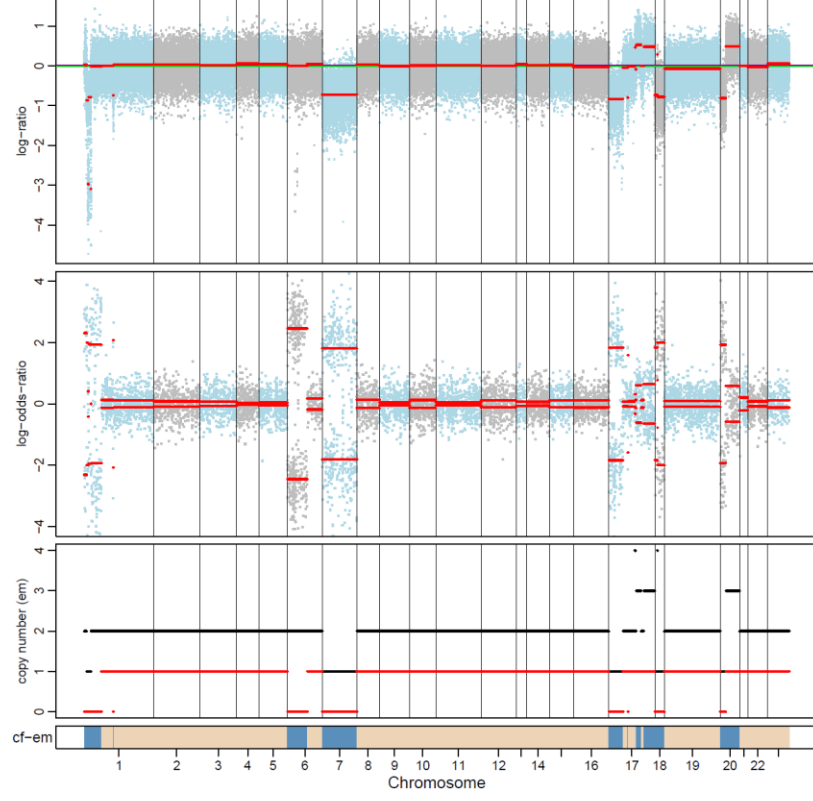
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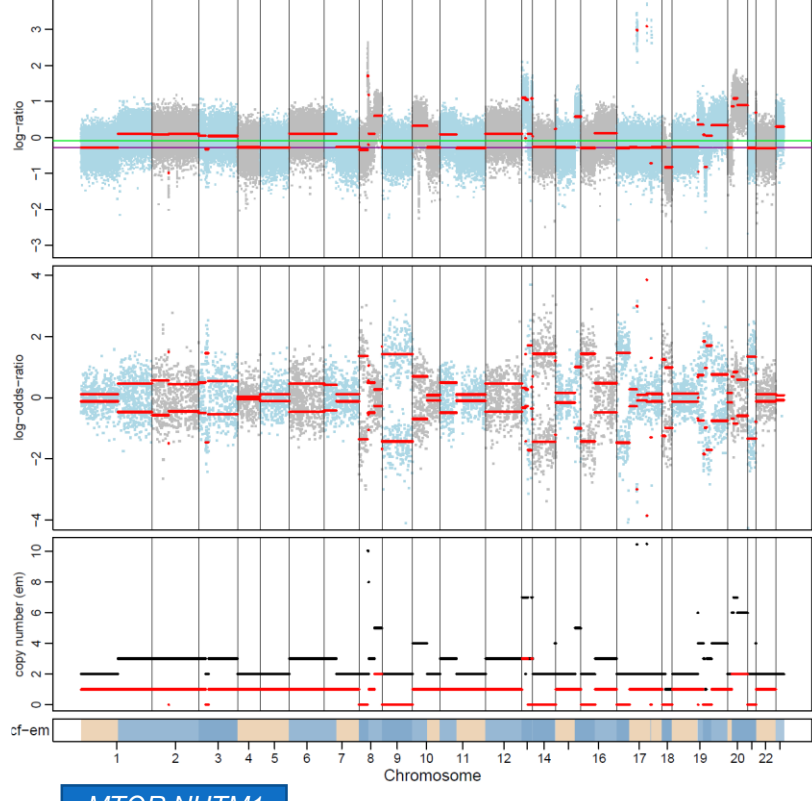
197-144-P



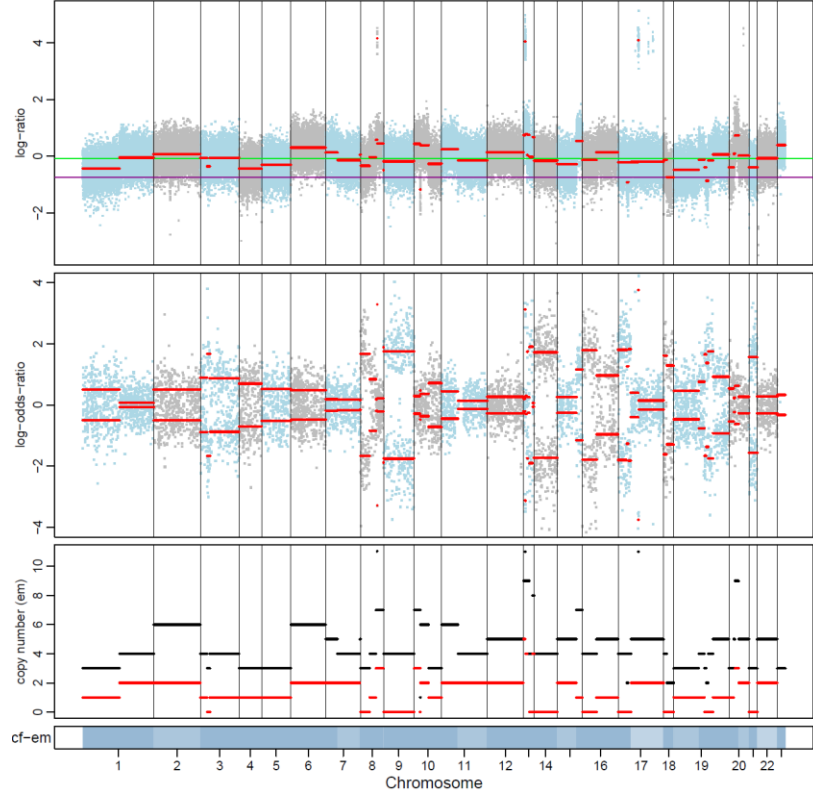
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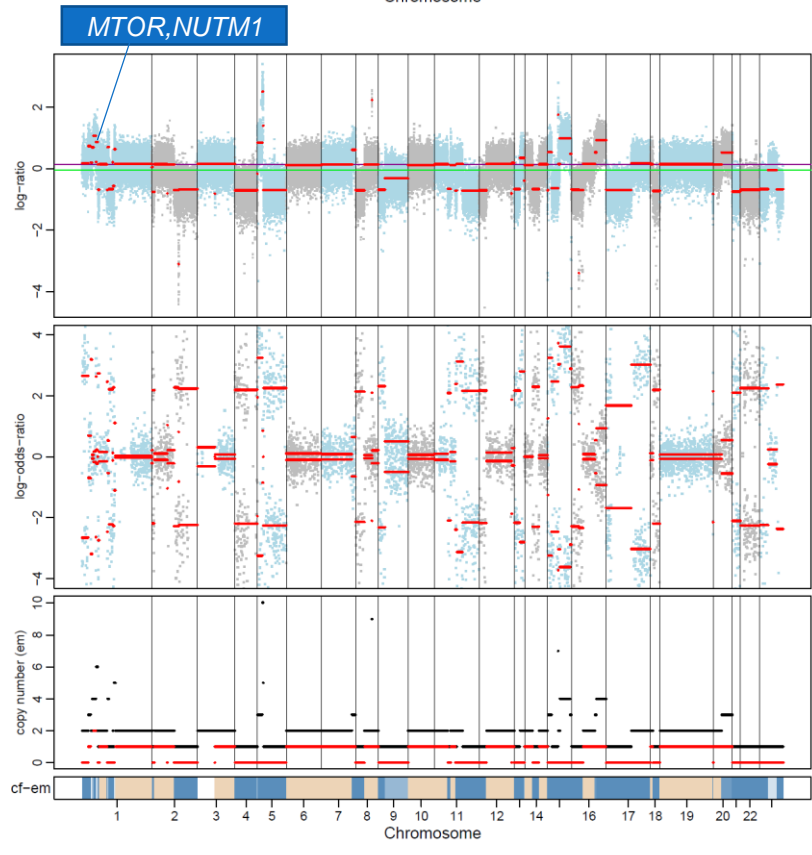
197-185-P



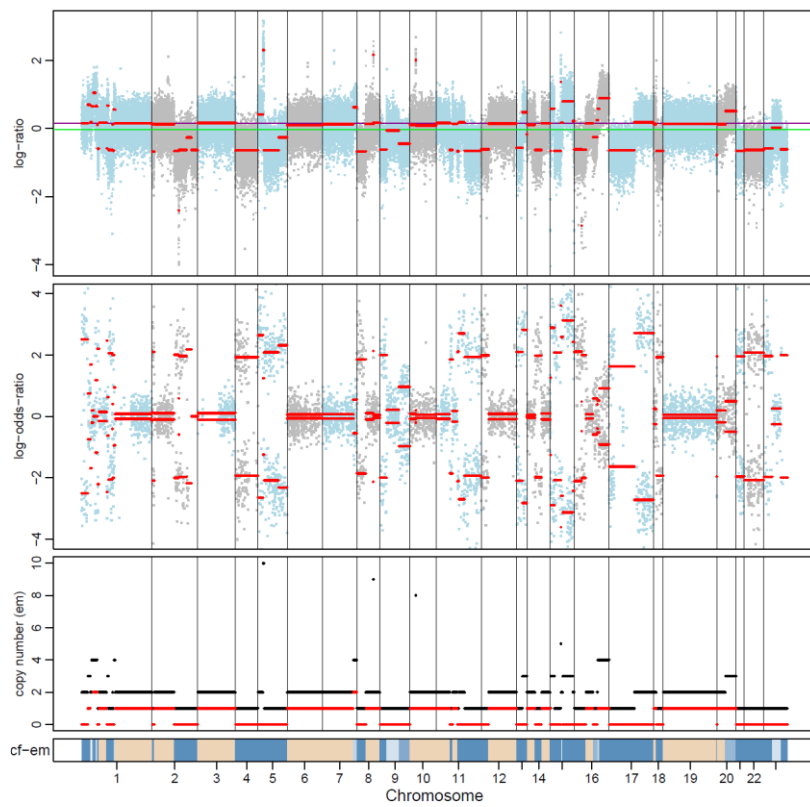
197-185-M



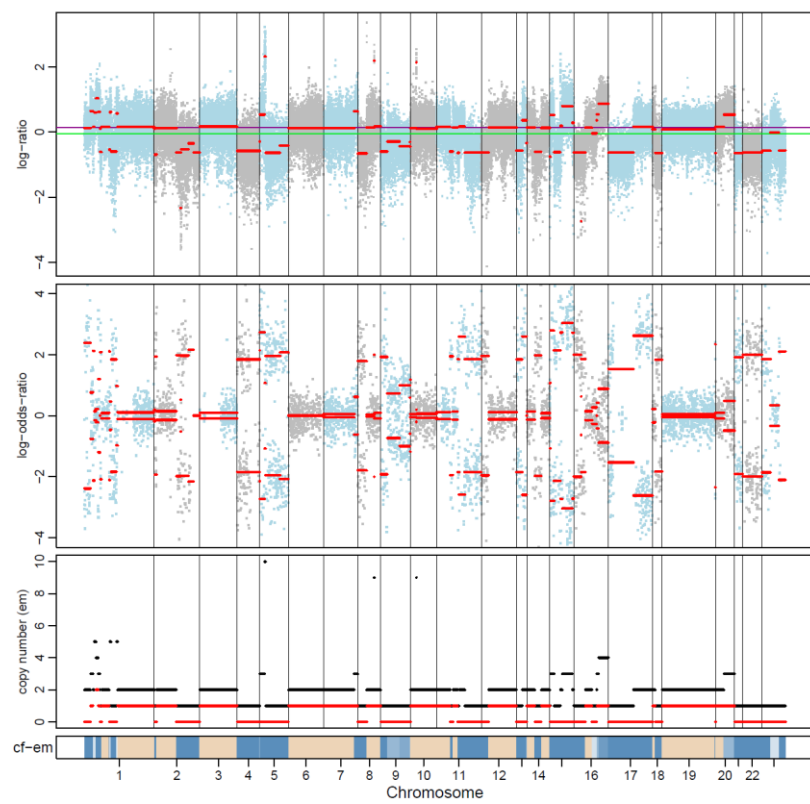
306-052-P



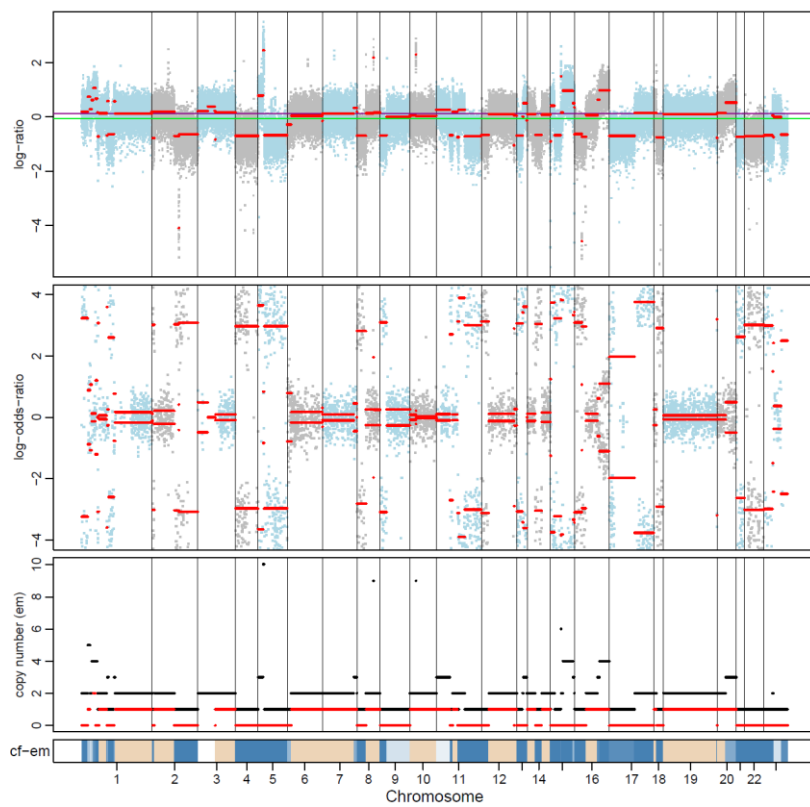
306-052-P1



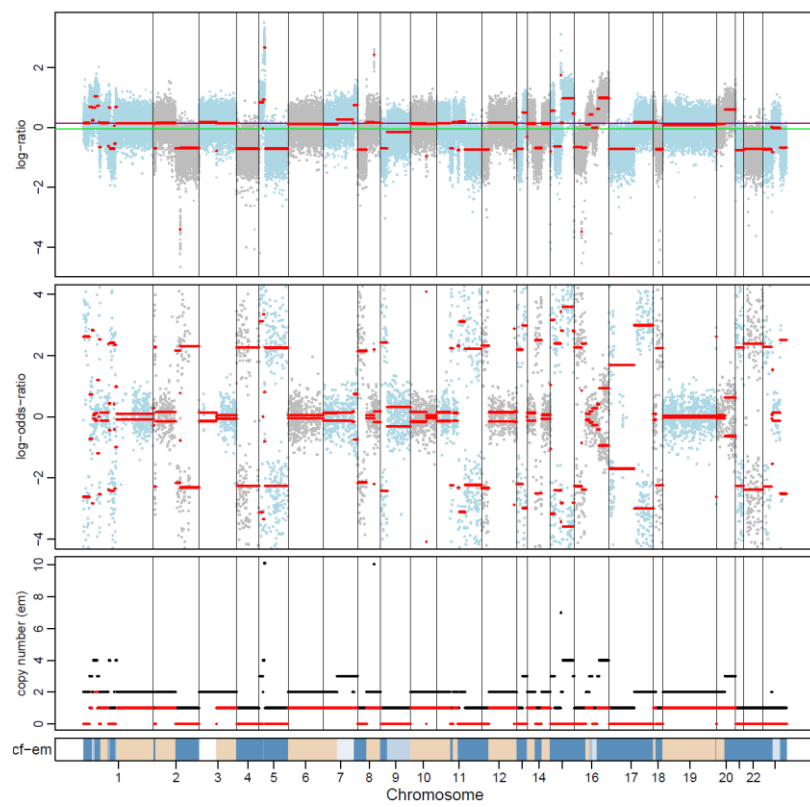
306-052-P2



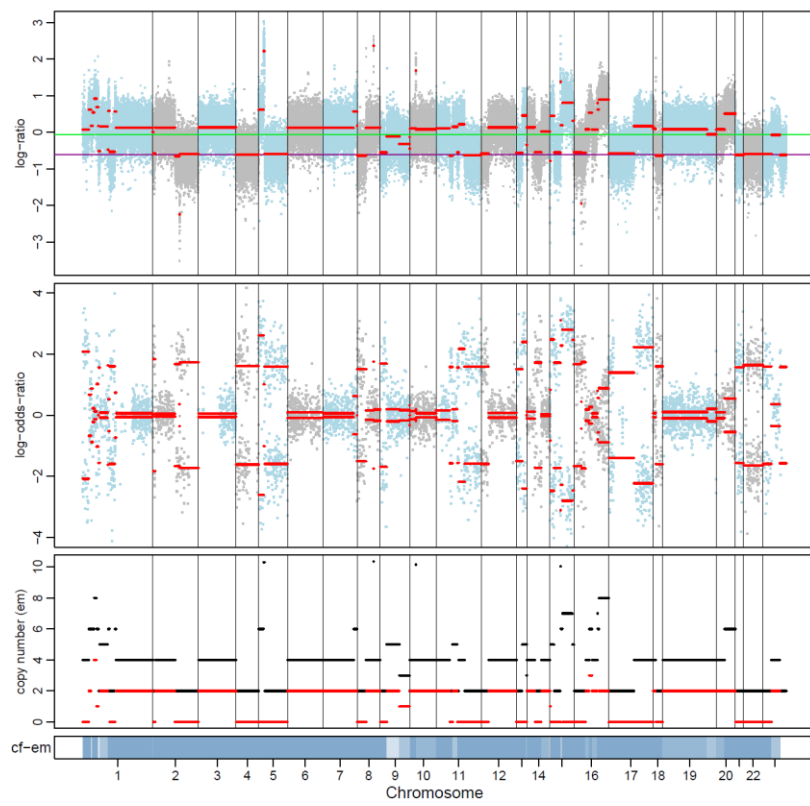
306-052-P3



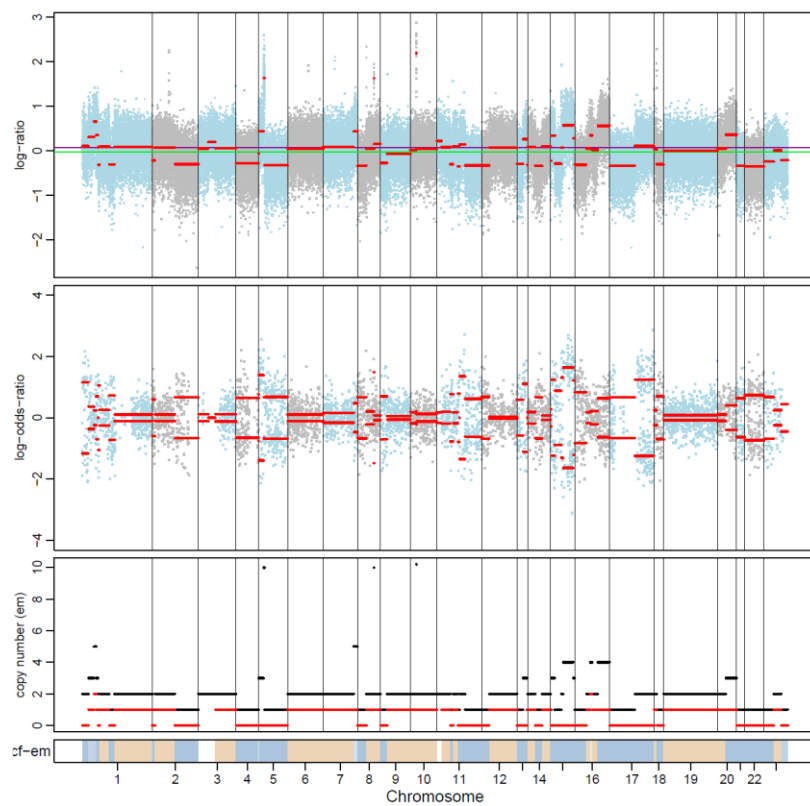
306-052-M



306-052-M1

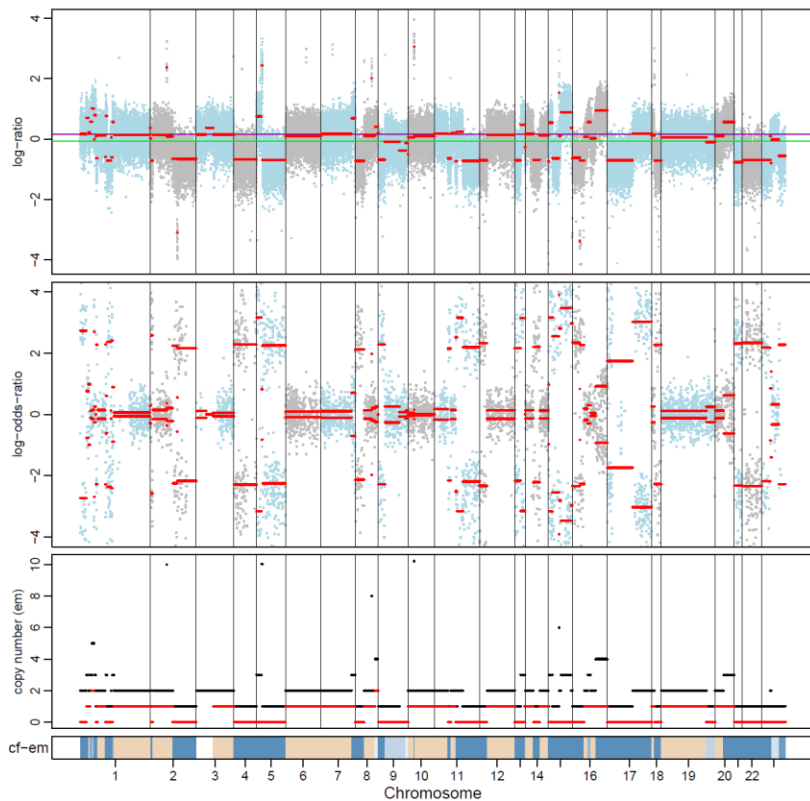


306-052-M2

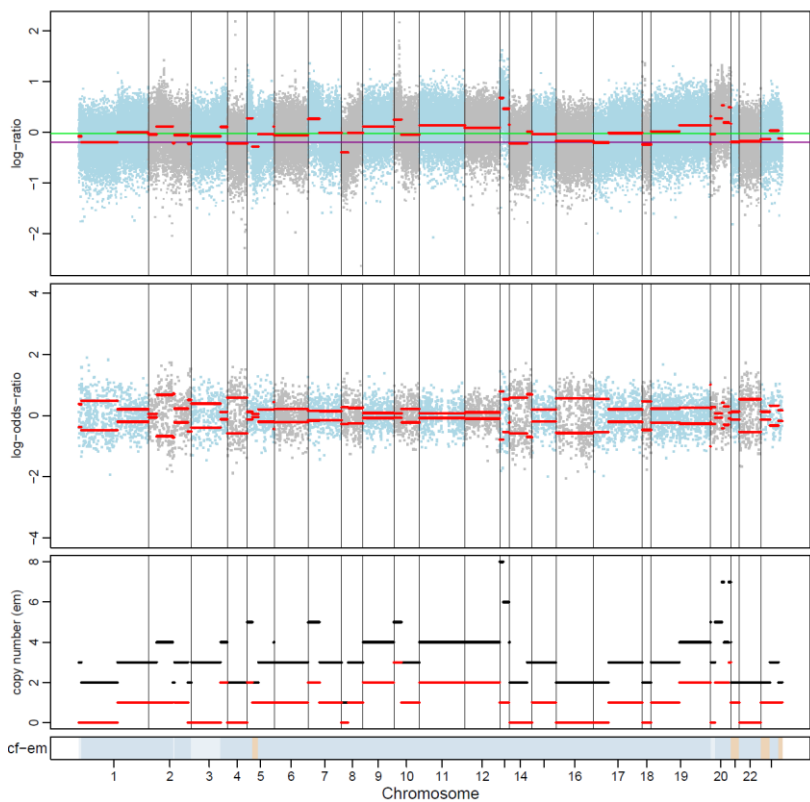




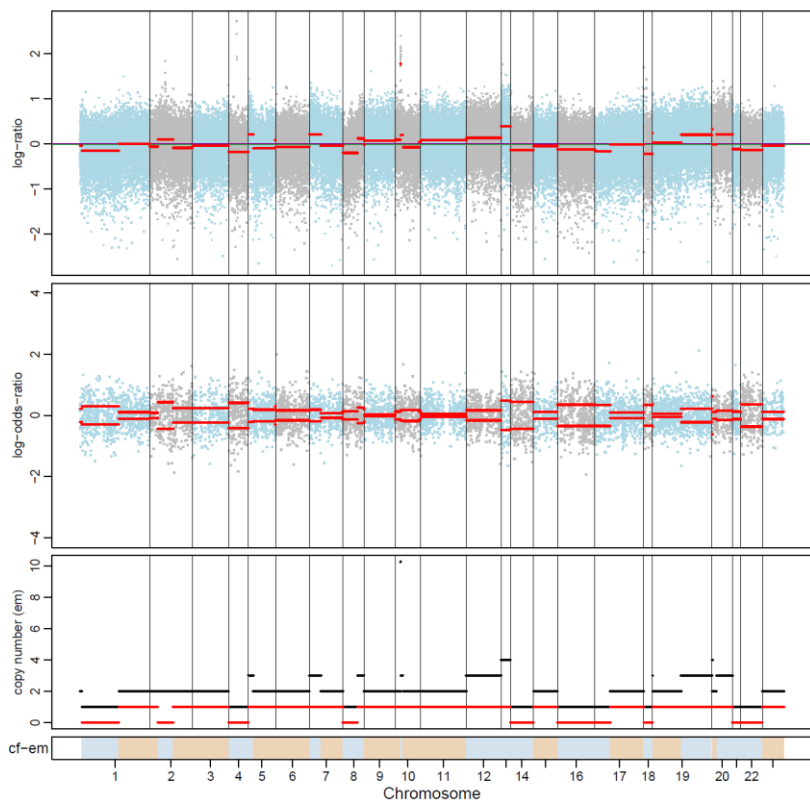
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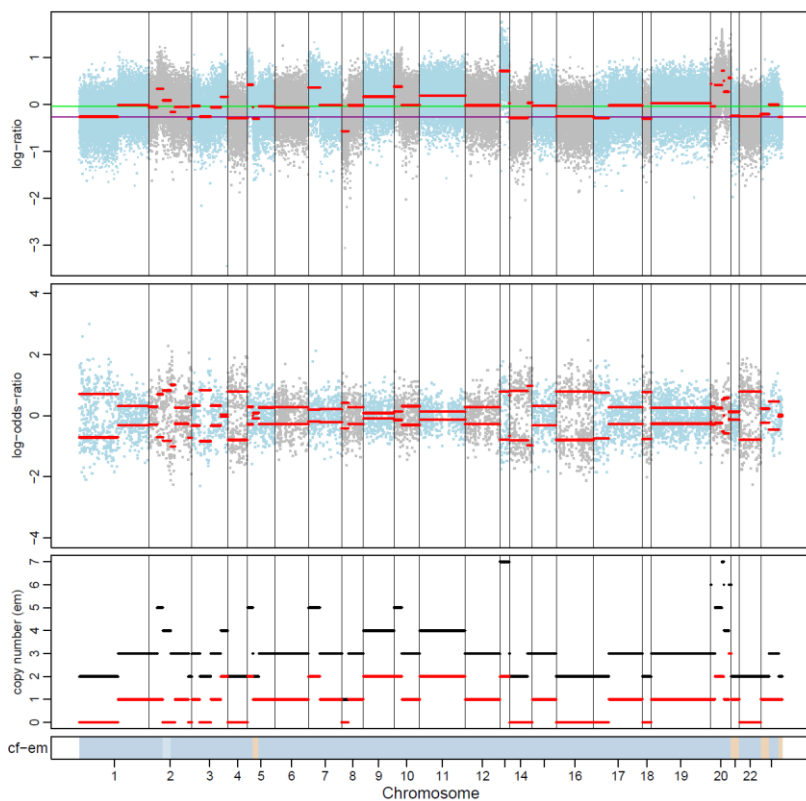
306-090-P1



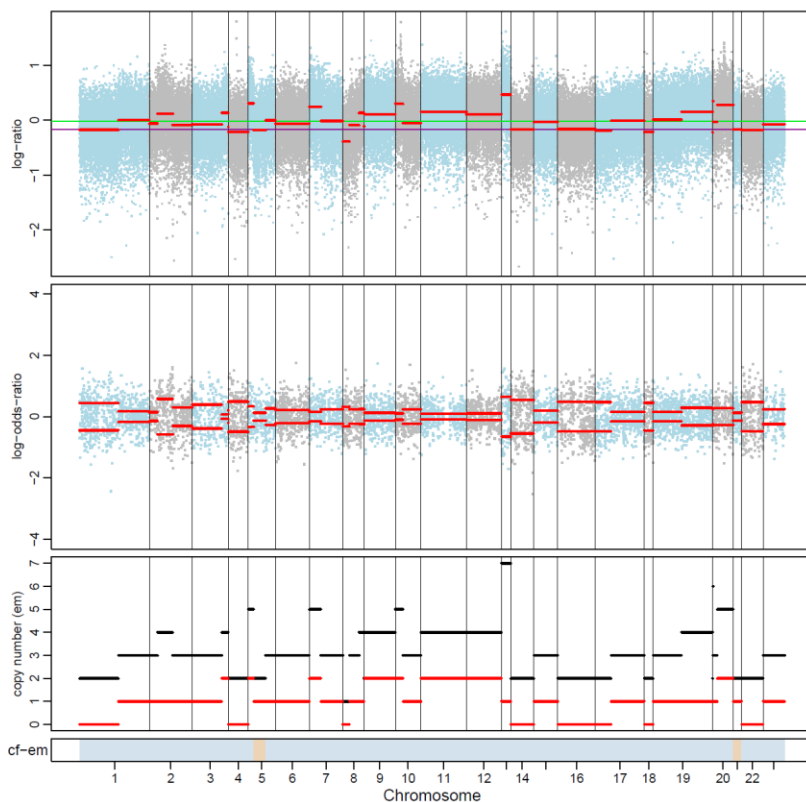
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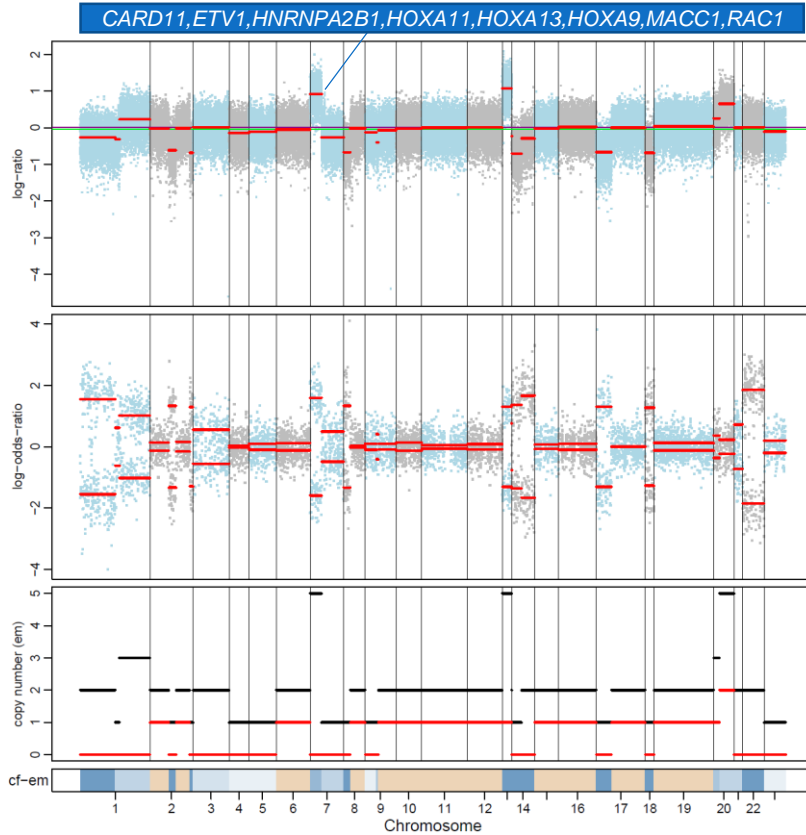
306-090-P



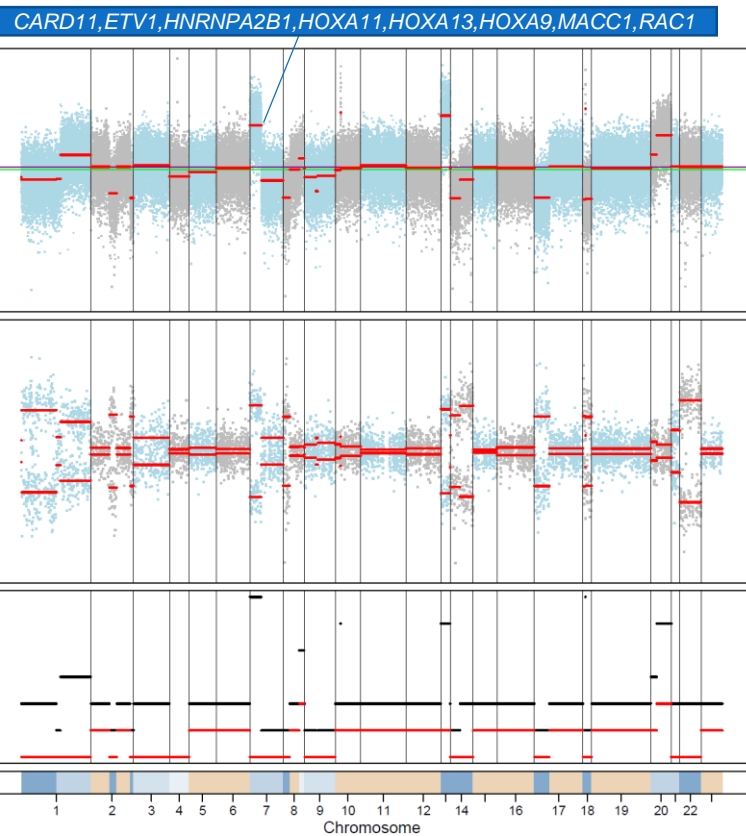
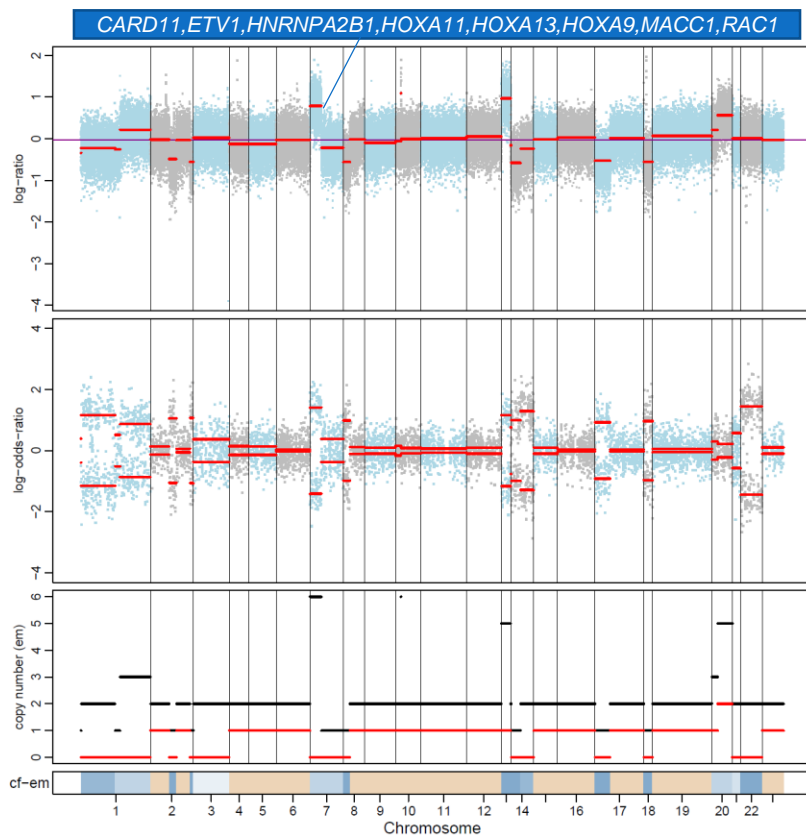
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306-090-M

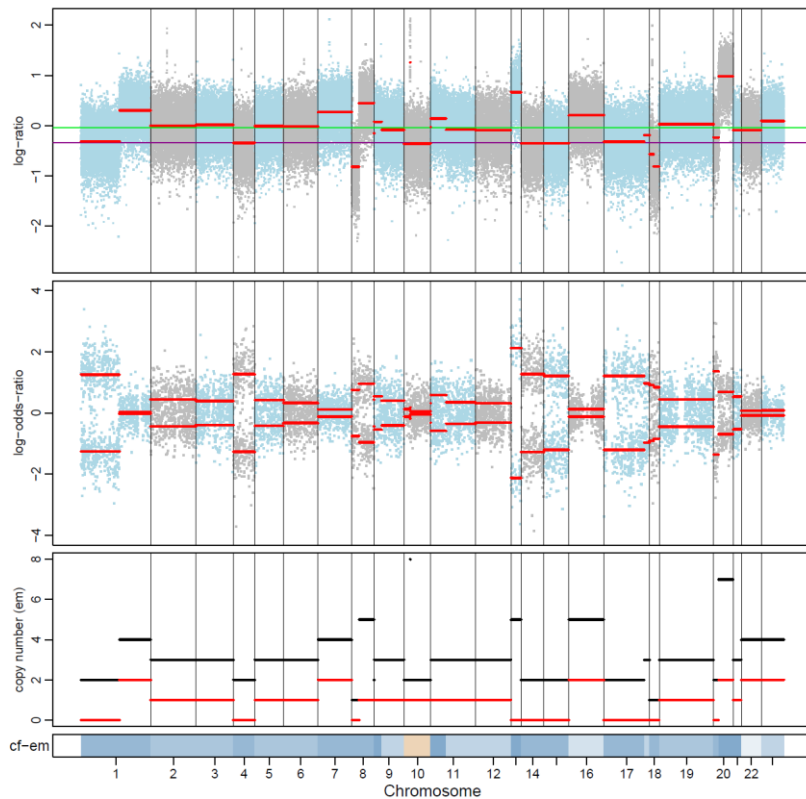
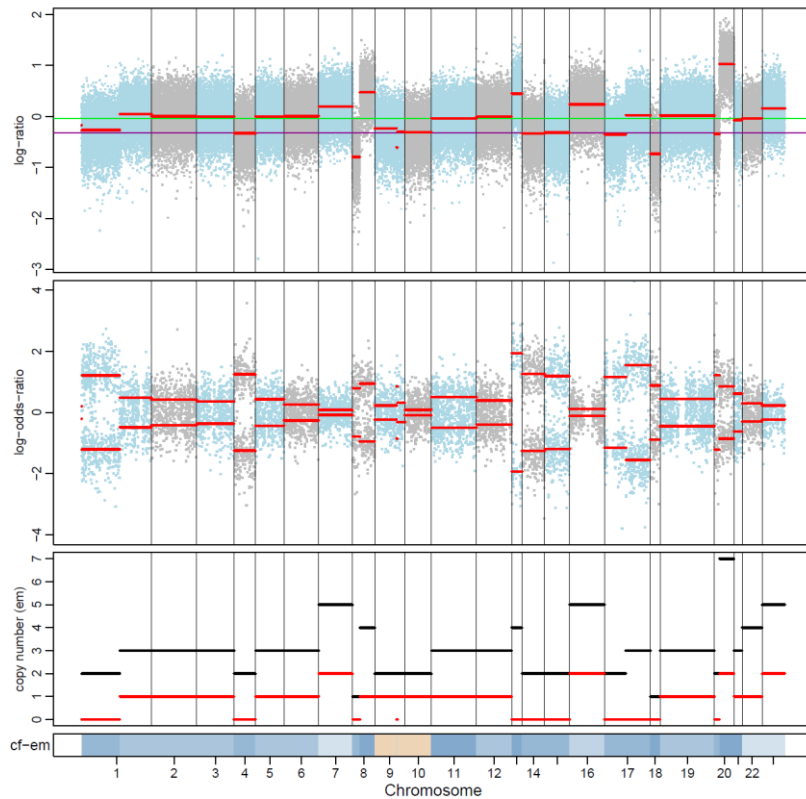


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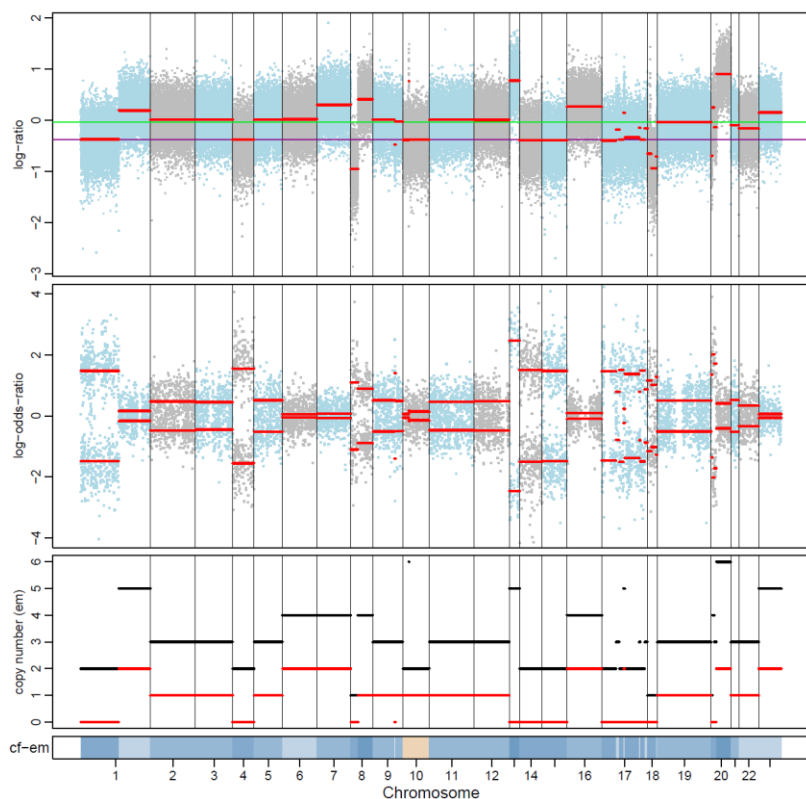
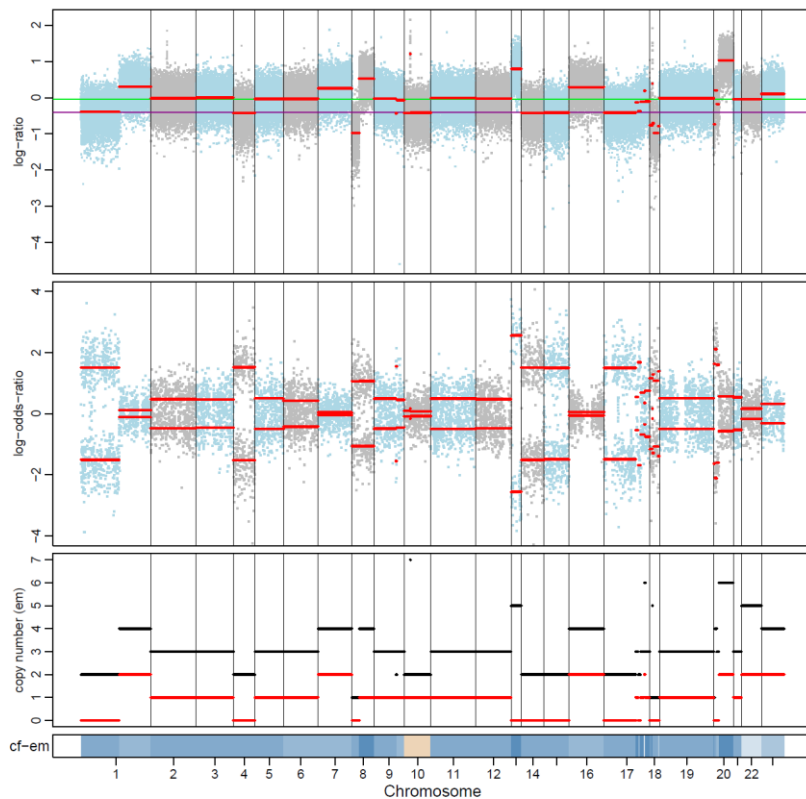
306-090-M2

306-165-P



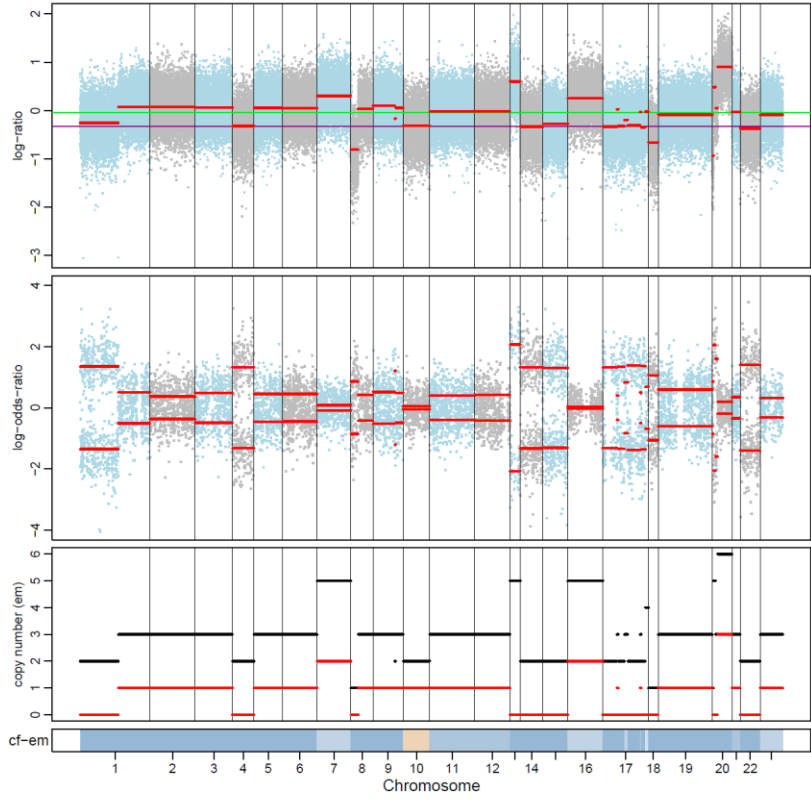
306-165-P1

306-165-P2

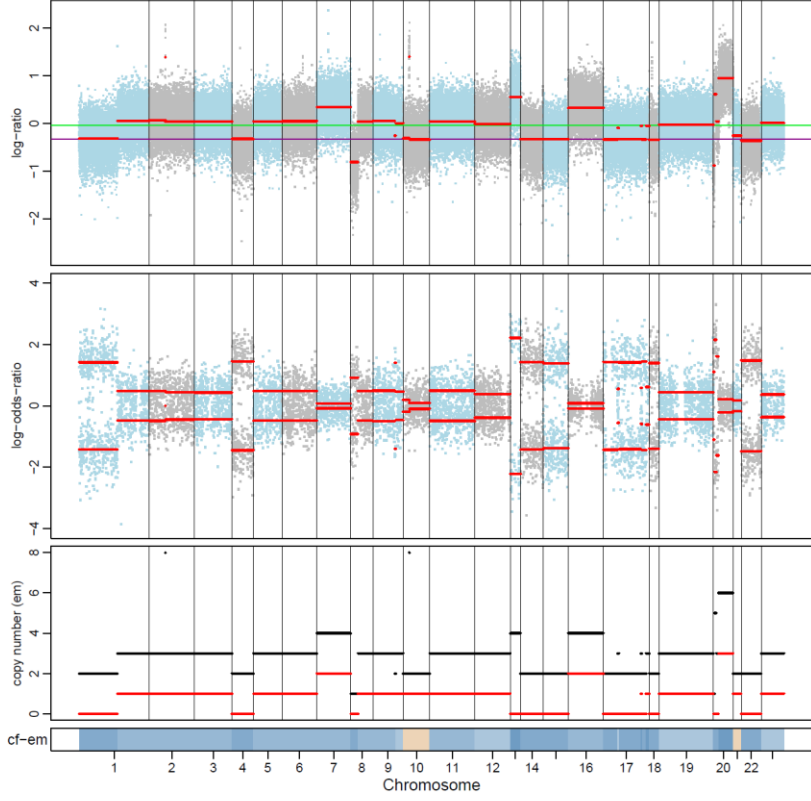


306-165-P3

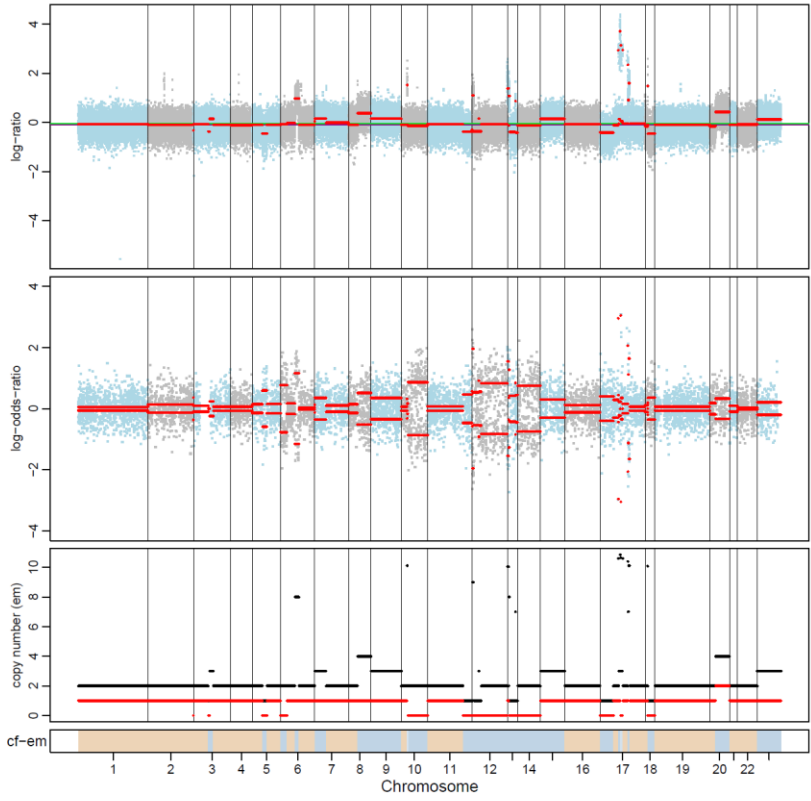
306-165-M



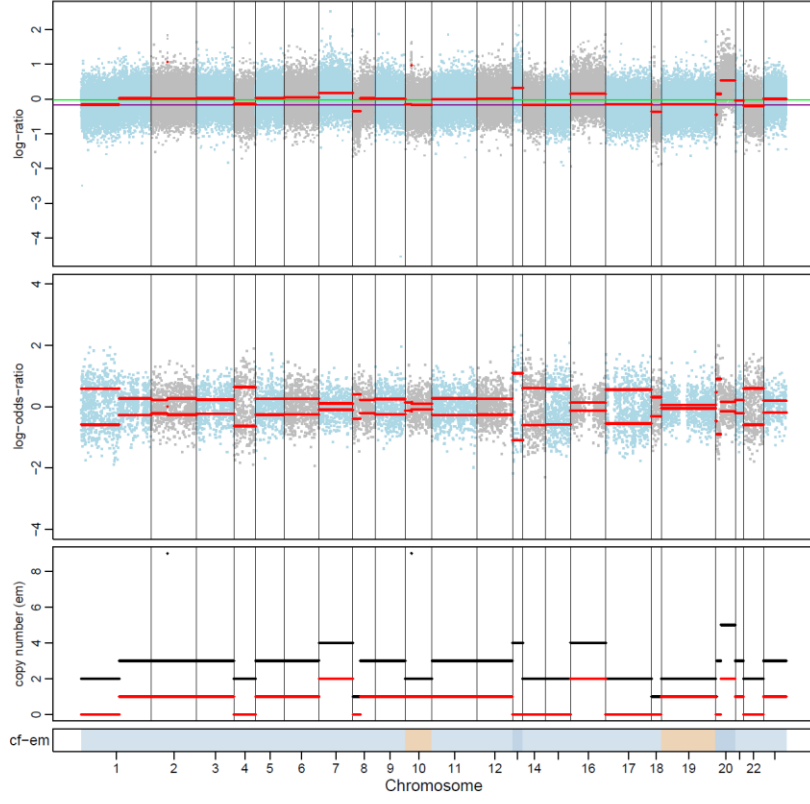
306-165-M2



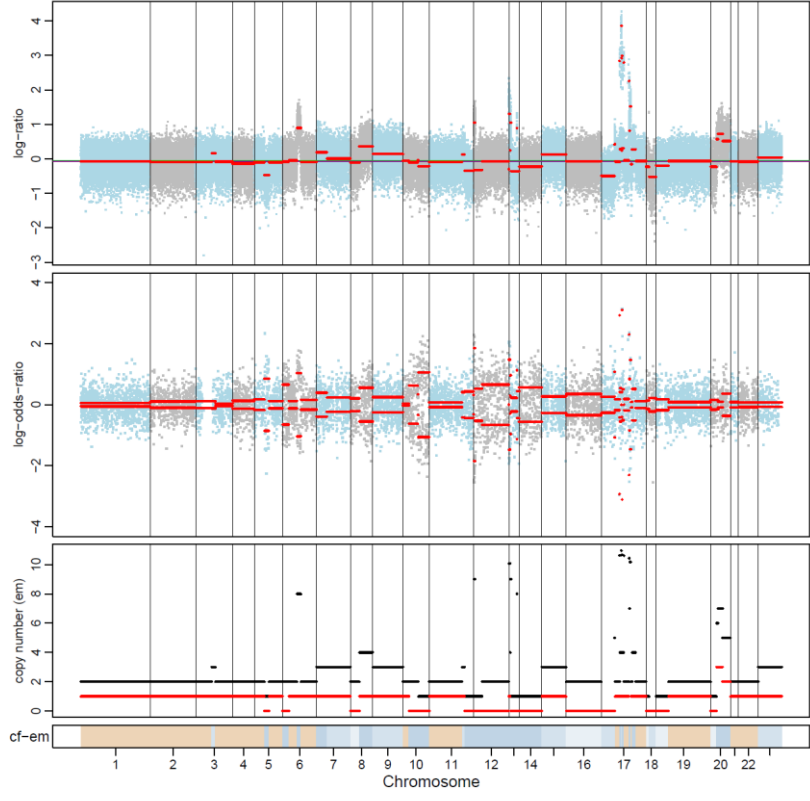
306-171-P1



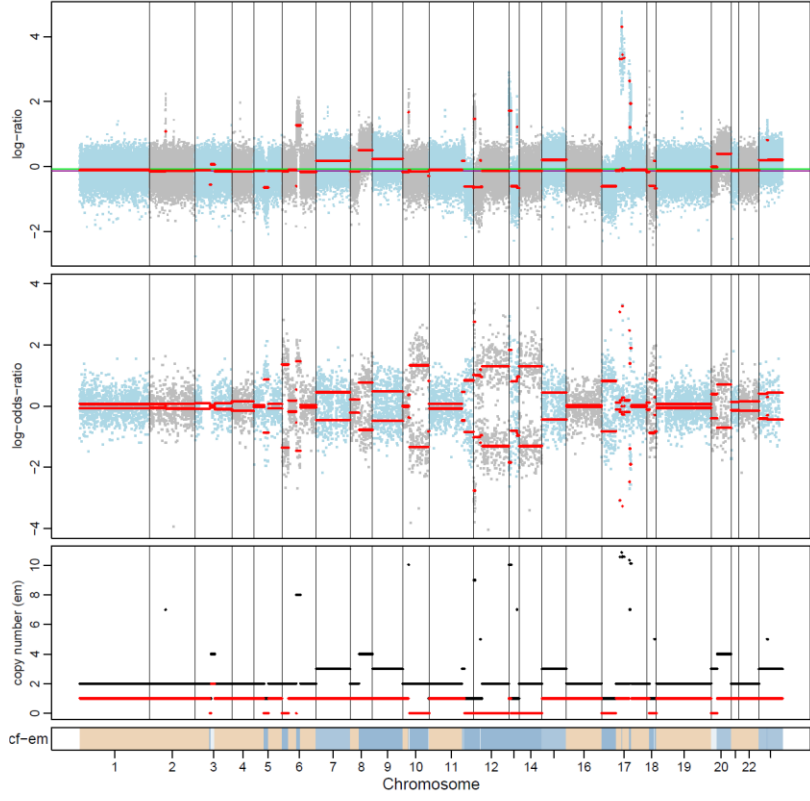
306-165-M1



306-171-P

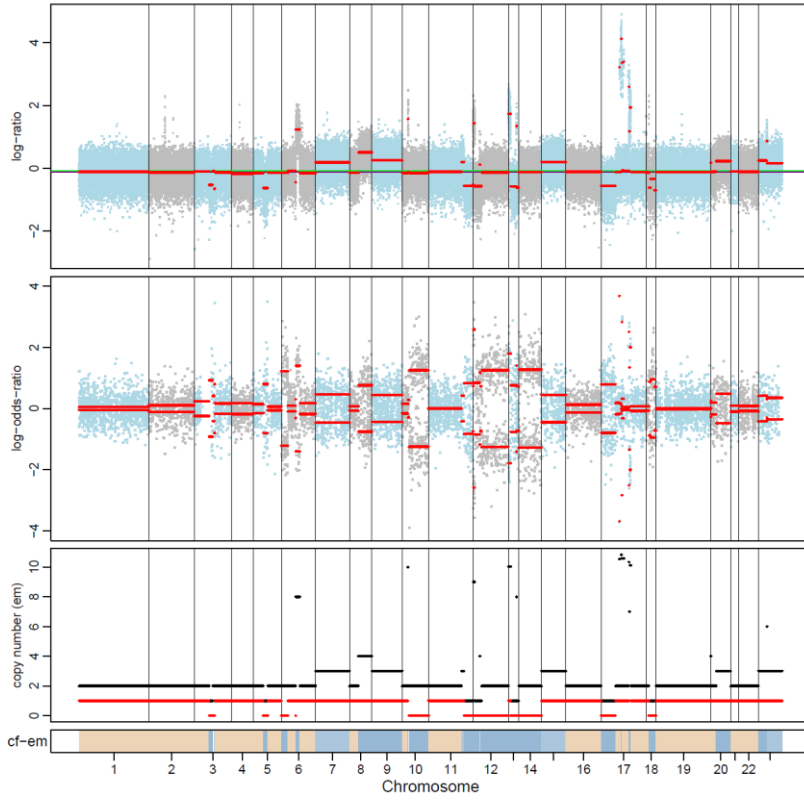


306-171-P2

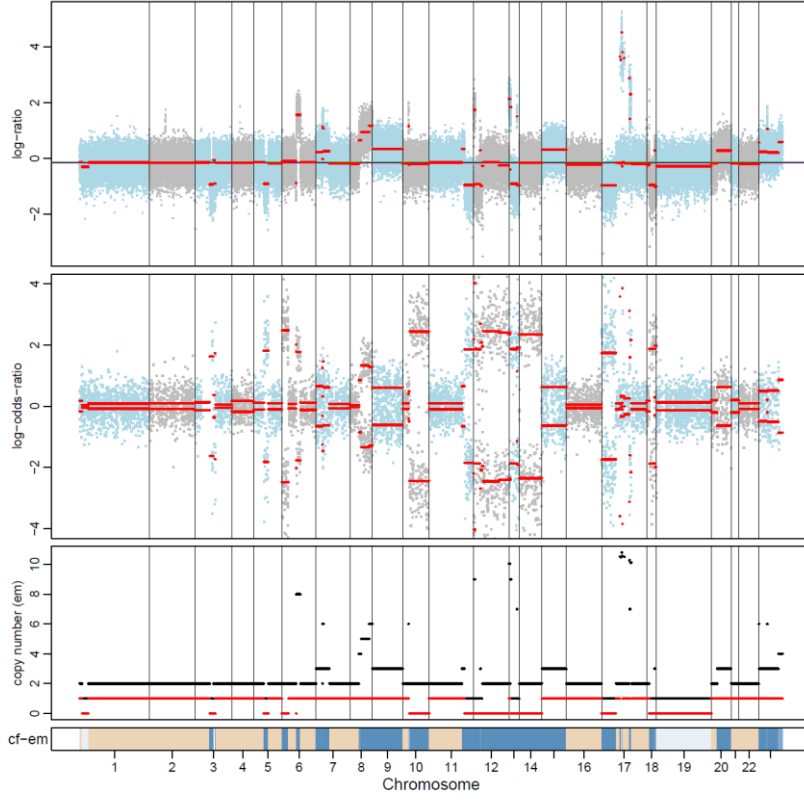




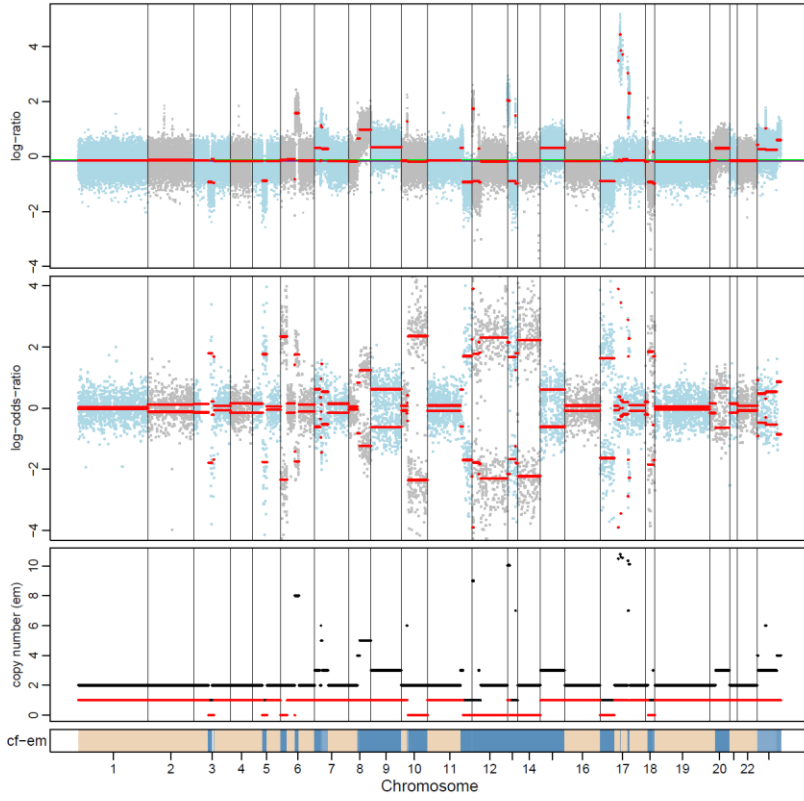
306-171-P3



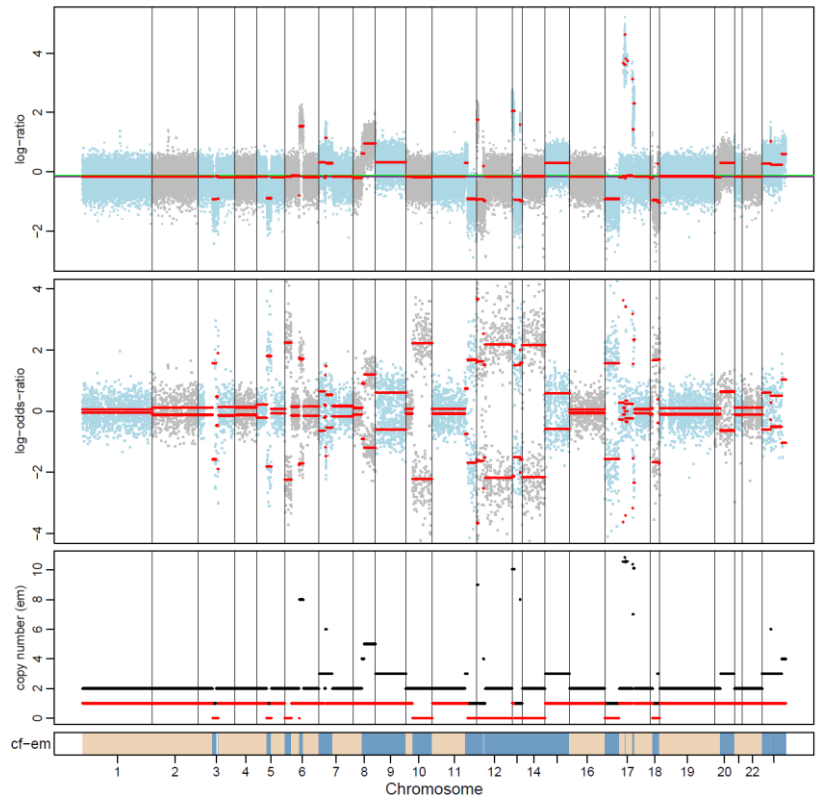
306-171-M1



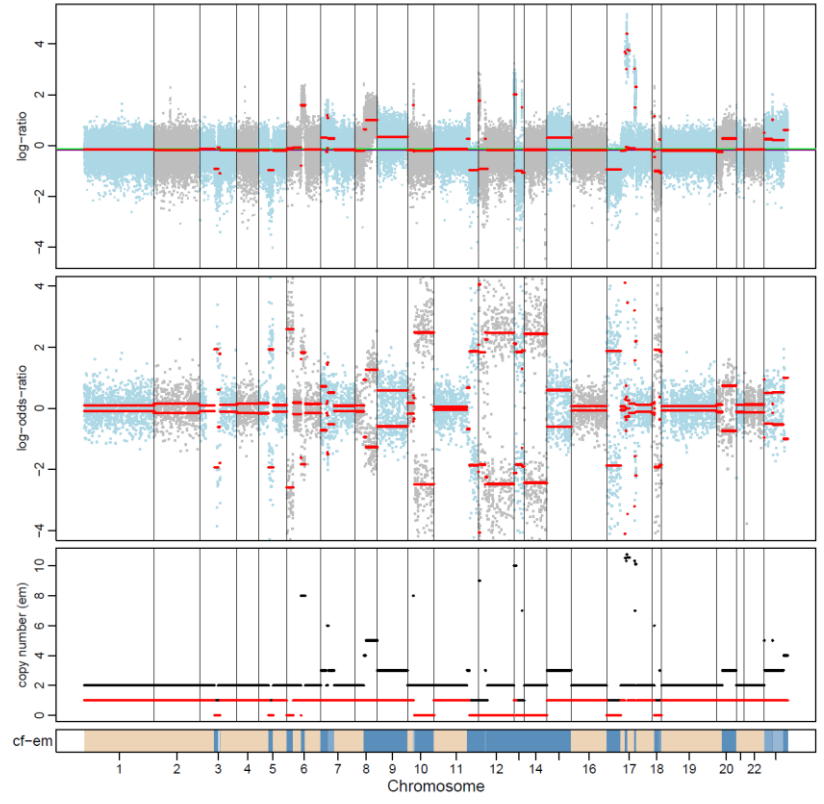
306-171-M3



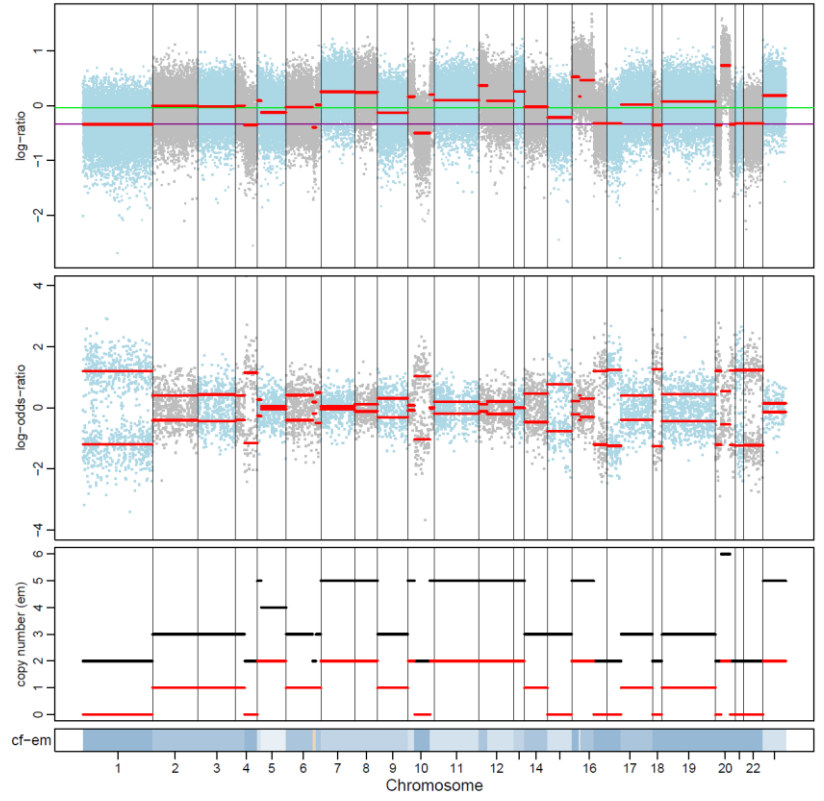
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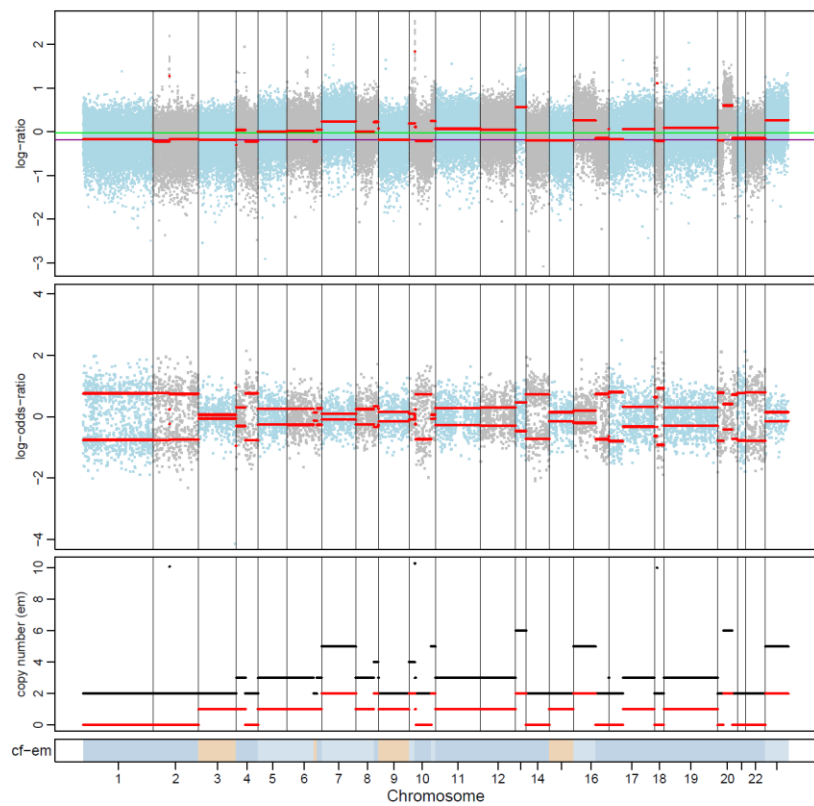
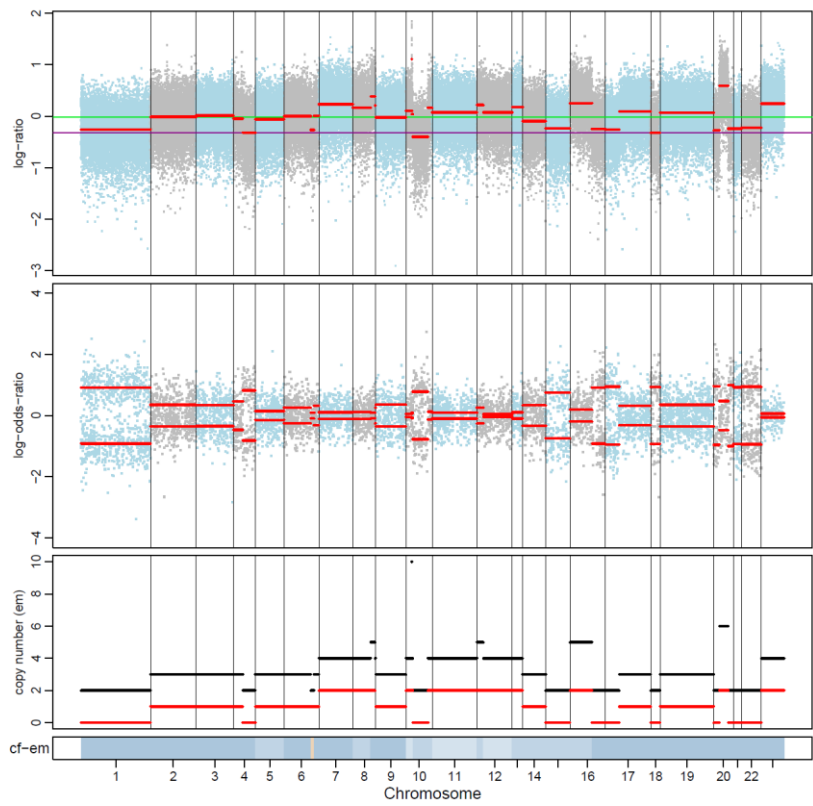
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306-212-P

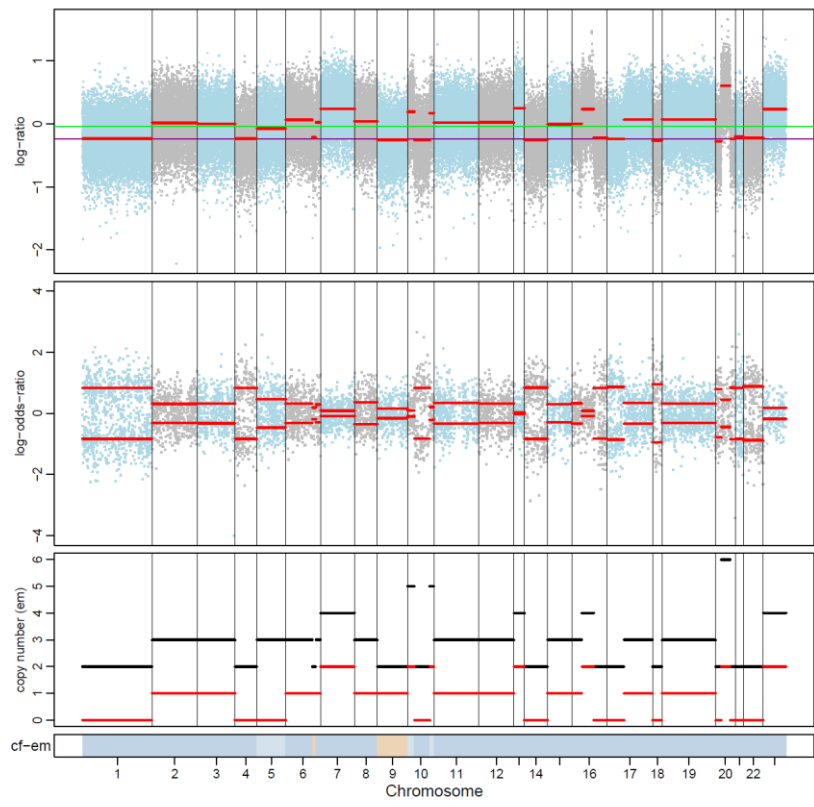
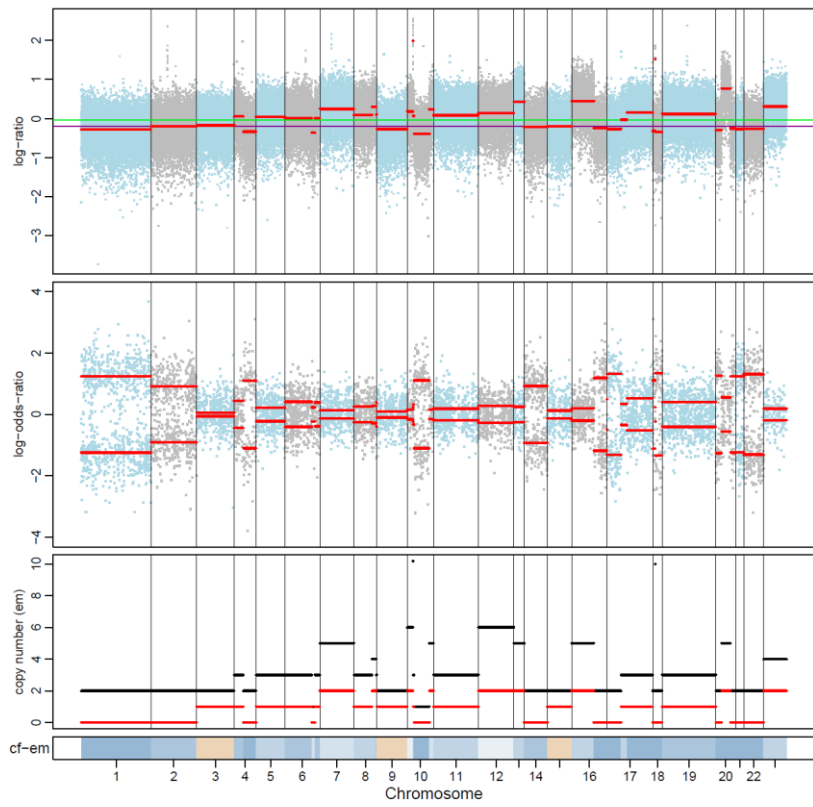


306-212-P1



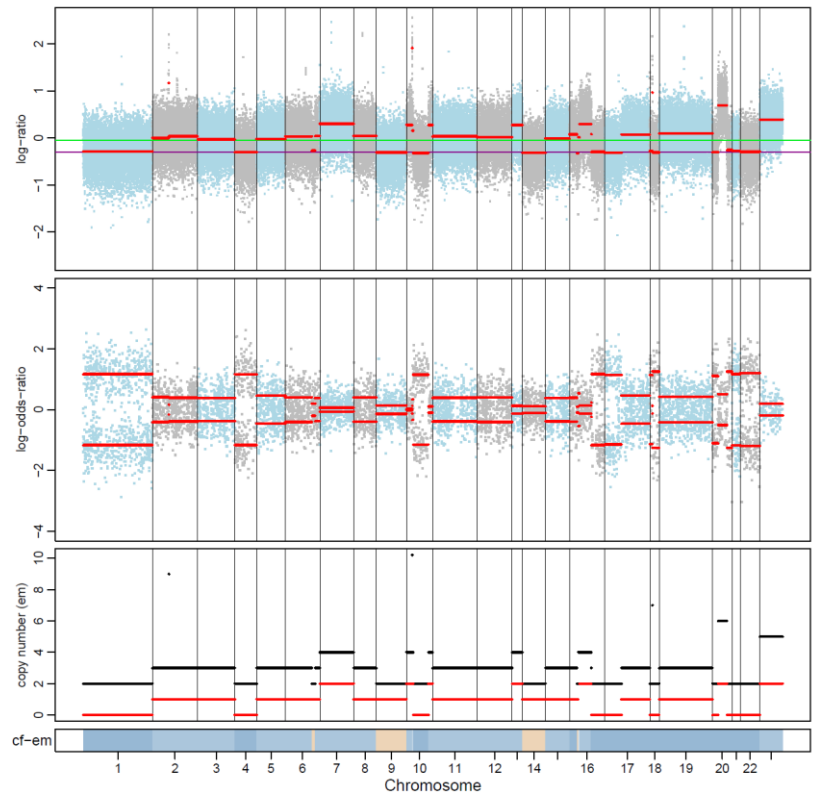
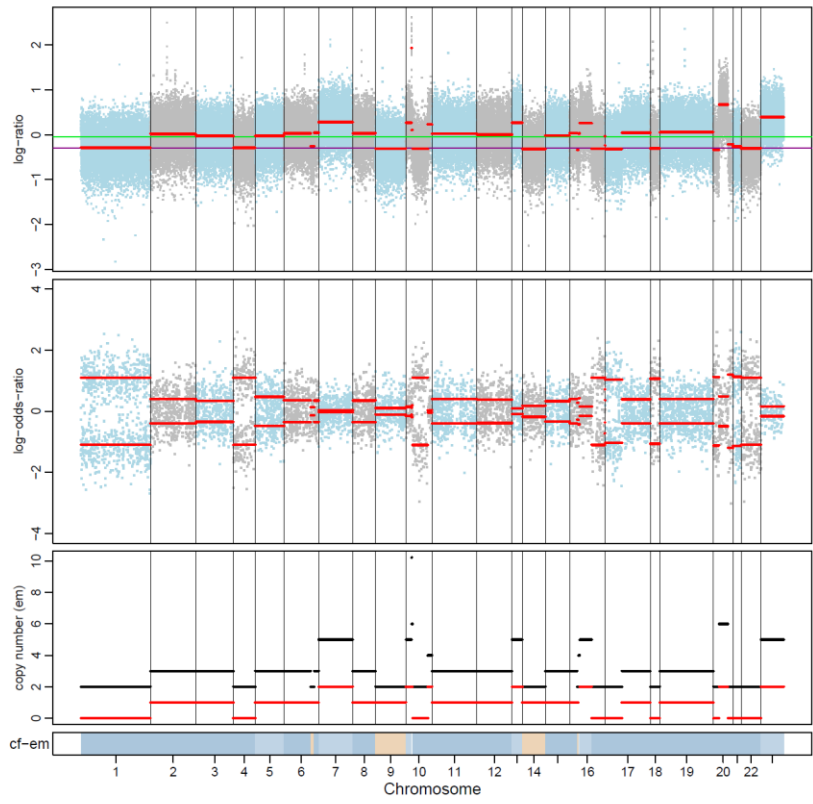
306-212-P2

306-212-P3



306-212-M

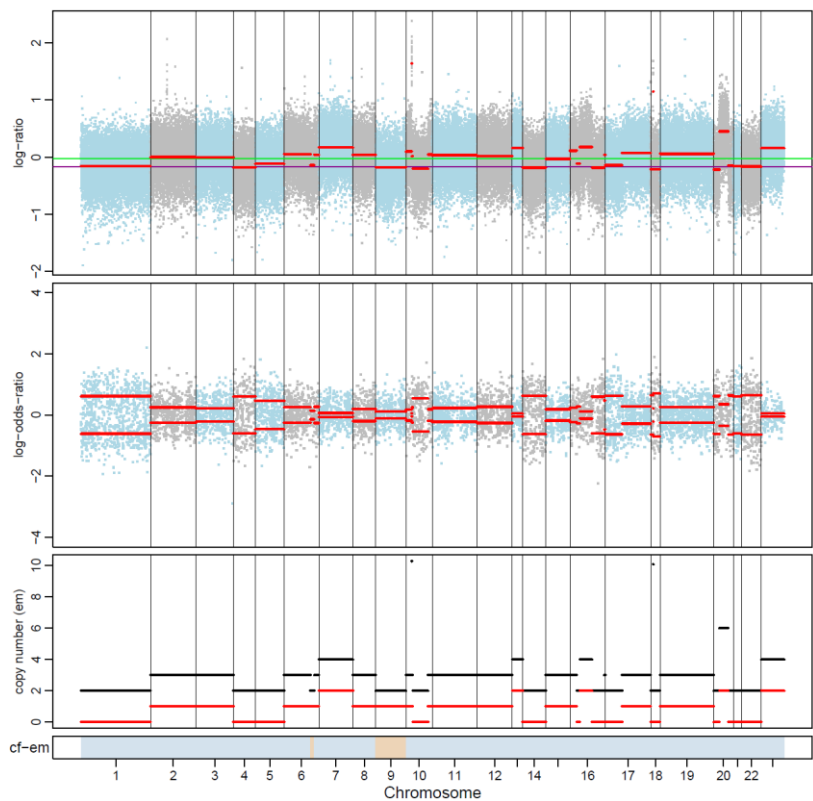
306-212-M1



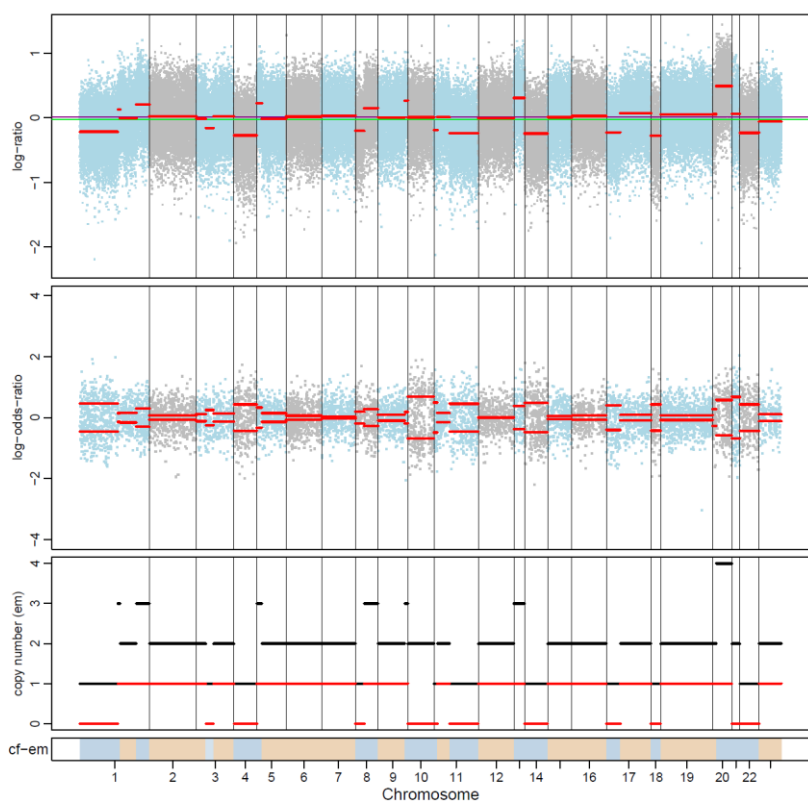
306-212-M2



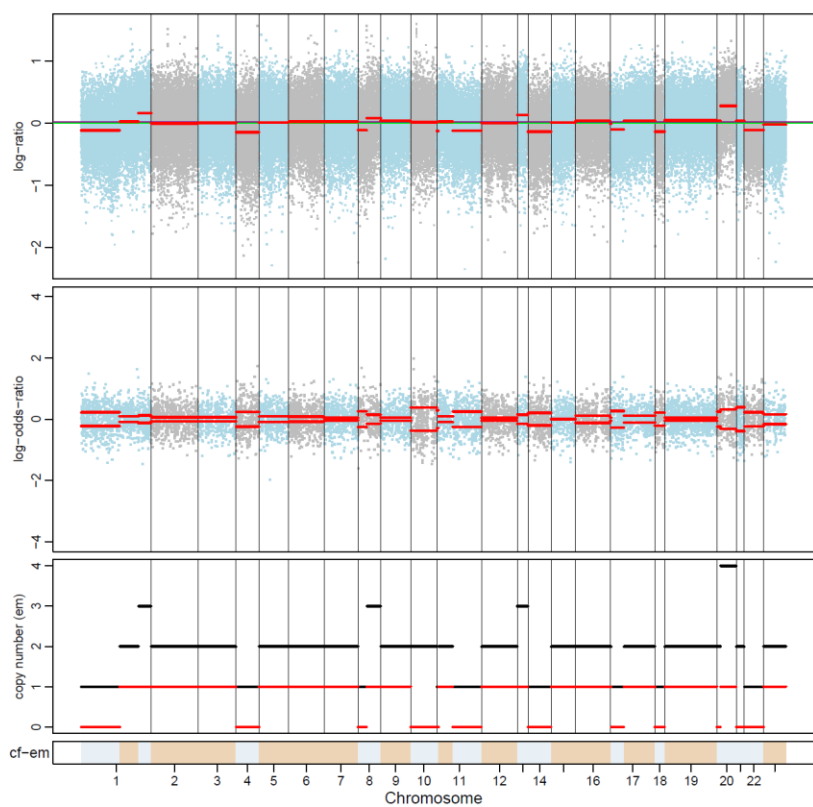
306-212-M3



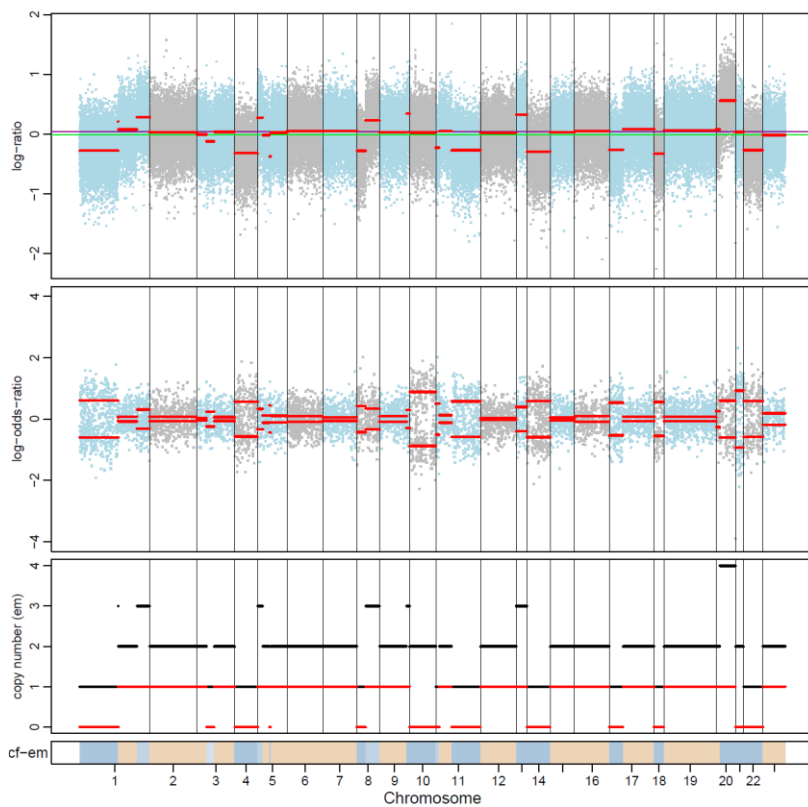
306-214-P



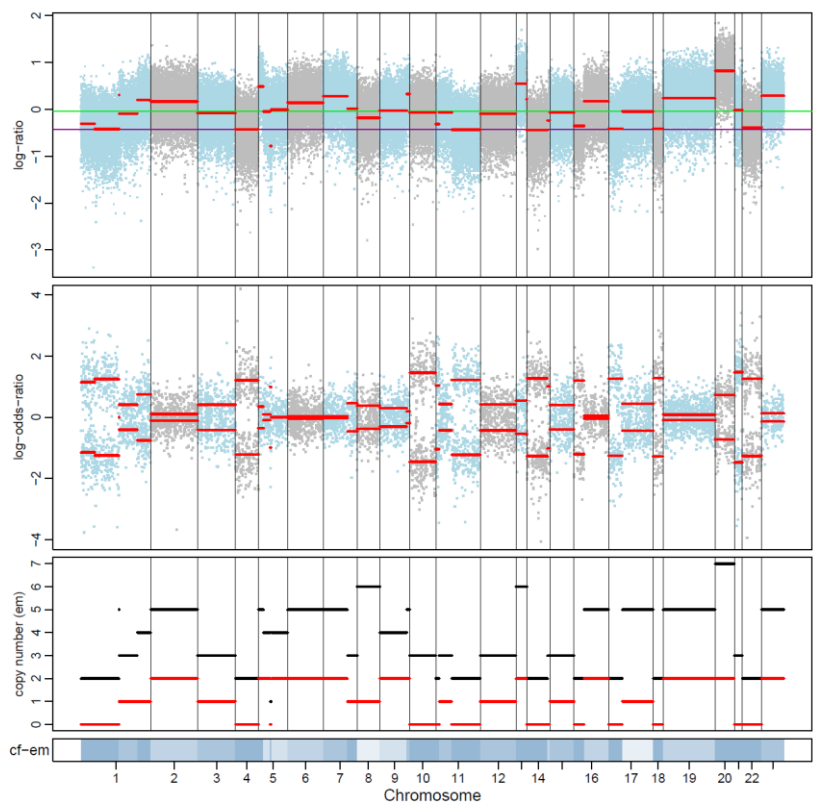
306-214-P1



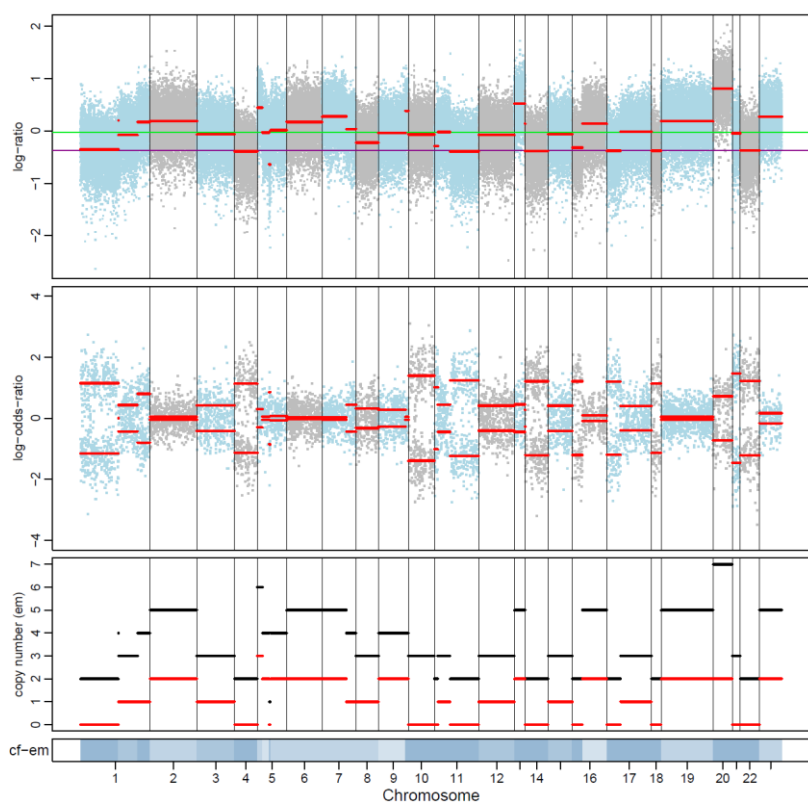
306-214-P2



306-214-M

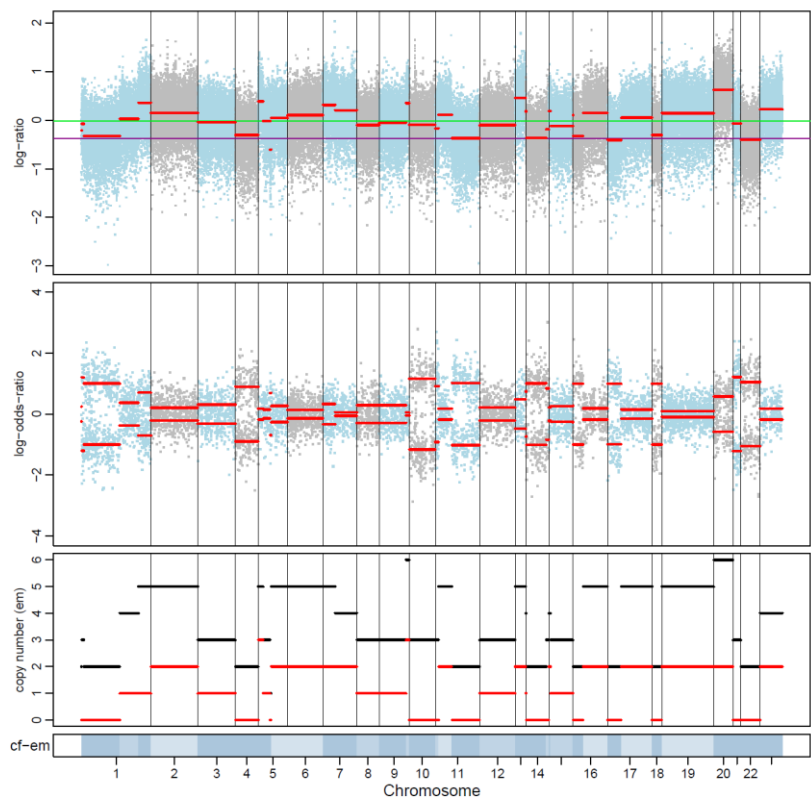


306-214-M1

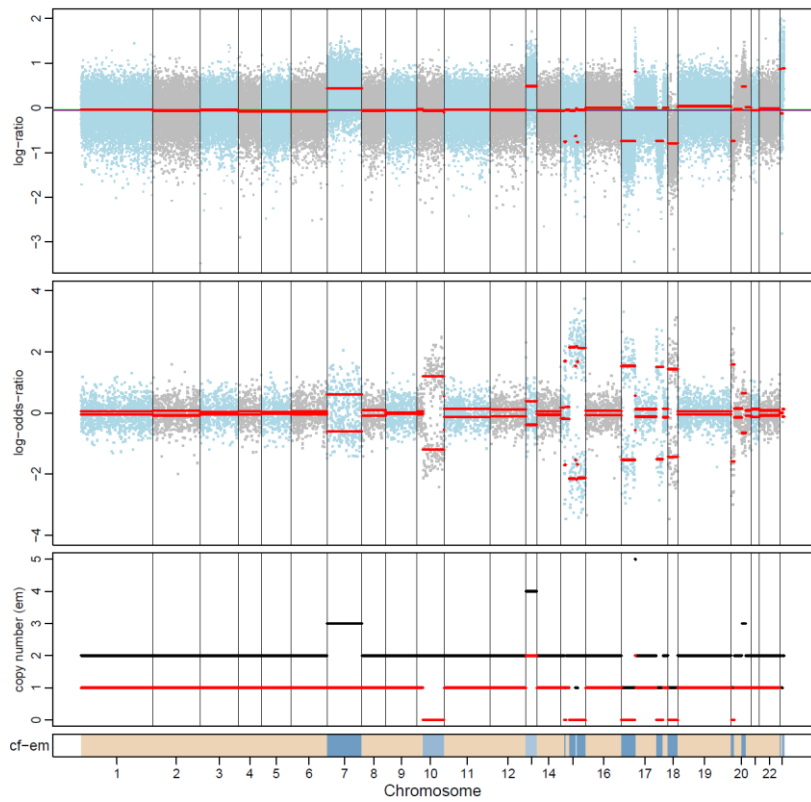




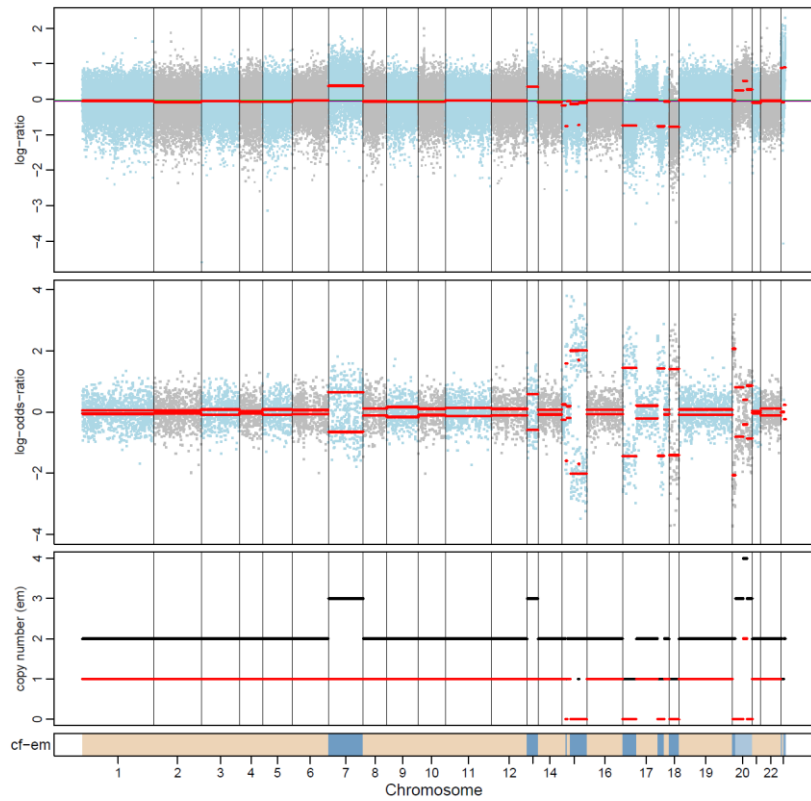
306-214-M2



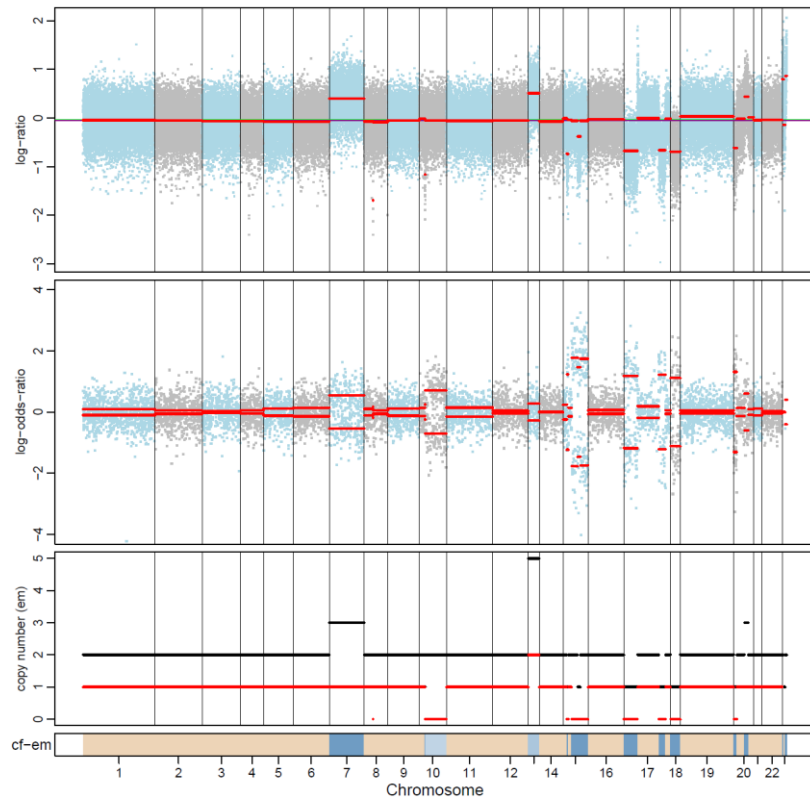
306-253-P1



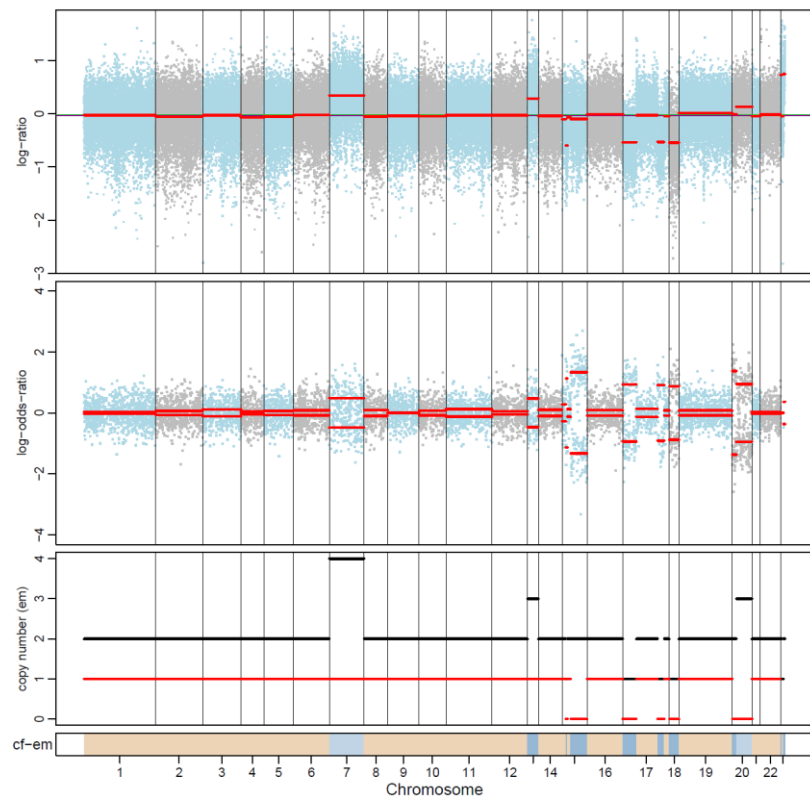
306-253-P3



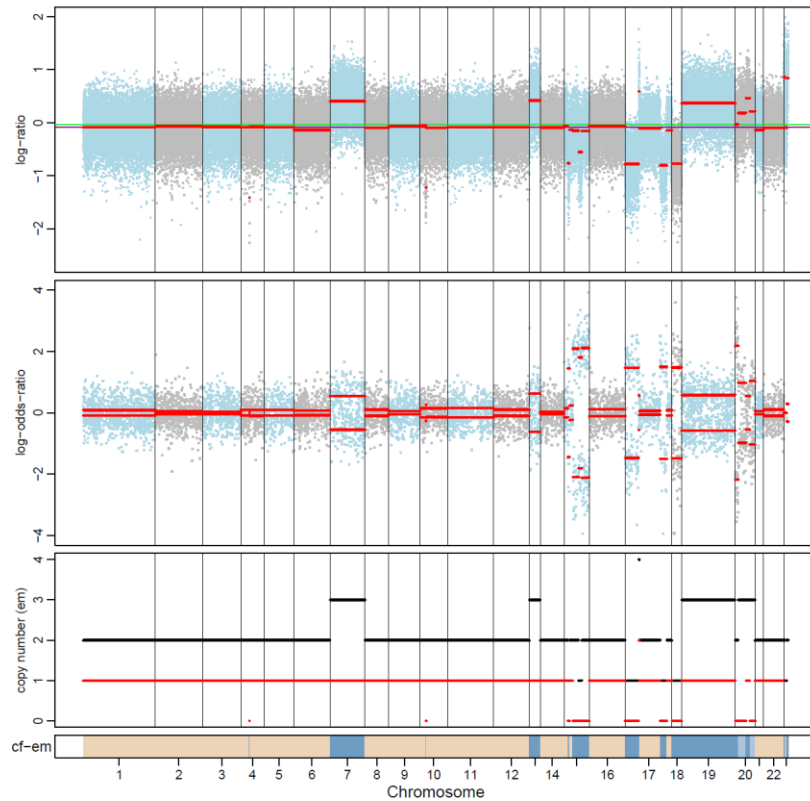
306-253-P



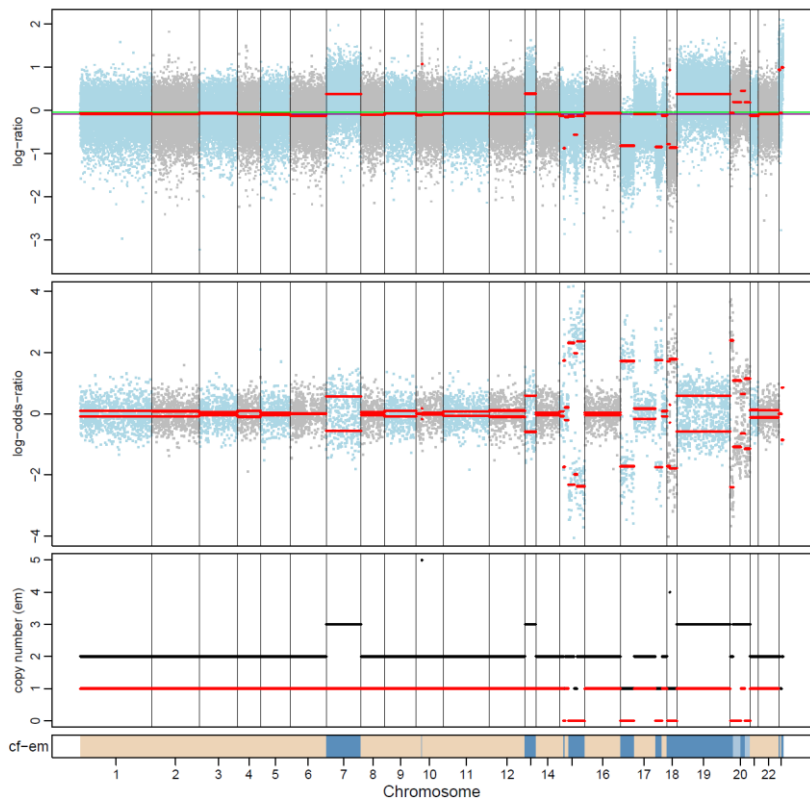
306-253-P2



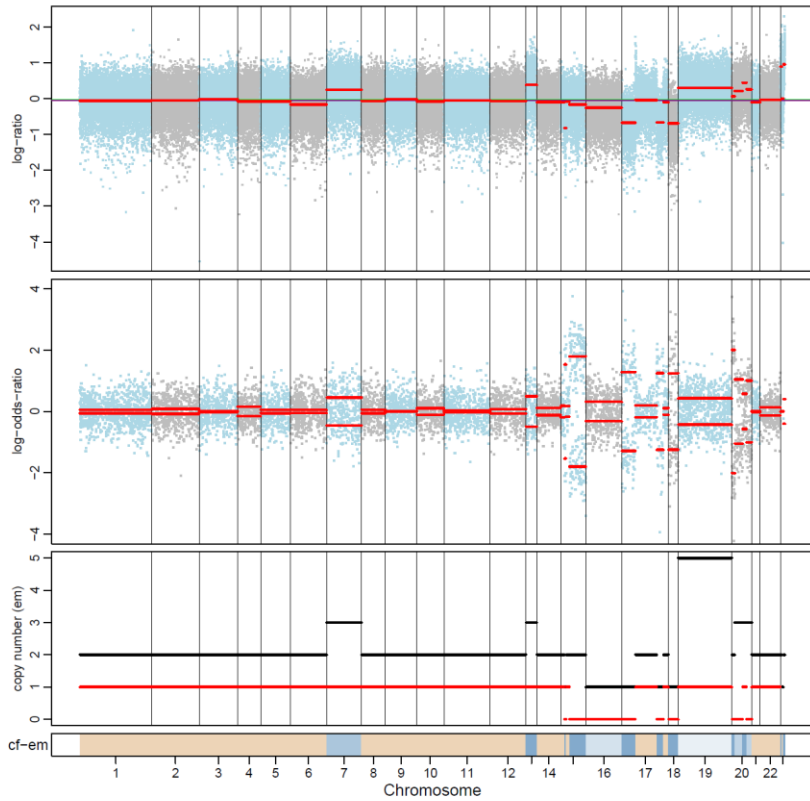
306-253-M



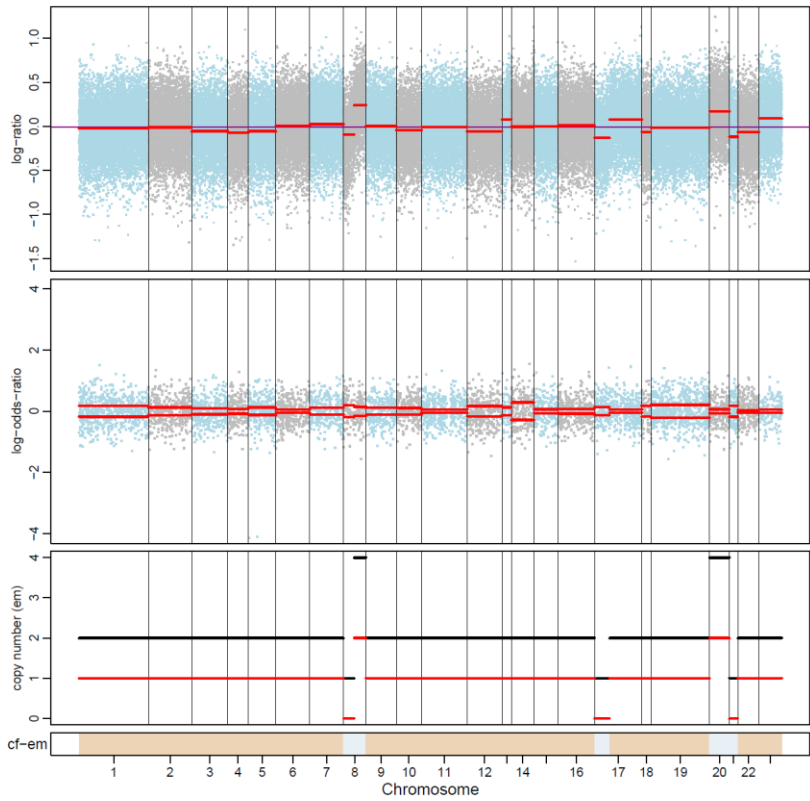
306-253-M1



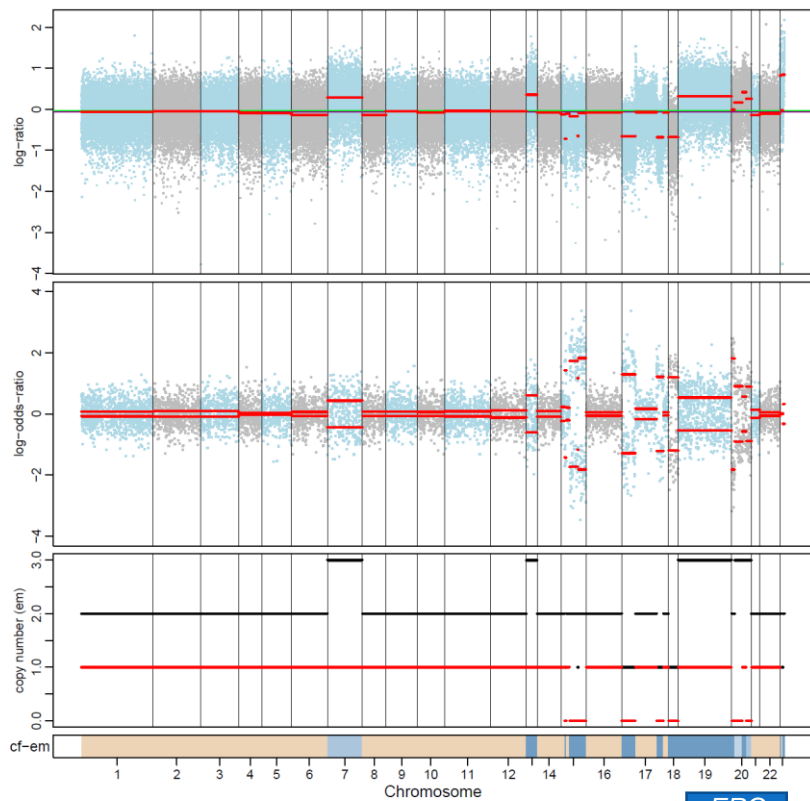
306-253-M3



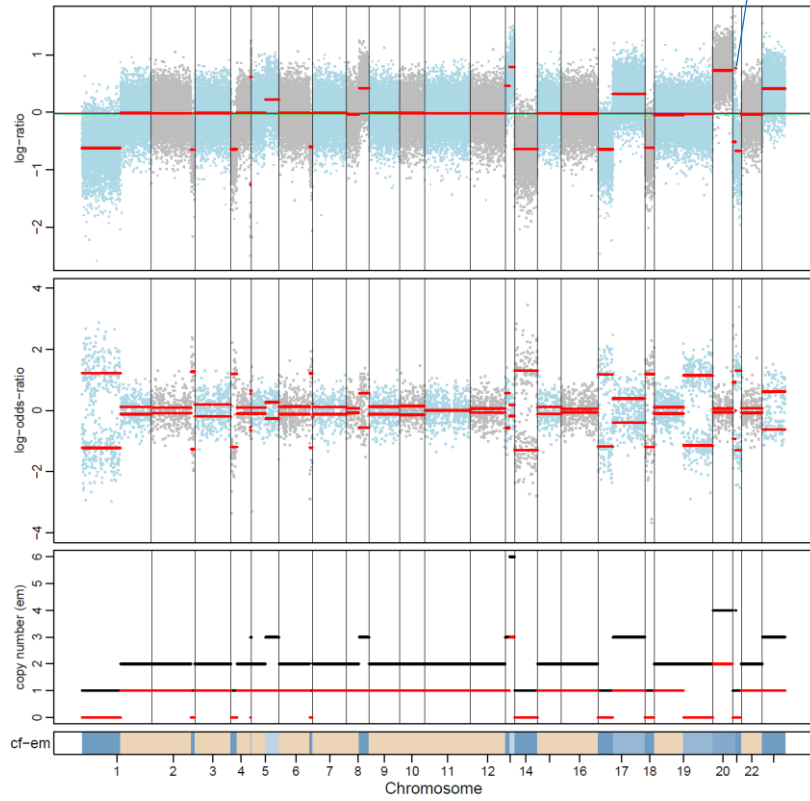
306-285-M



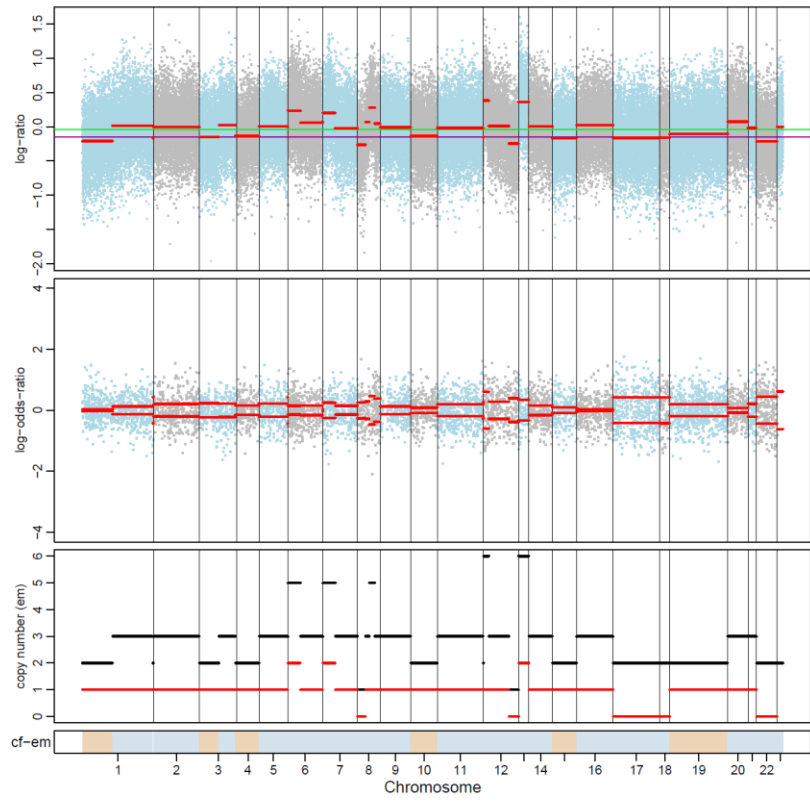
306-253-M2



306-285-P

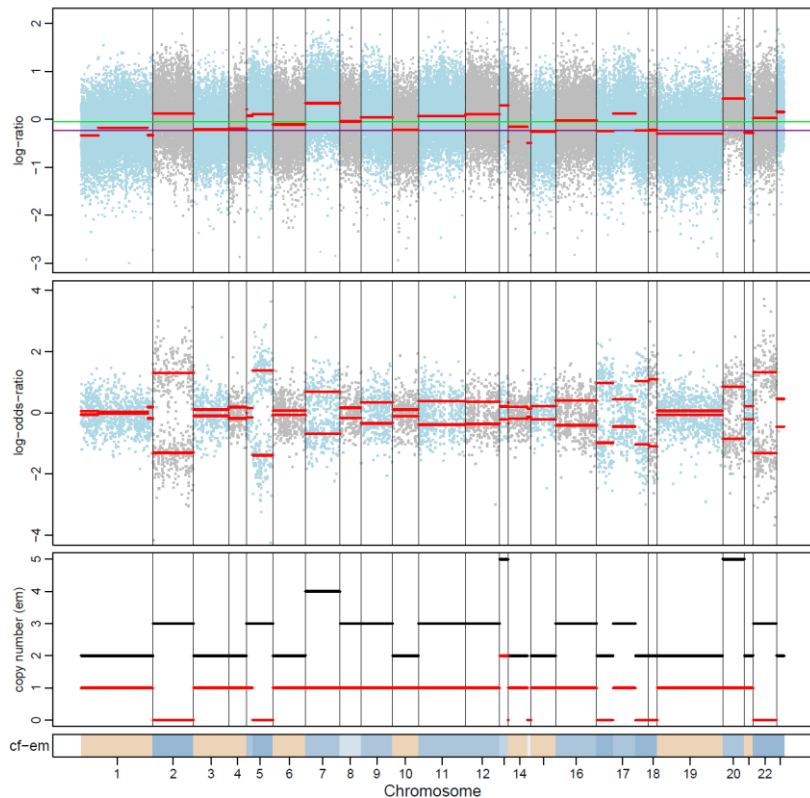
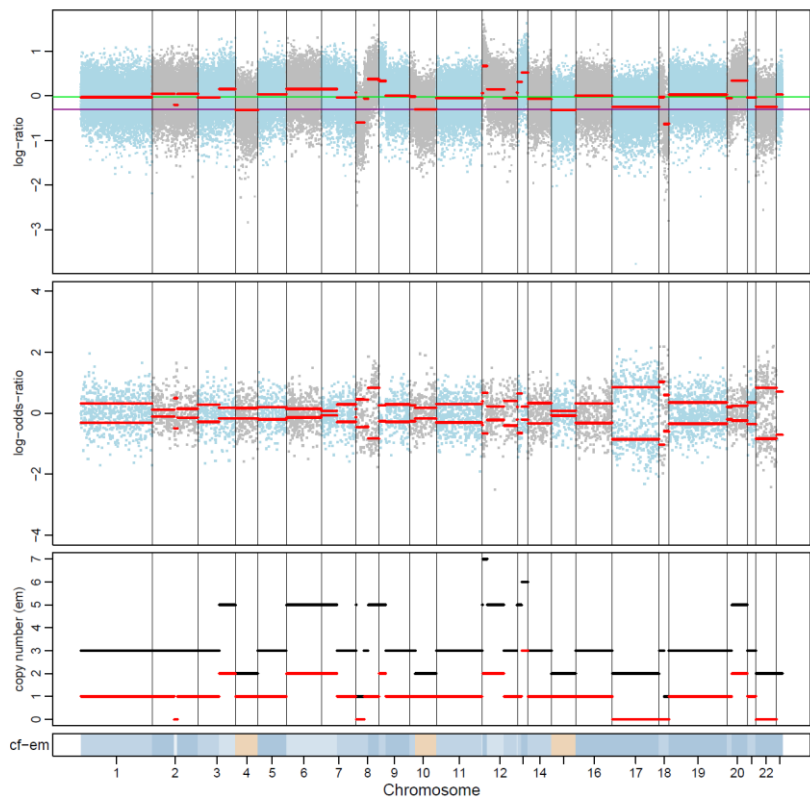


CRC-139-P



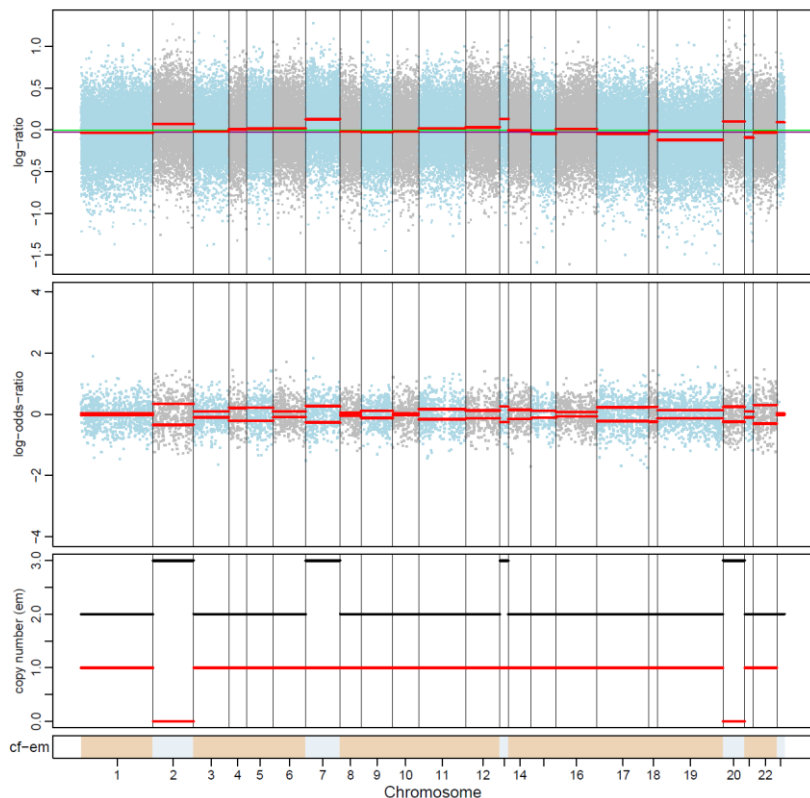
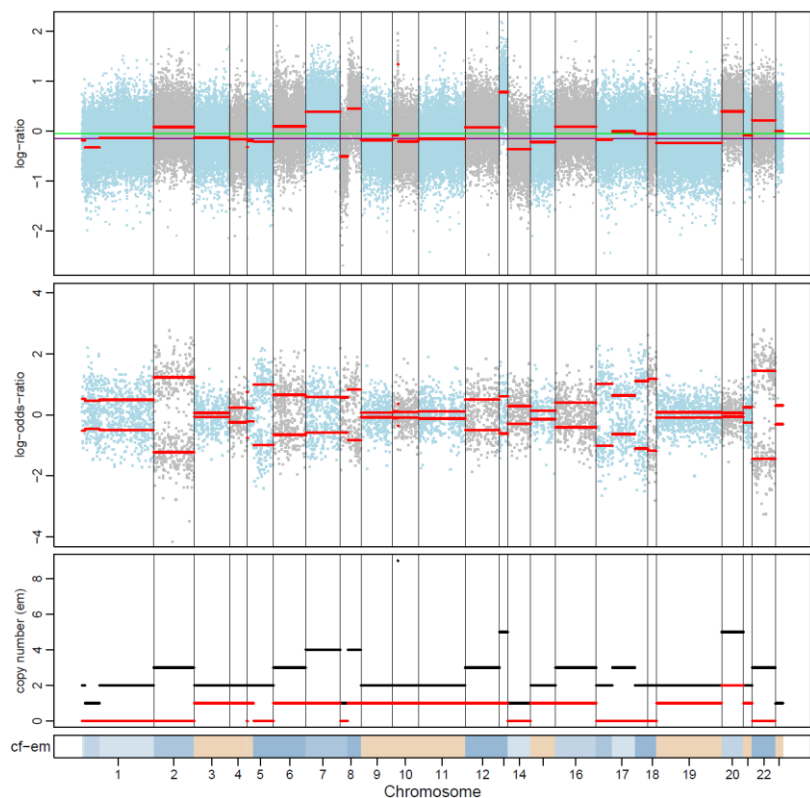


CRC-139-M



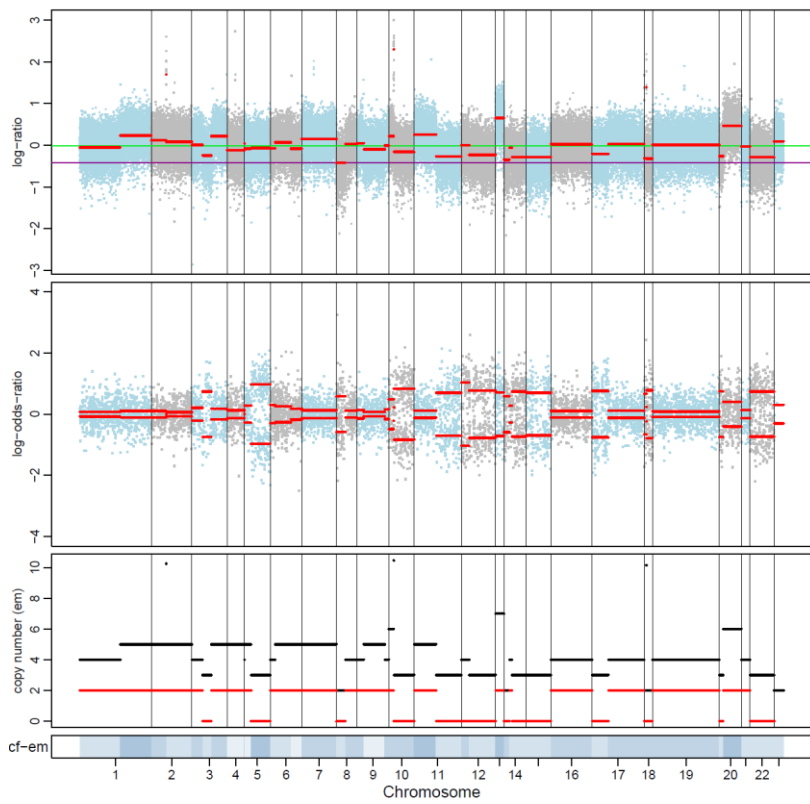
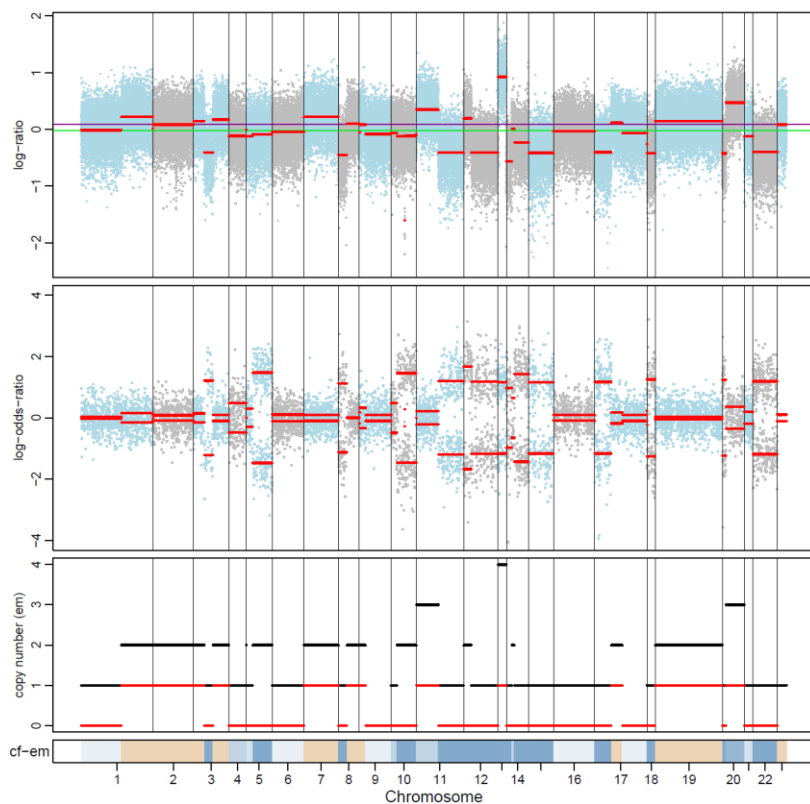
CRC-141-P

CRC-141-LN



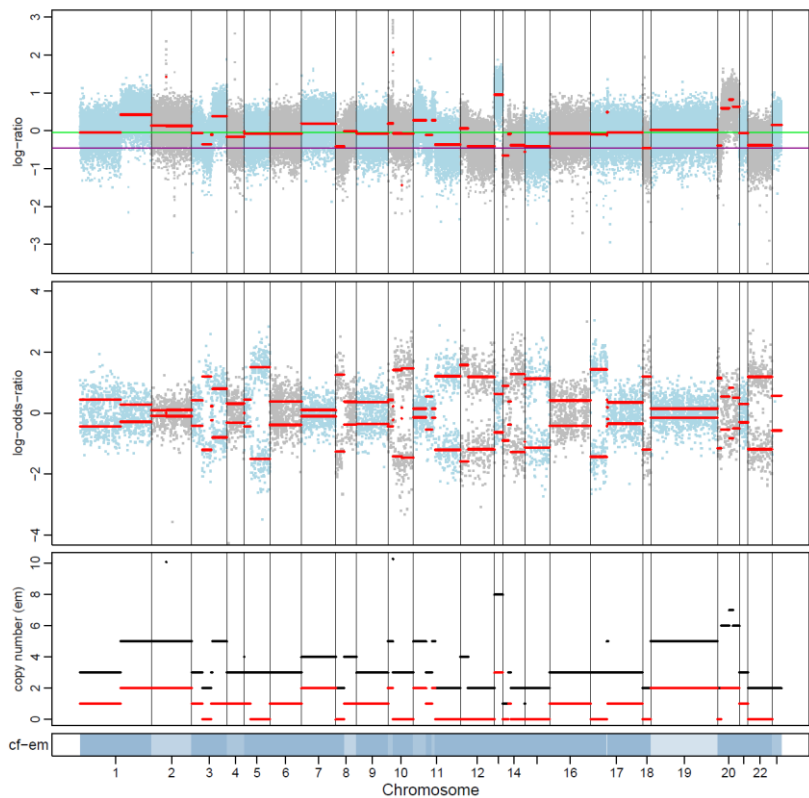
CRC-141-M

CRC-190-P

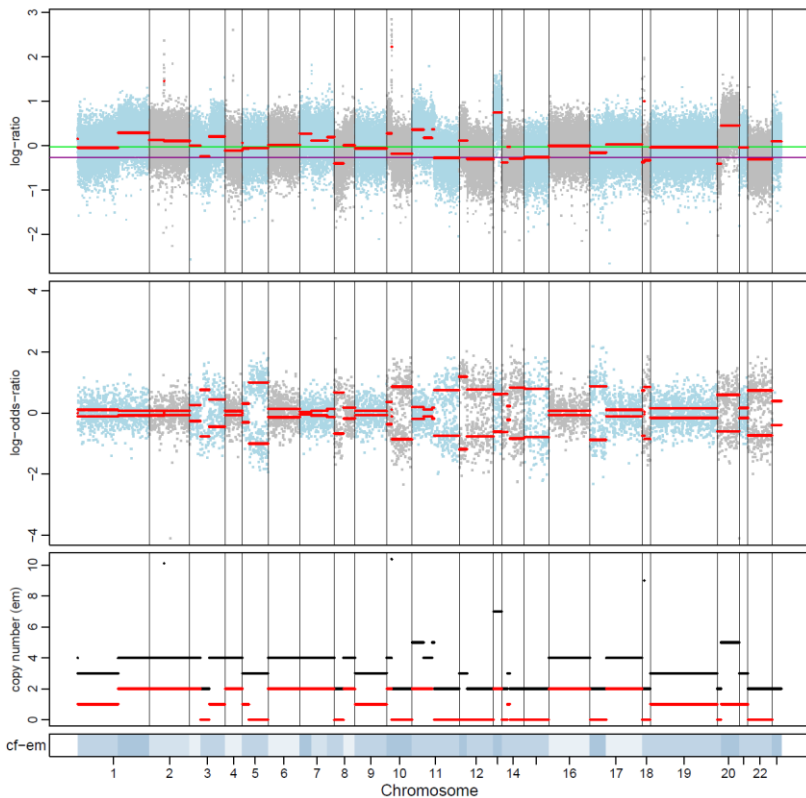


CRC-190-P1

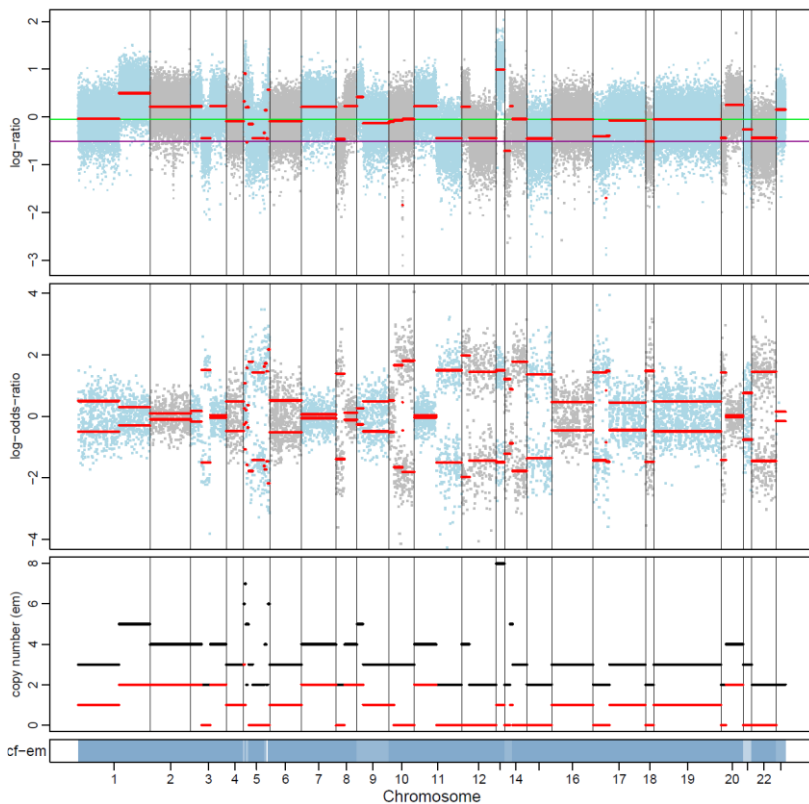
CRC-190-P2



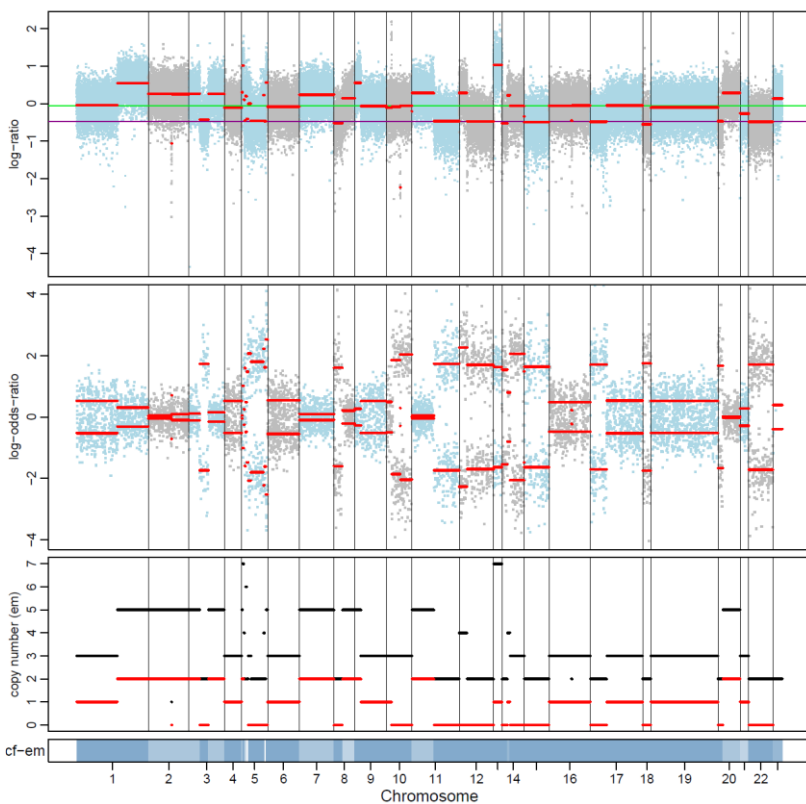
CRC-190-P3



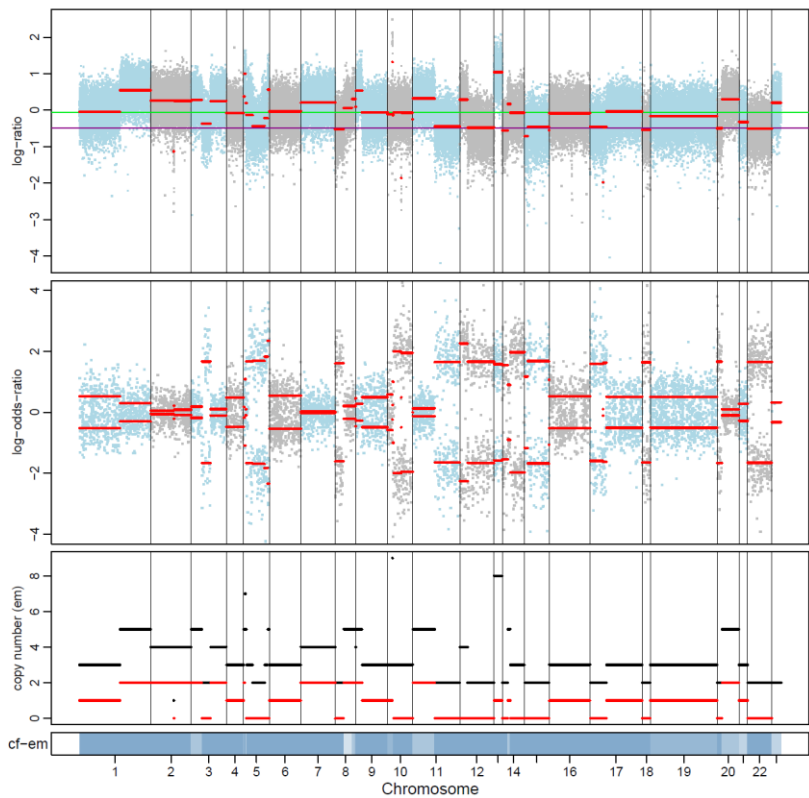
CRC-190-M



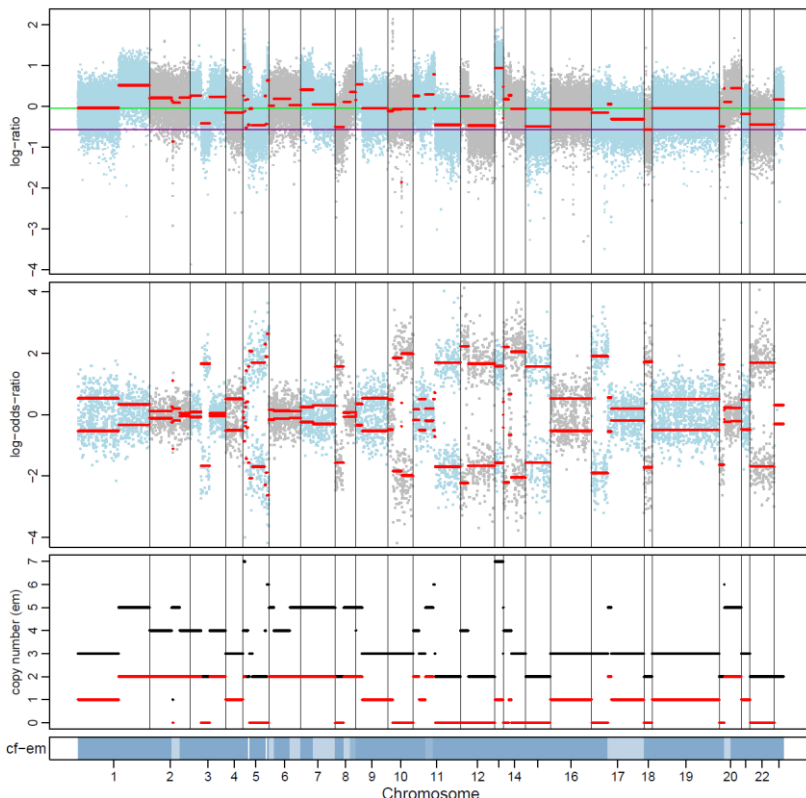
CRC-190-M1



CRC-190-M2

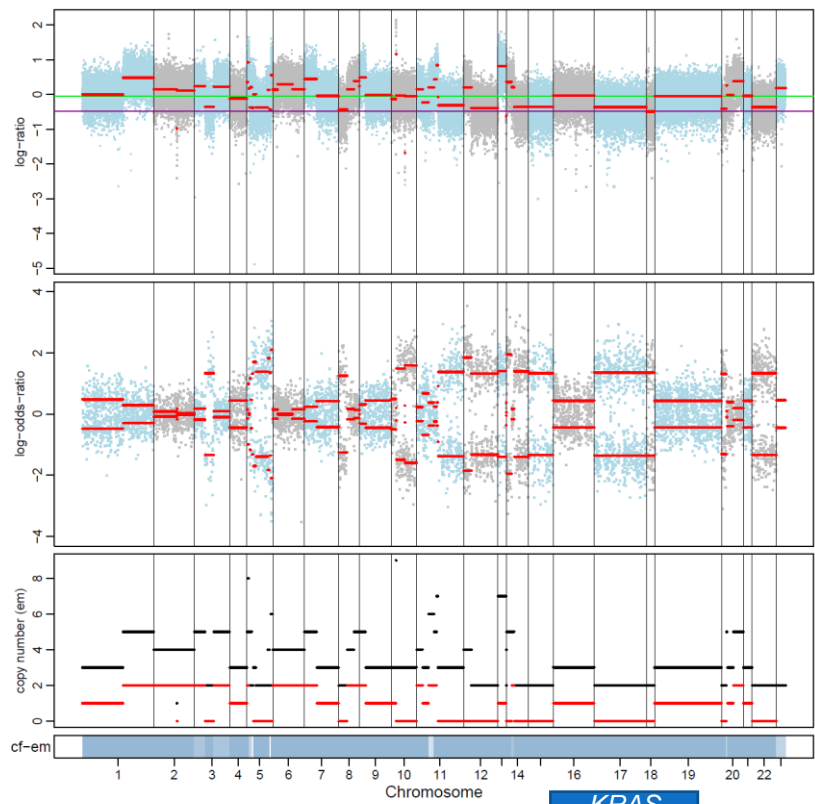


CRC-190-M3

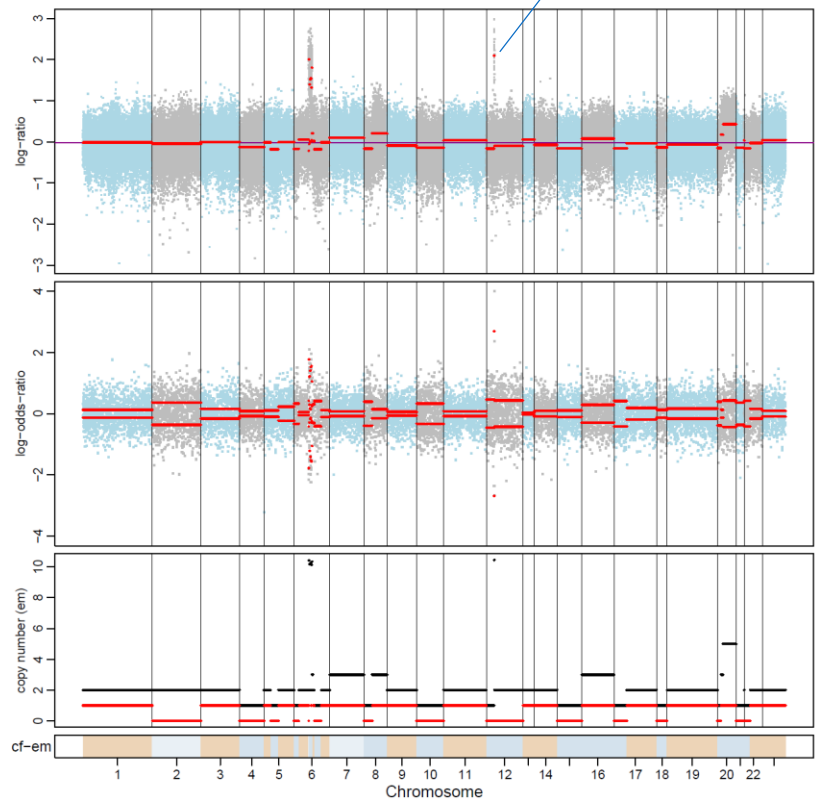




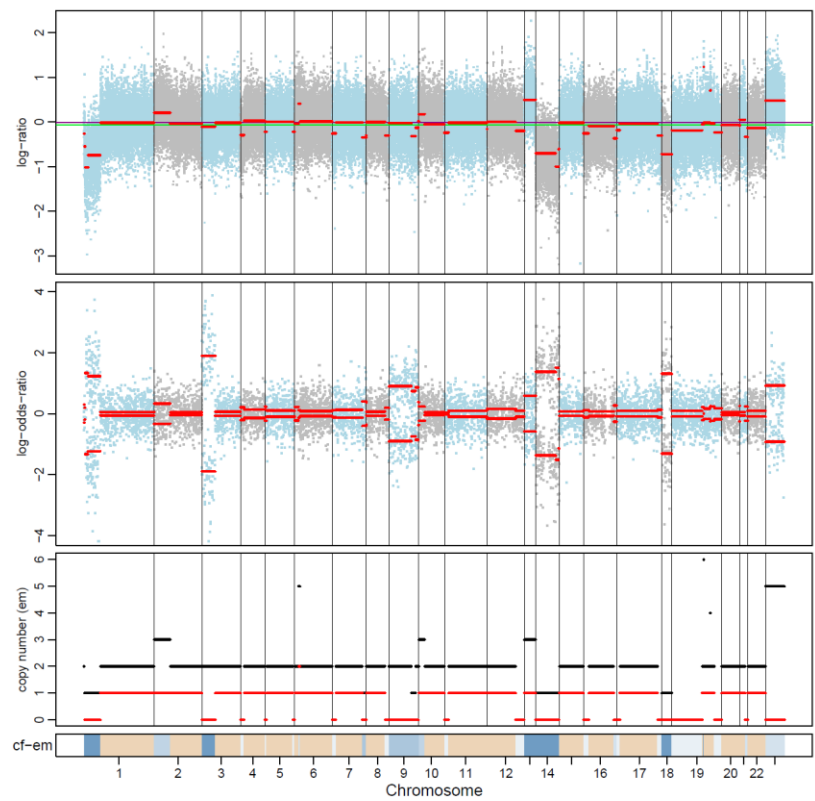
CRC-190-M4



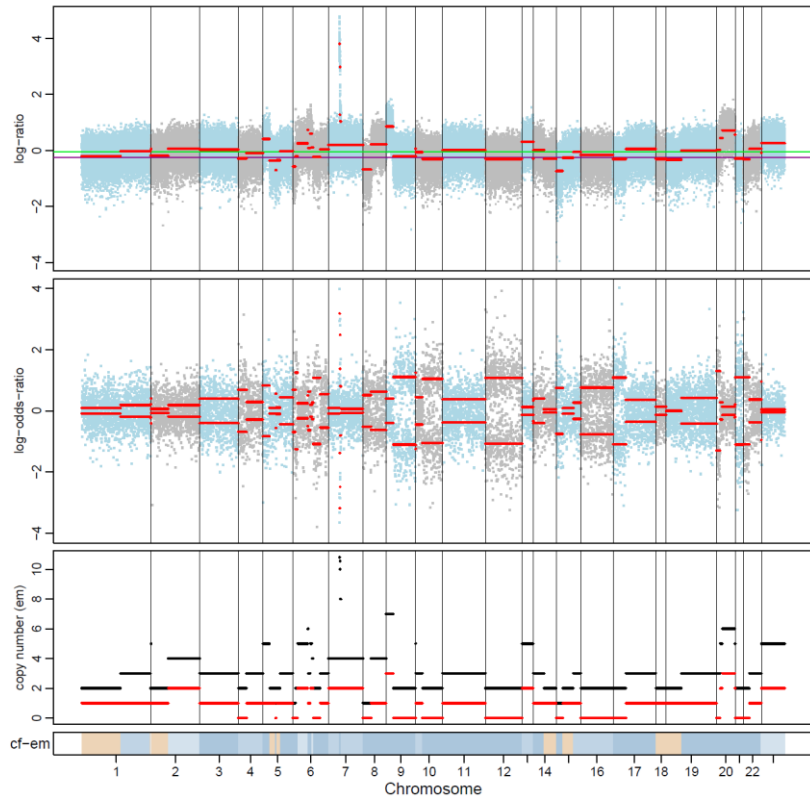
CRC-233-LN



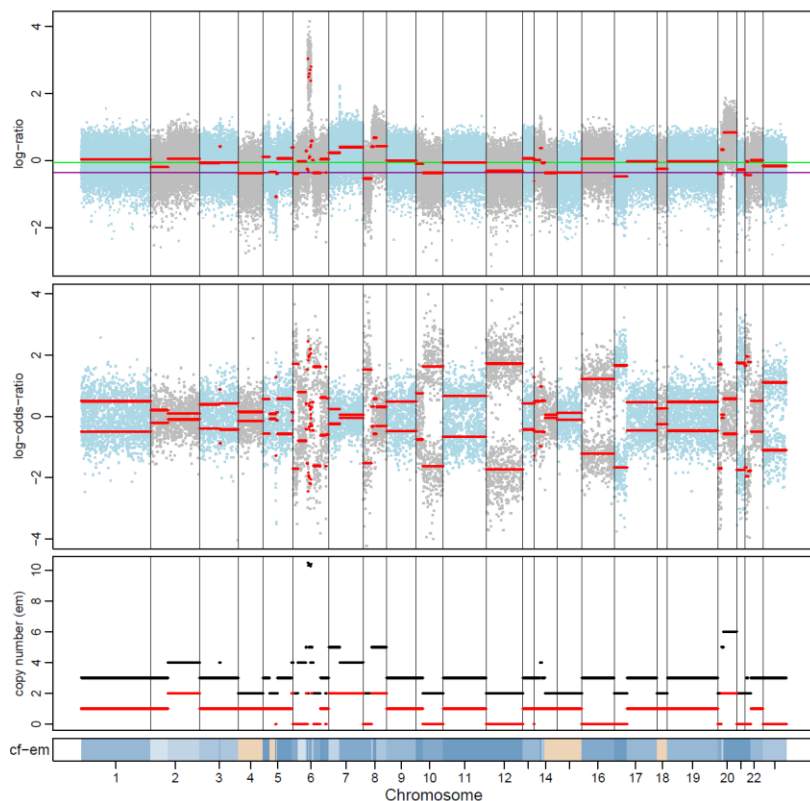
CRC-293-P



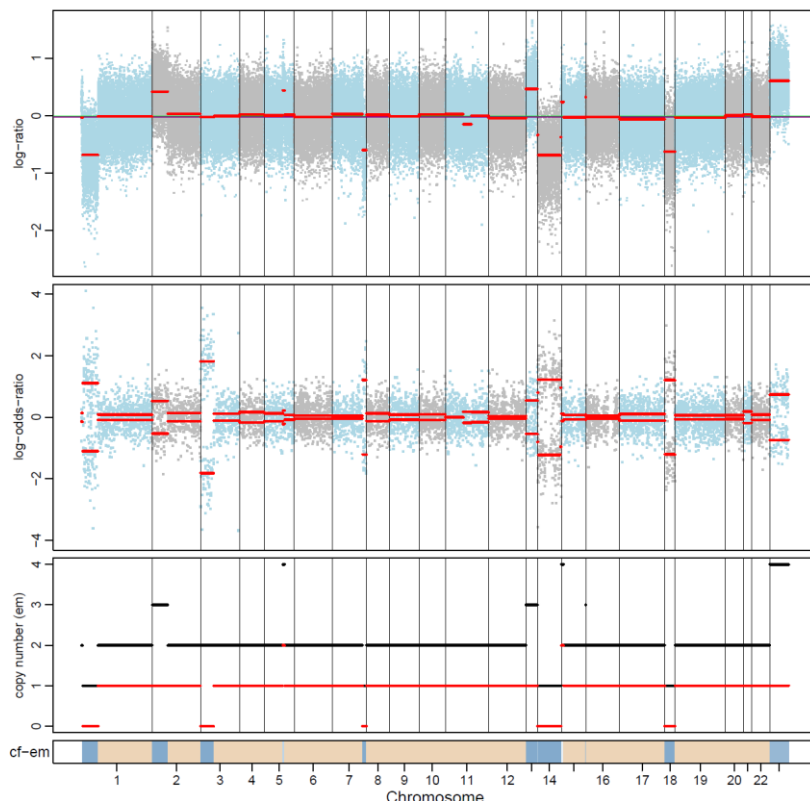
CRC-233-P



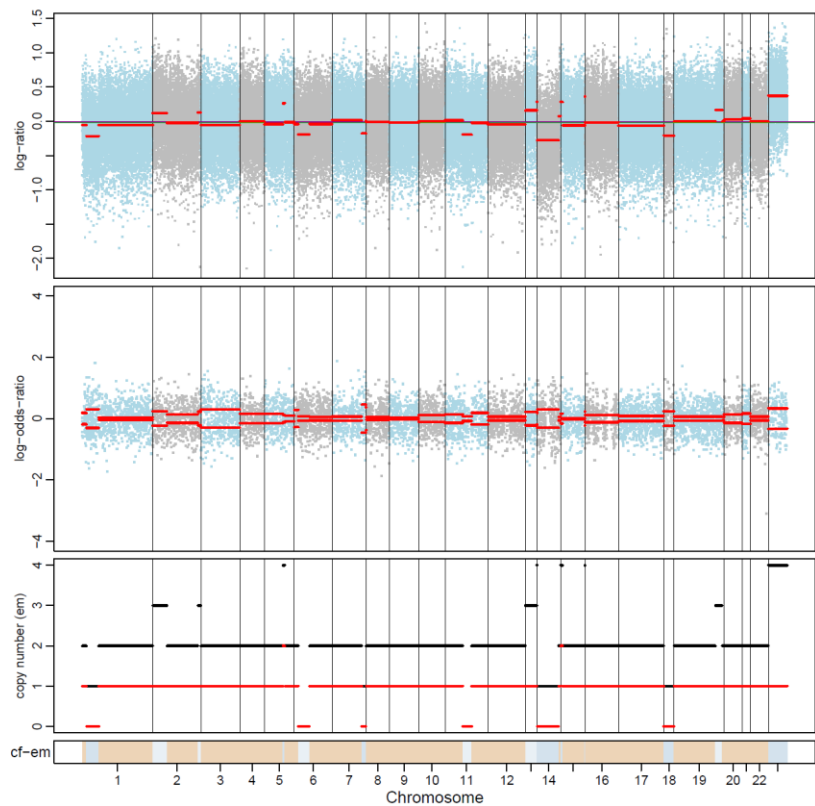
CRC-233-M



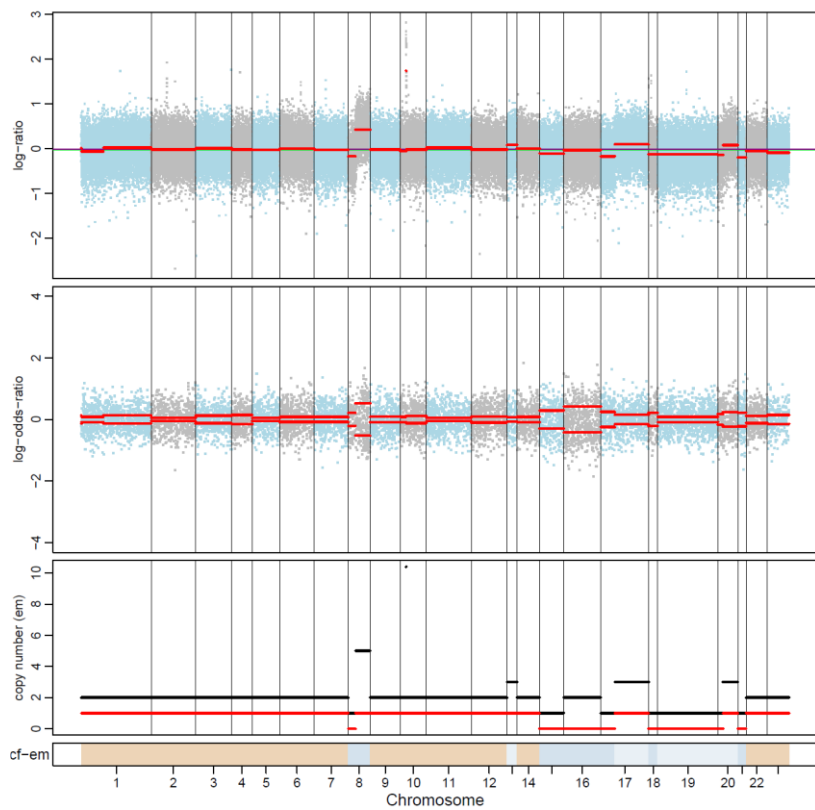
CRC-293-LN



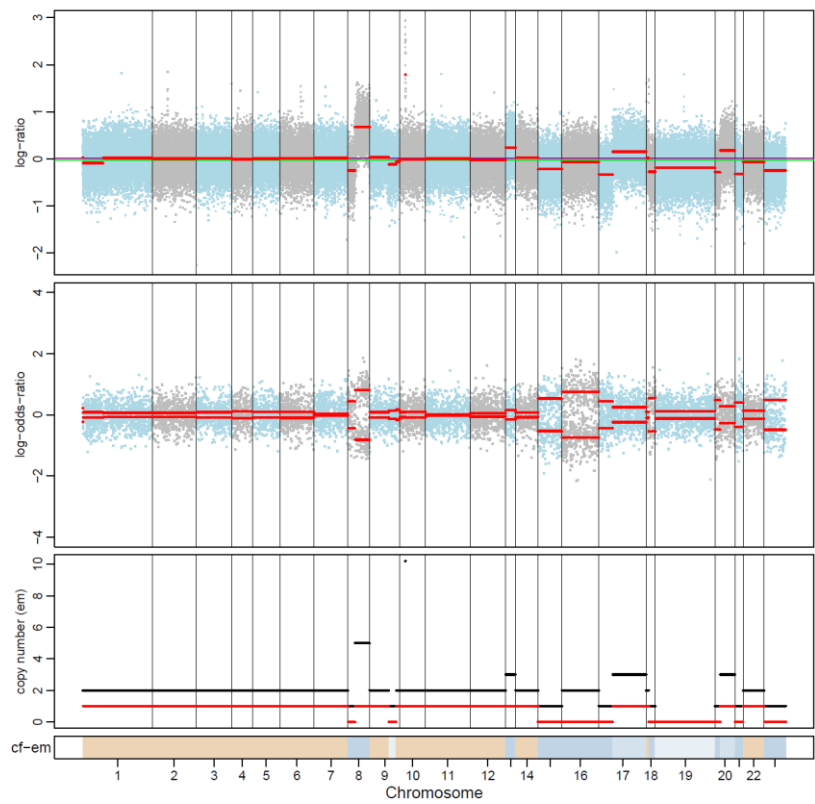
CRC-293-M



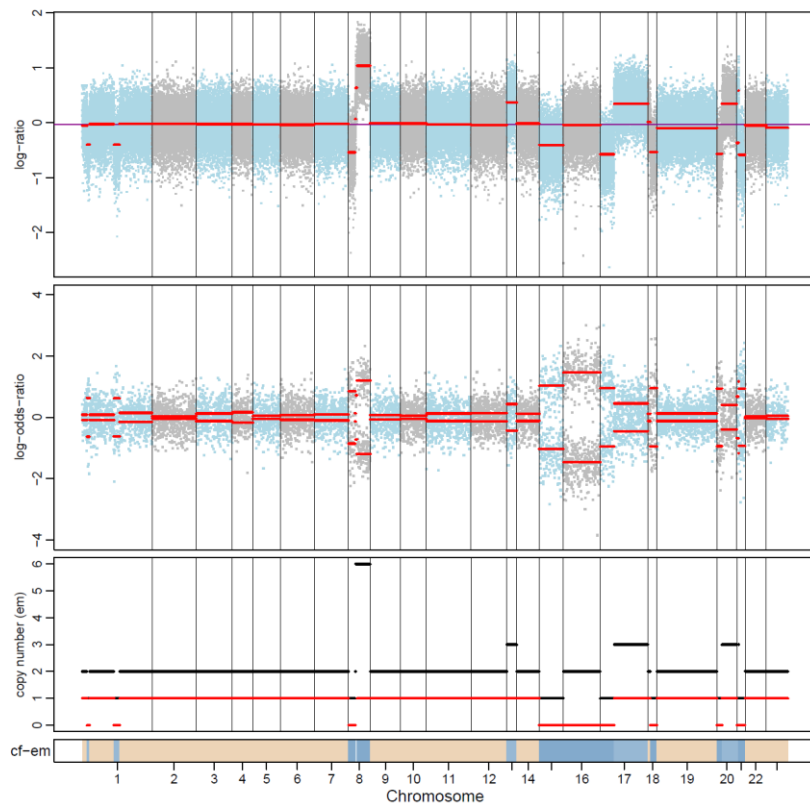
CRC-320-P1



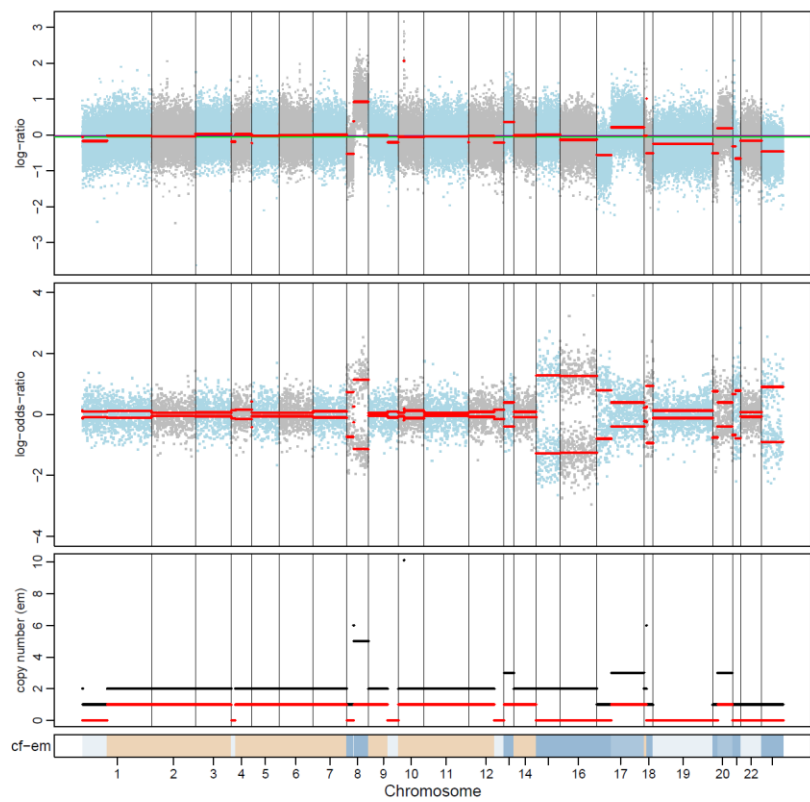
CRC-320-P3



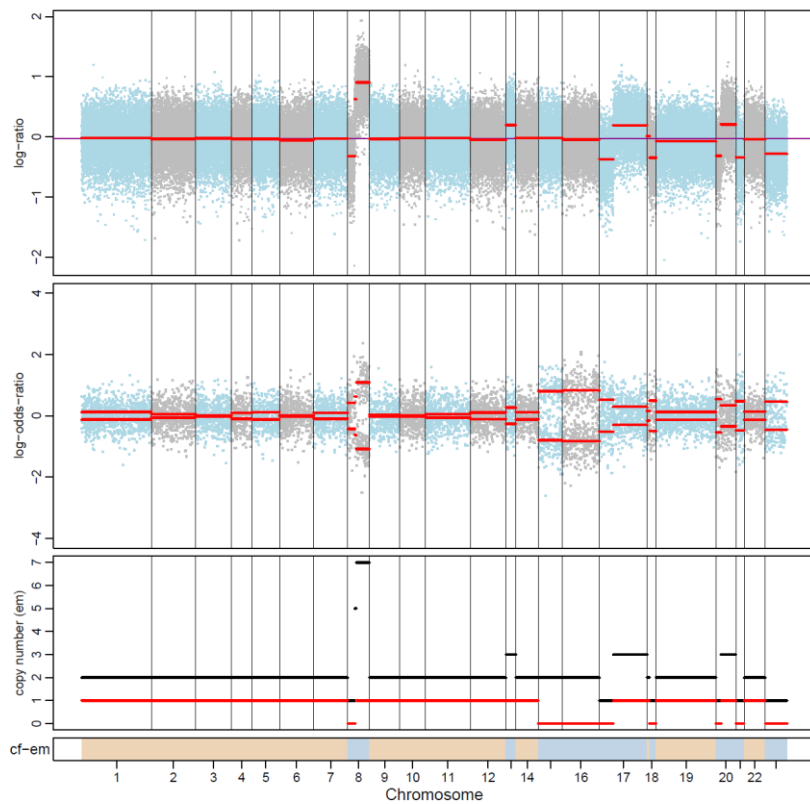
CRC-320-P



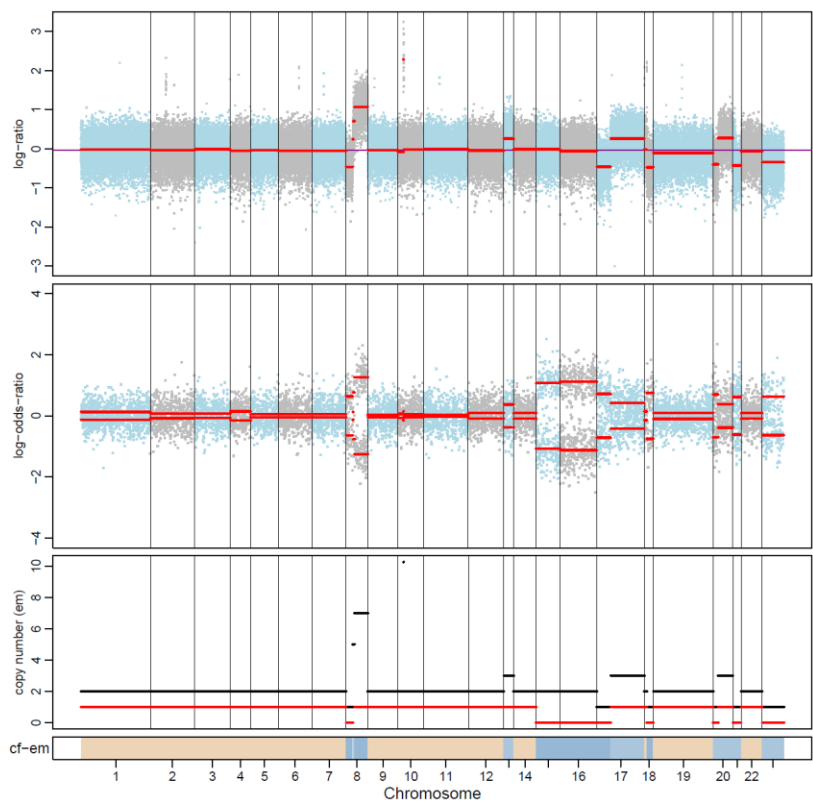
CRC-320-P2



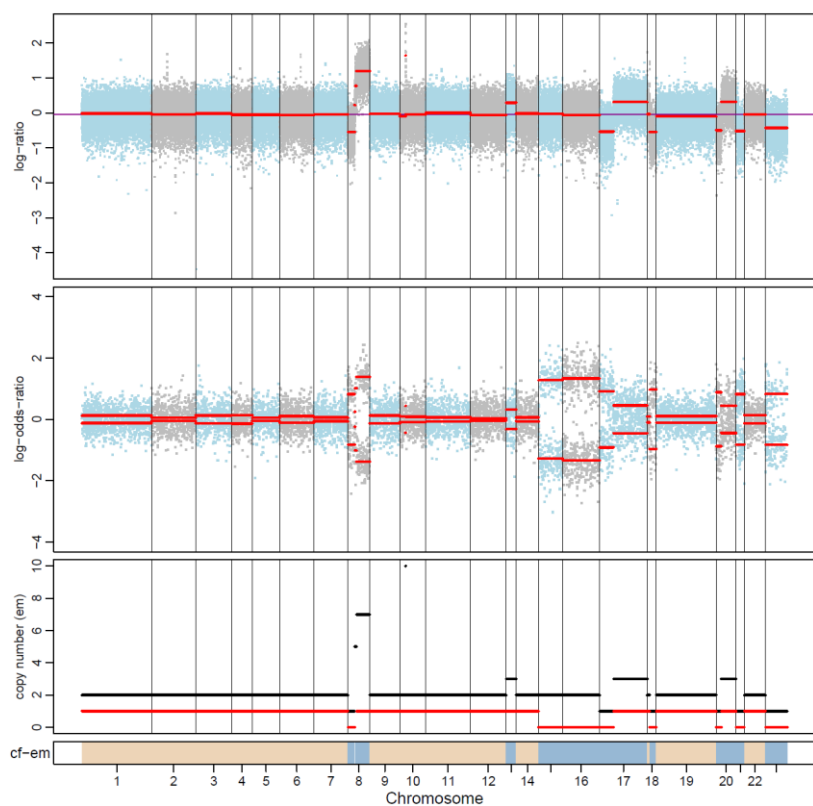
CRC-320-M



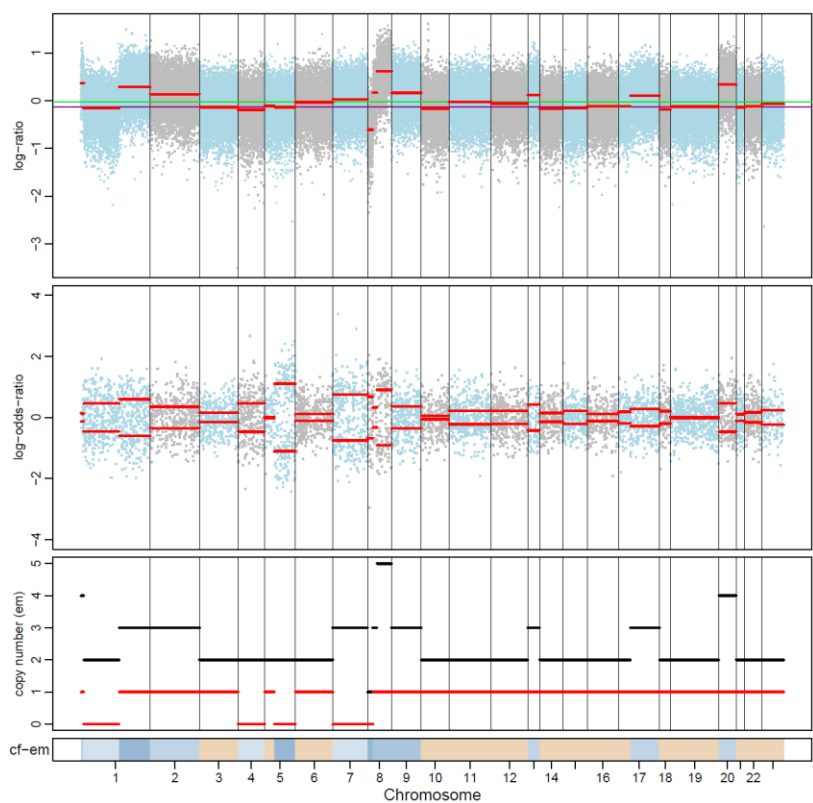
CRC-320-M1



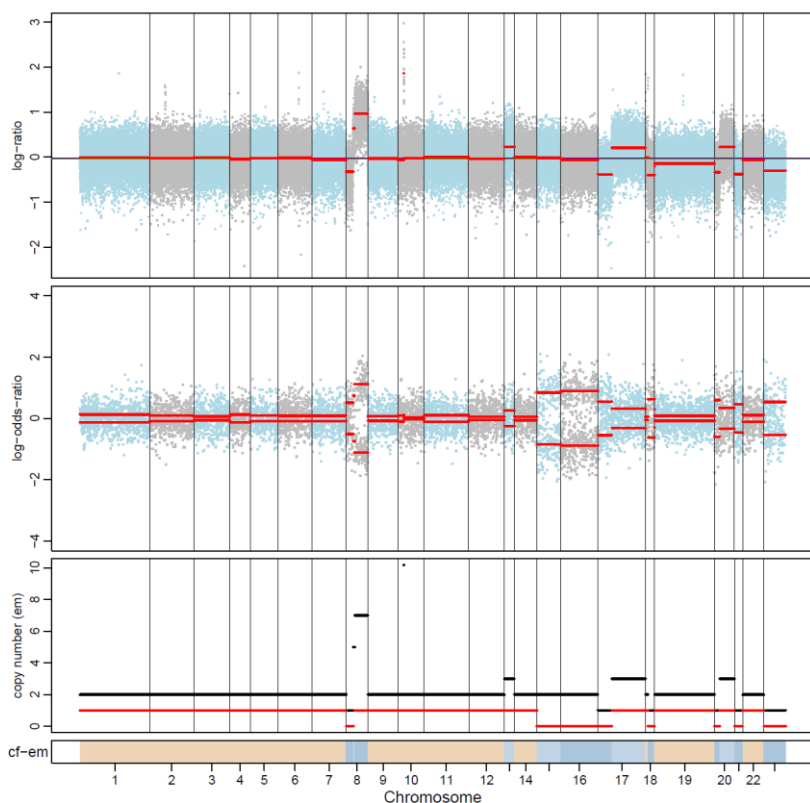
CRC-320-M3



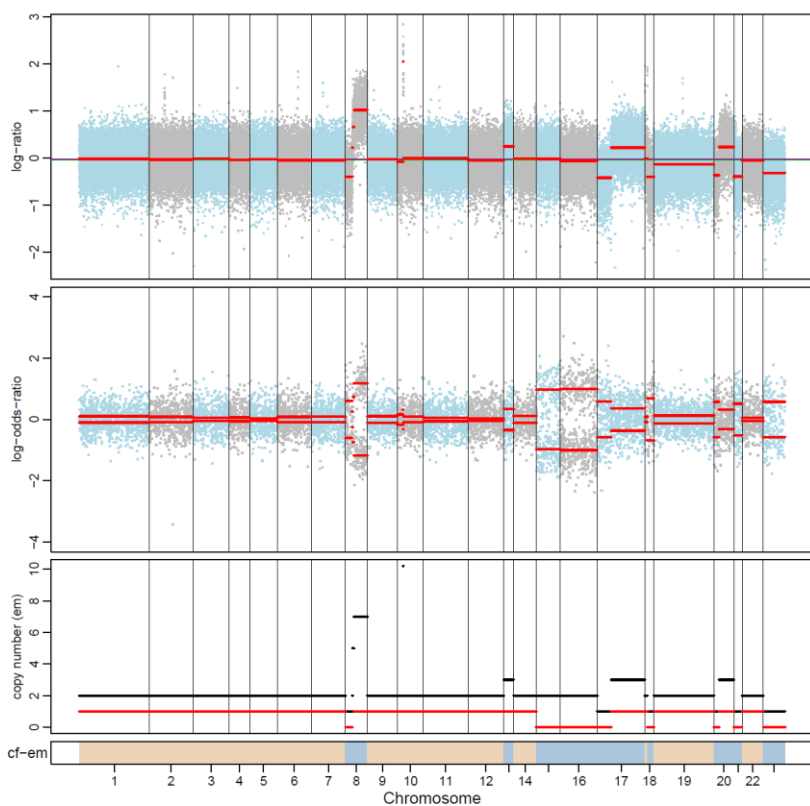
CRC-363-P



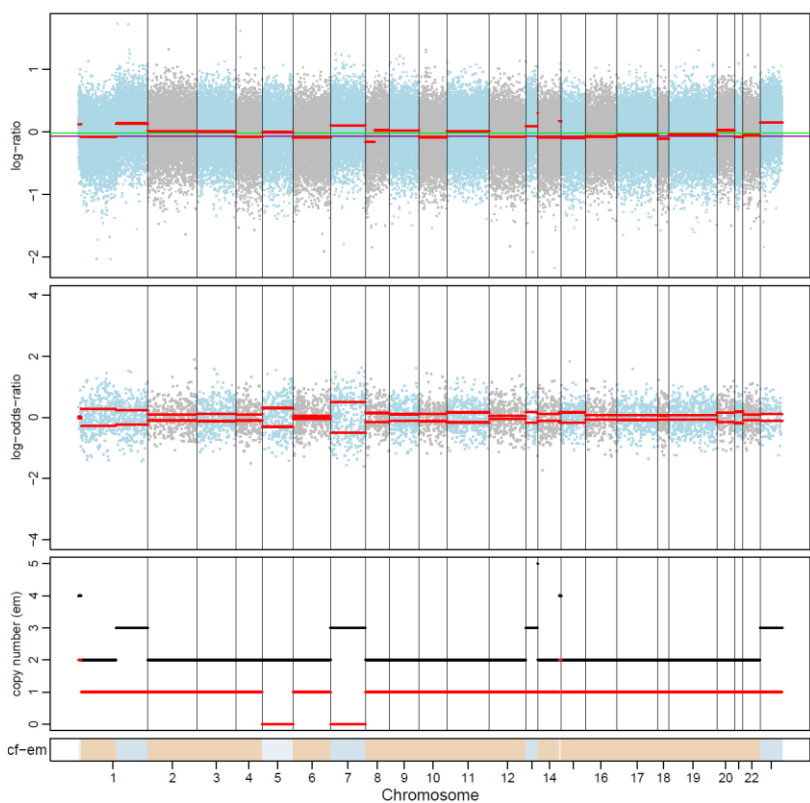
CRC-320-M2



CRC-320-M4

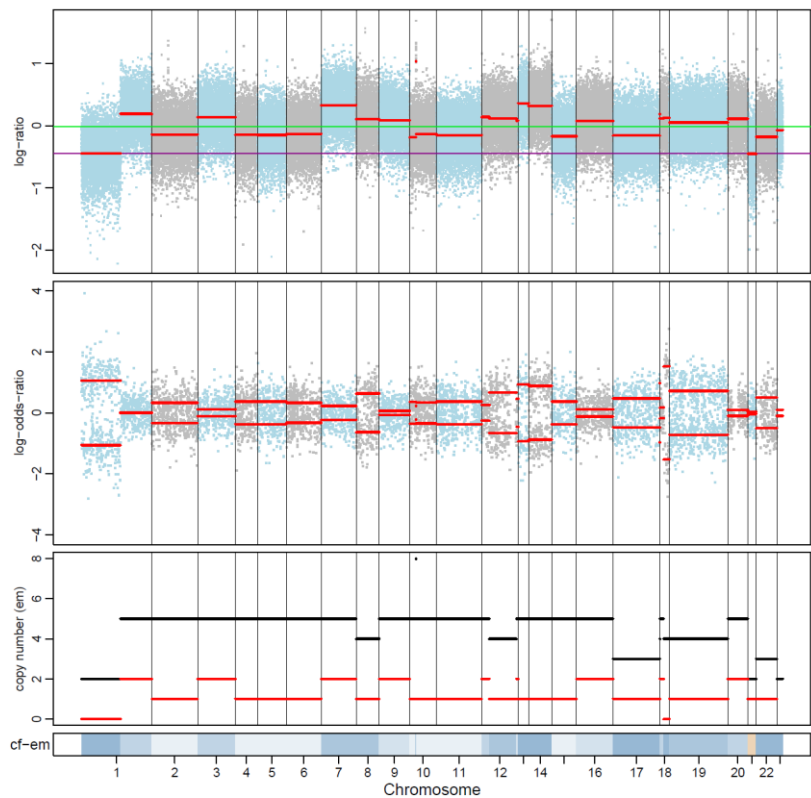


CRC-363-M

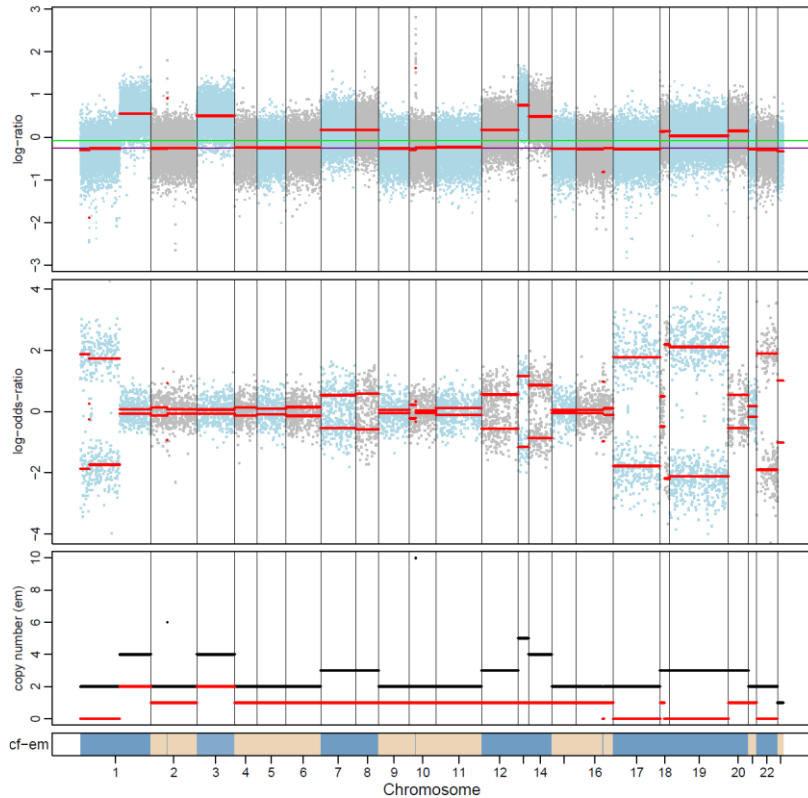




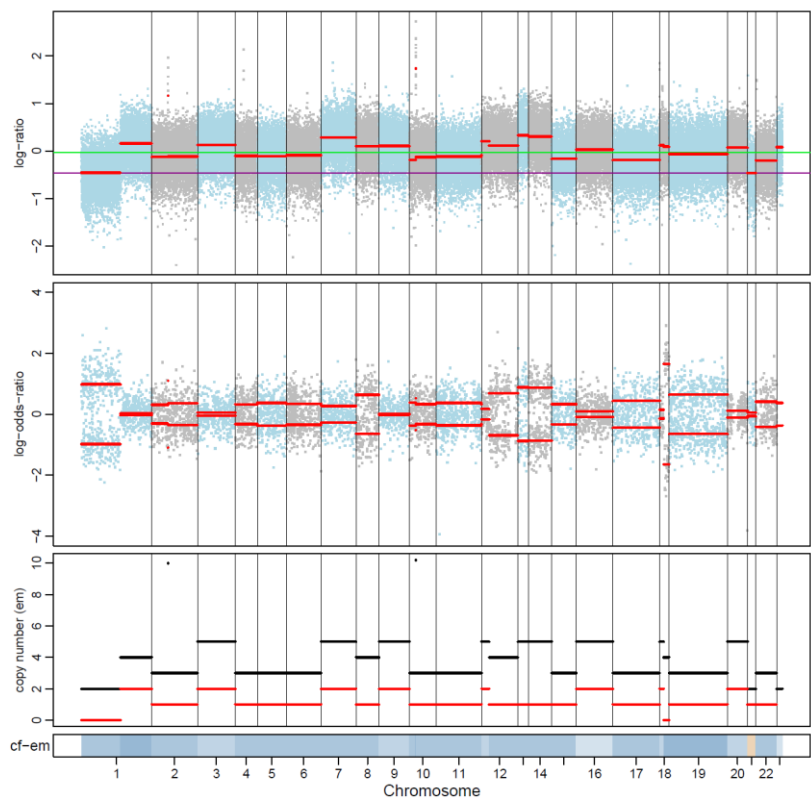
CRC-443-P



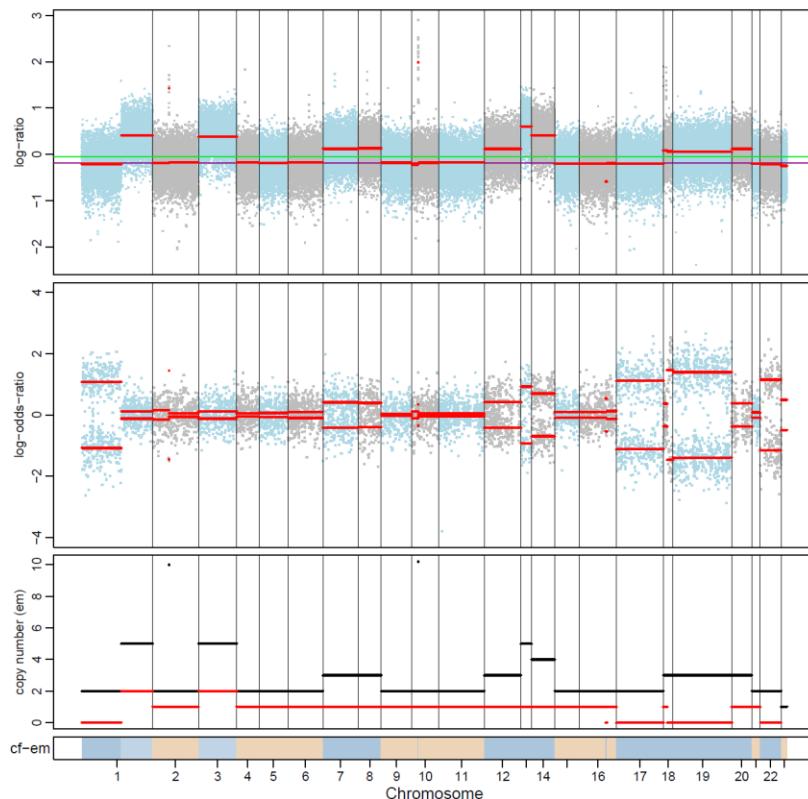
CRC-443-P1



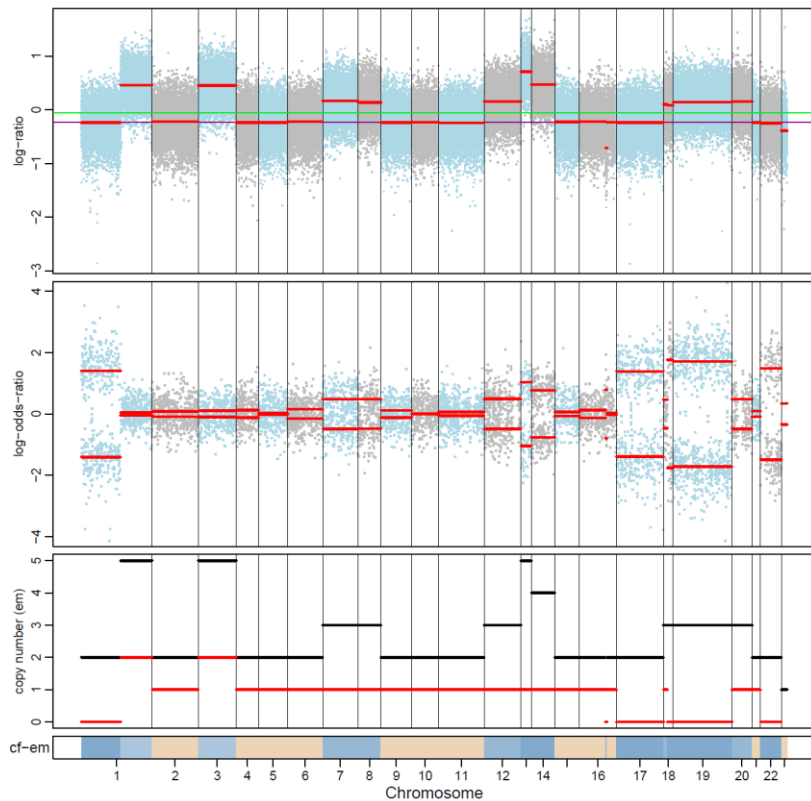
CRC-443-P2



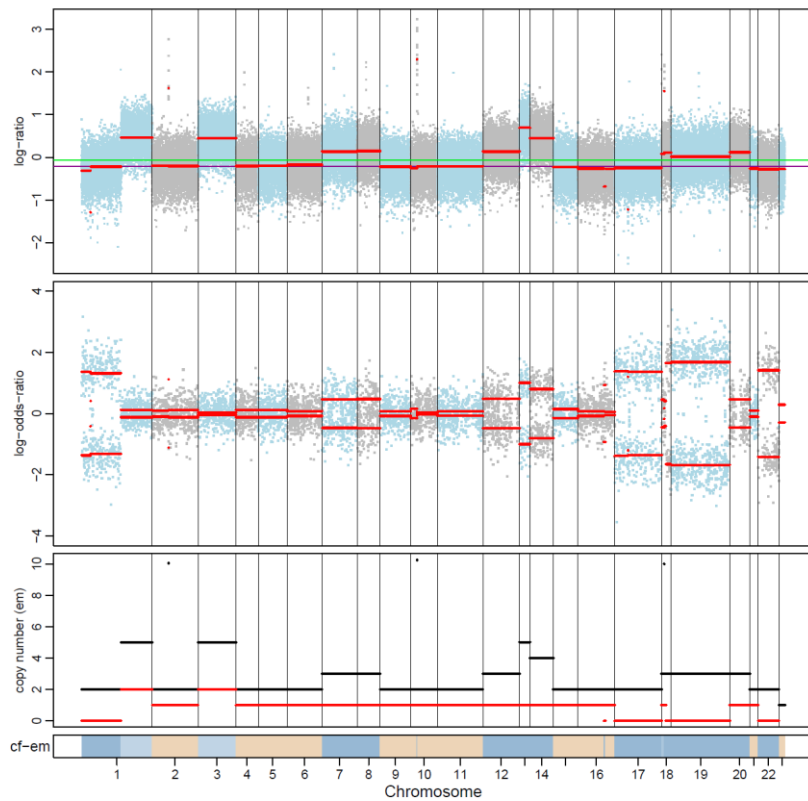
CRC-443-P3



CRC-443-M

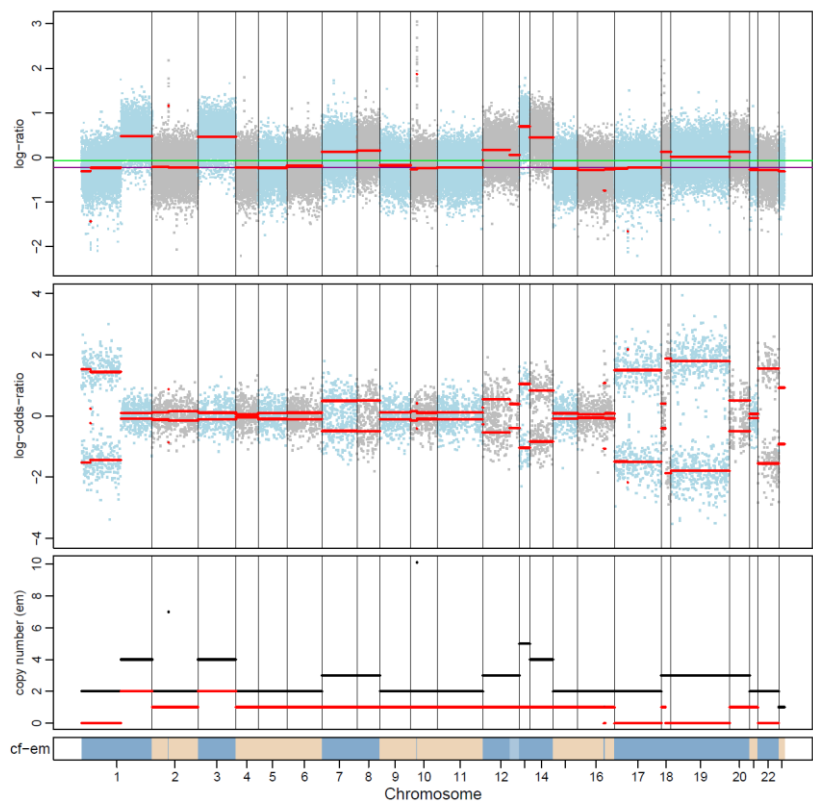


CRC-443-M1

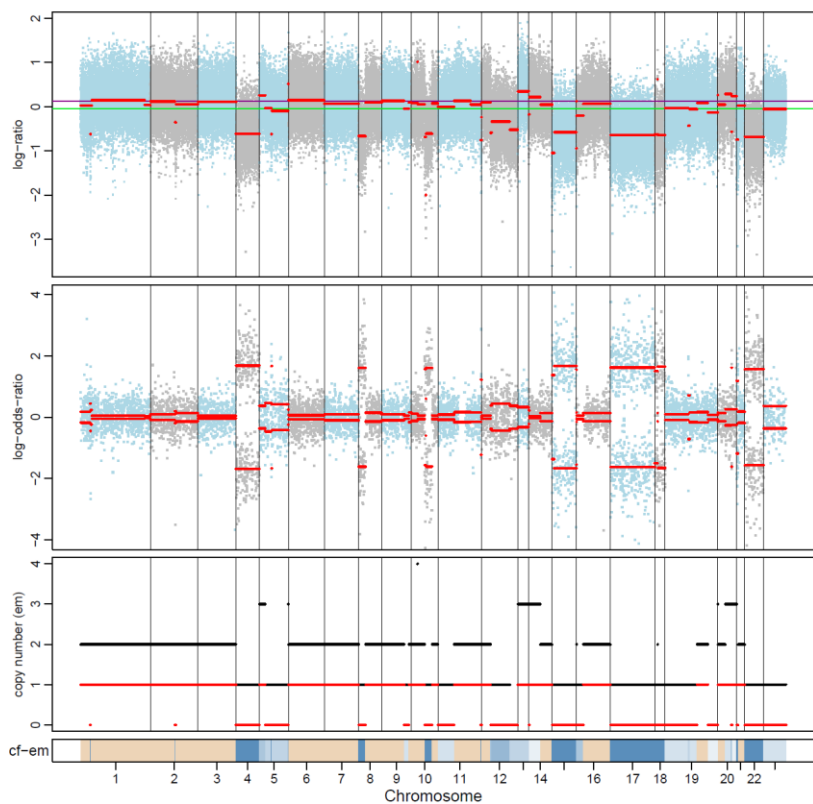




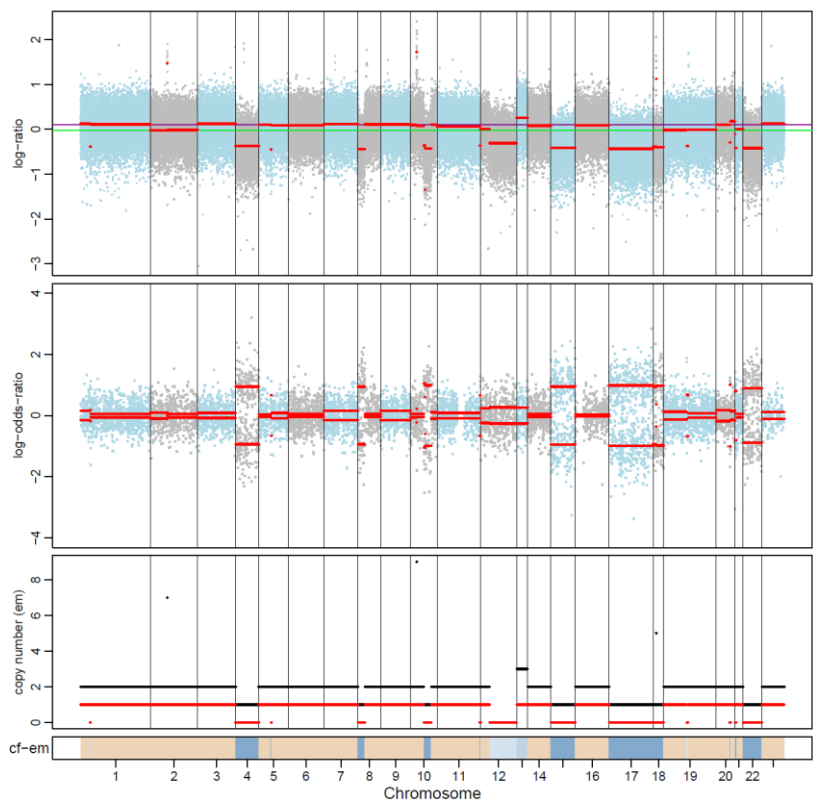
CRC-443-M2



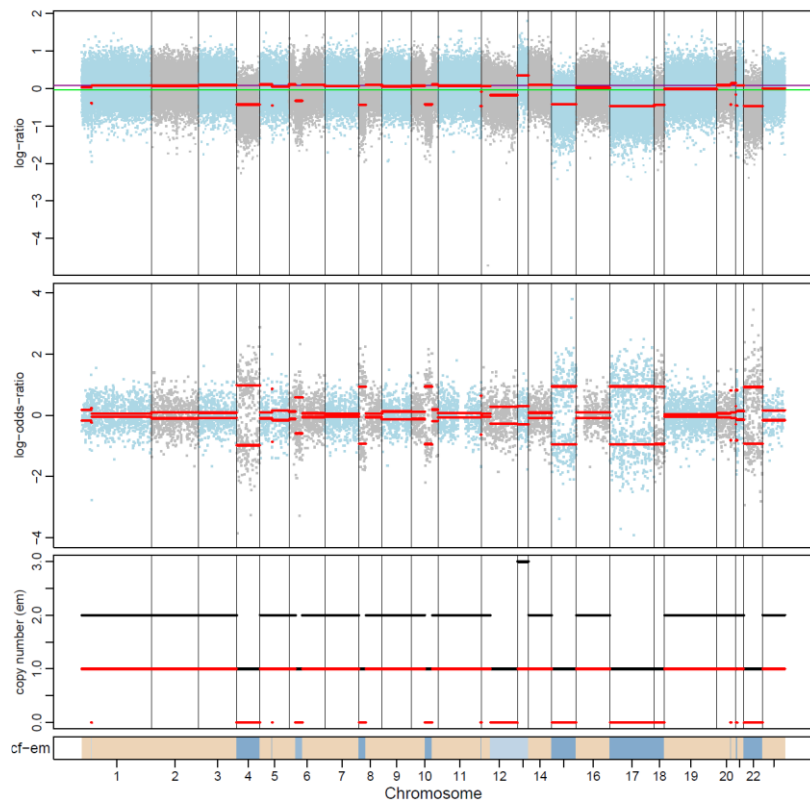
CRC-449-P1



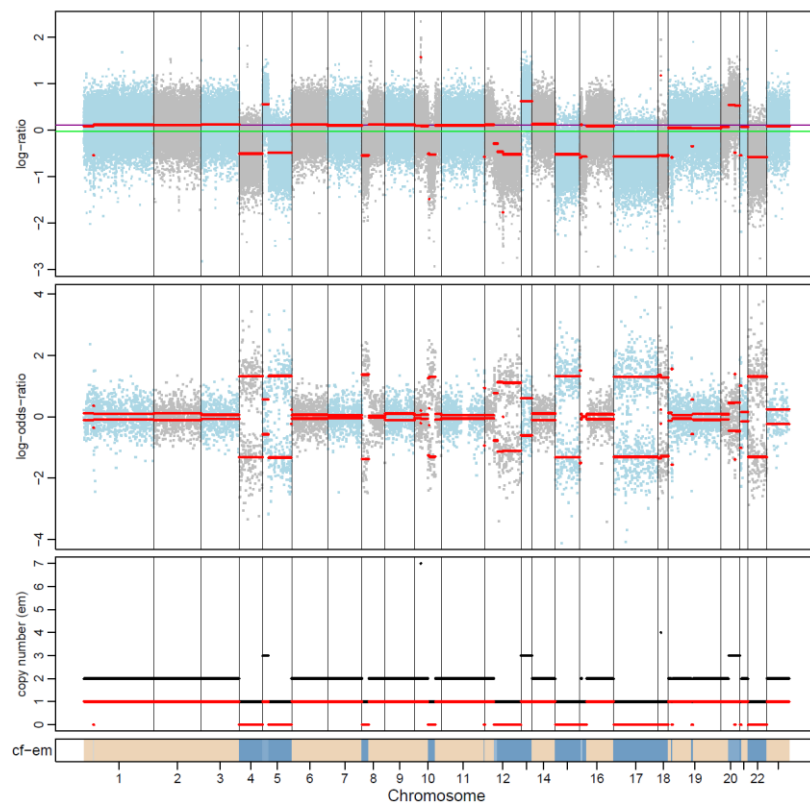
CRC-449-P3



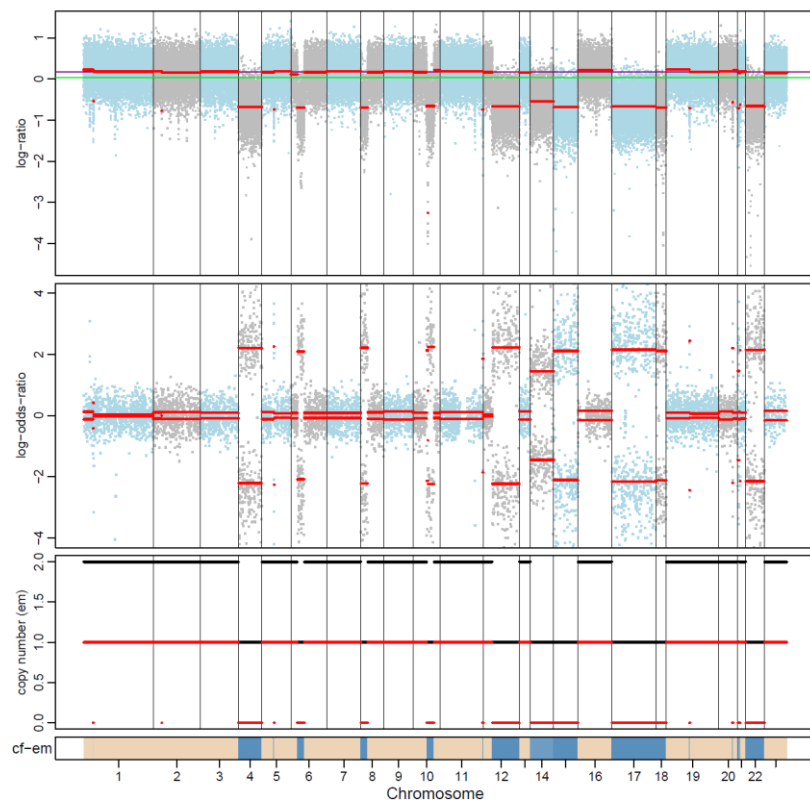
CRC-449-P



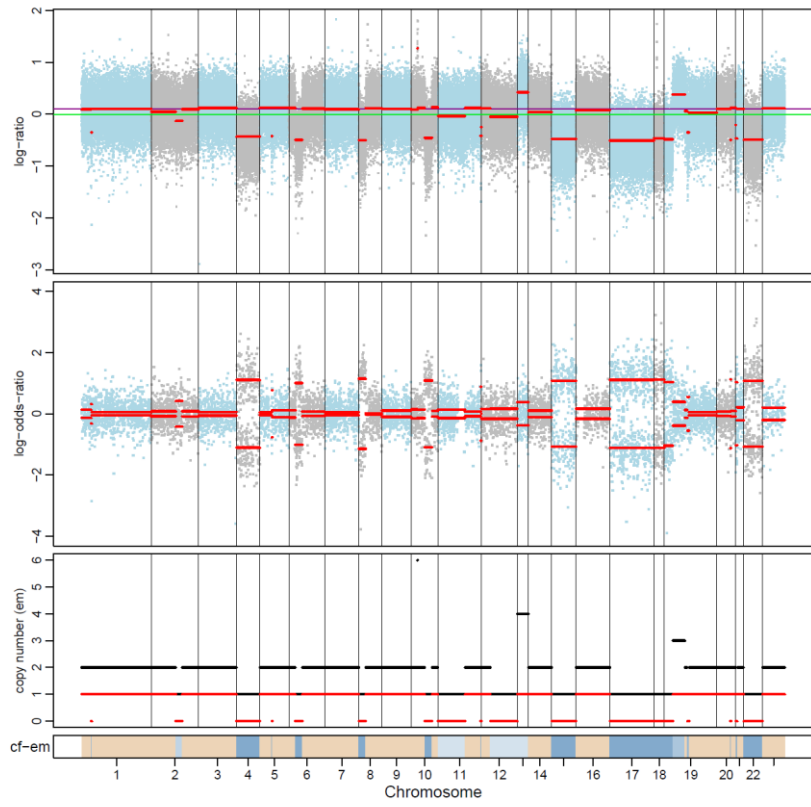
CRC-449-P2



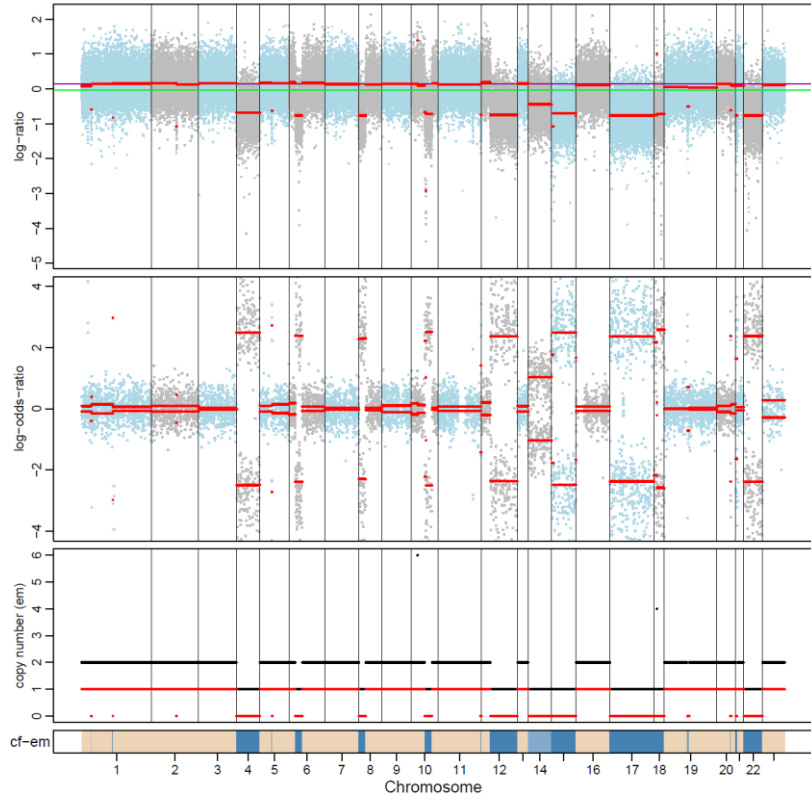
CRC-449-M



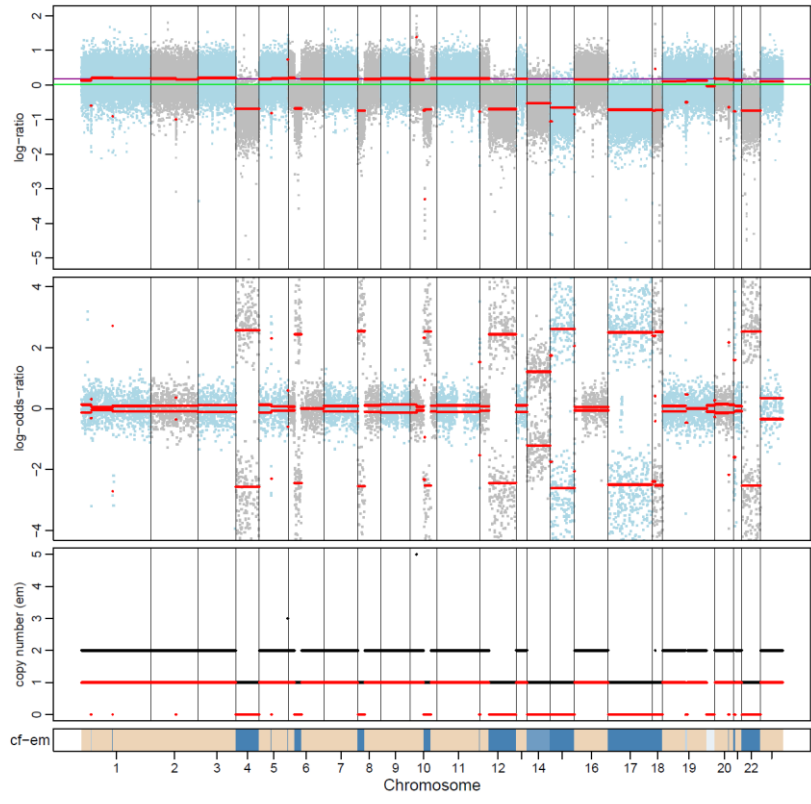
CRC-449-M5



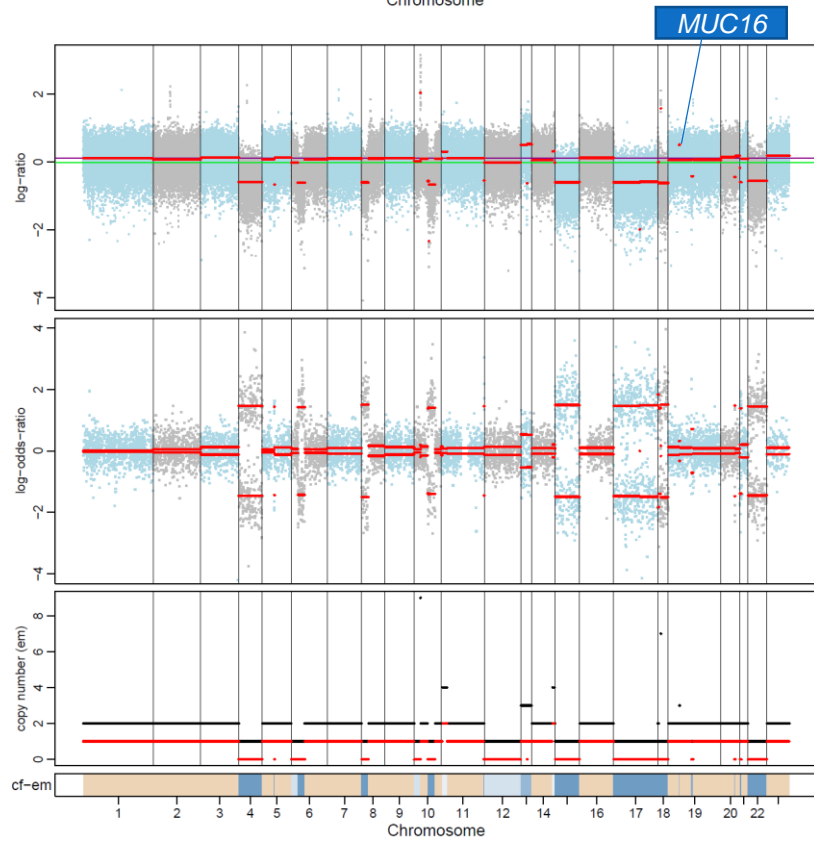
CRC-449-M3



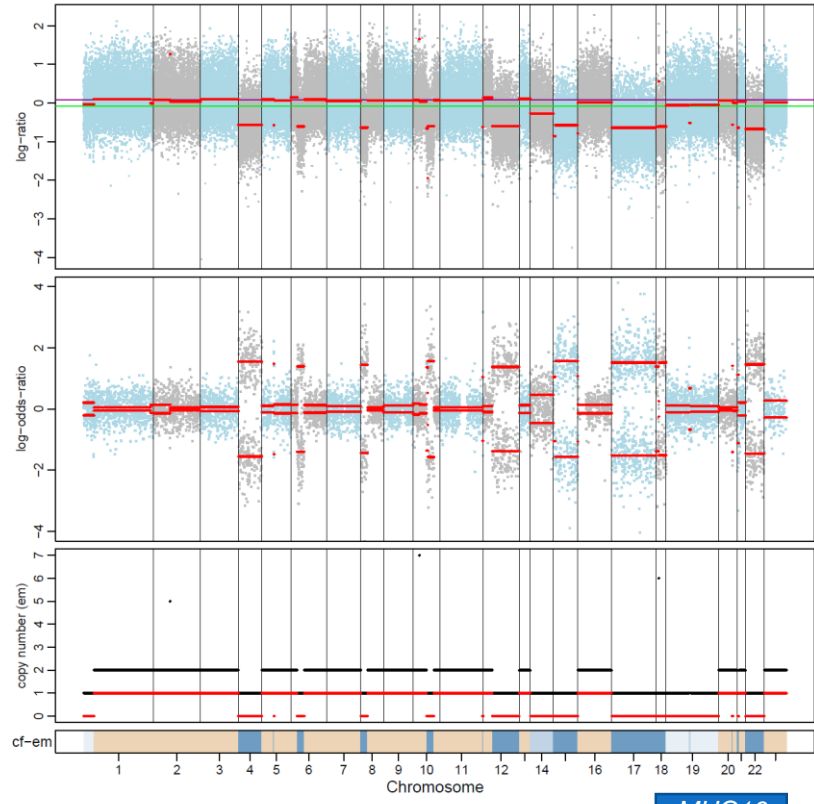
CRC-449-M1



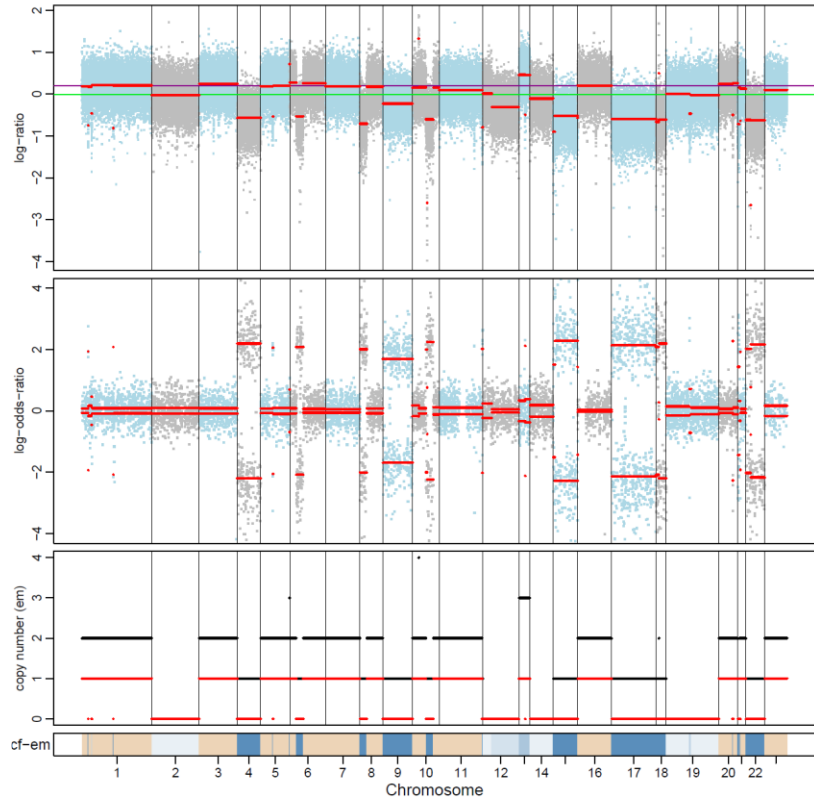
CRC-449-M6



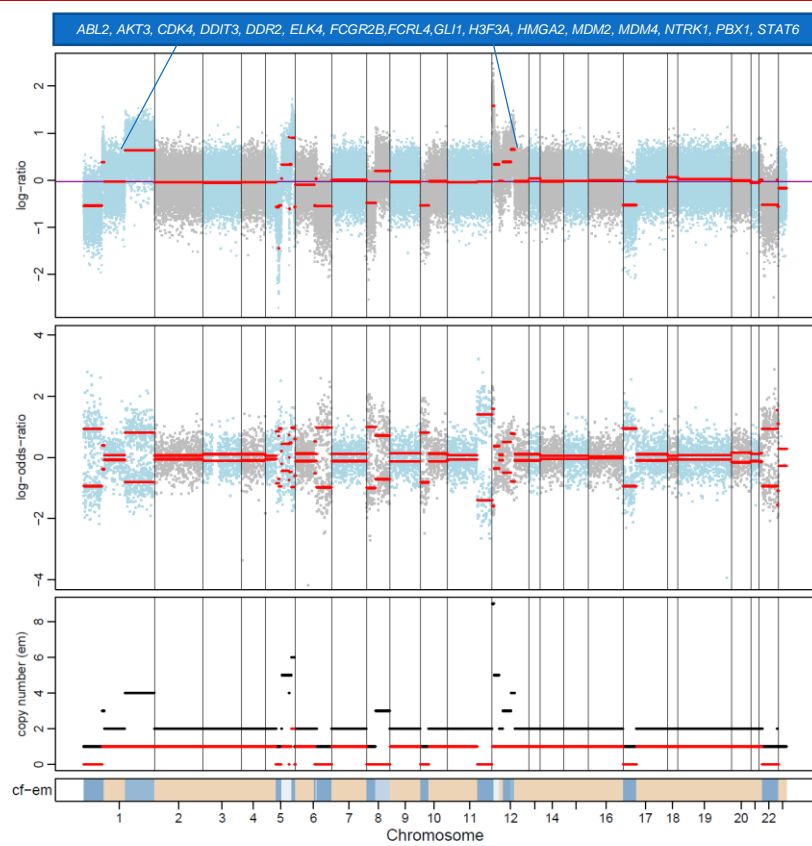
CRC-449-M4



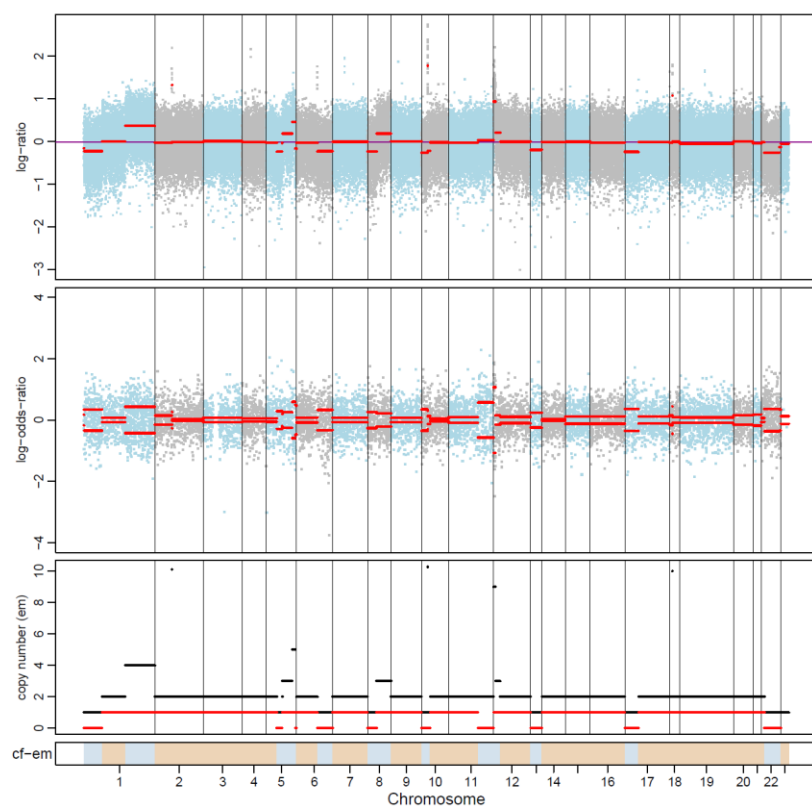
CRC-449-M2



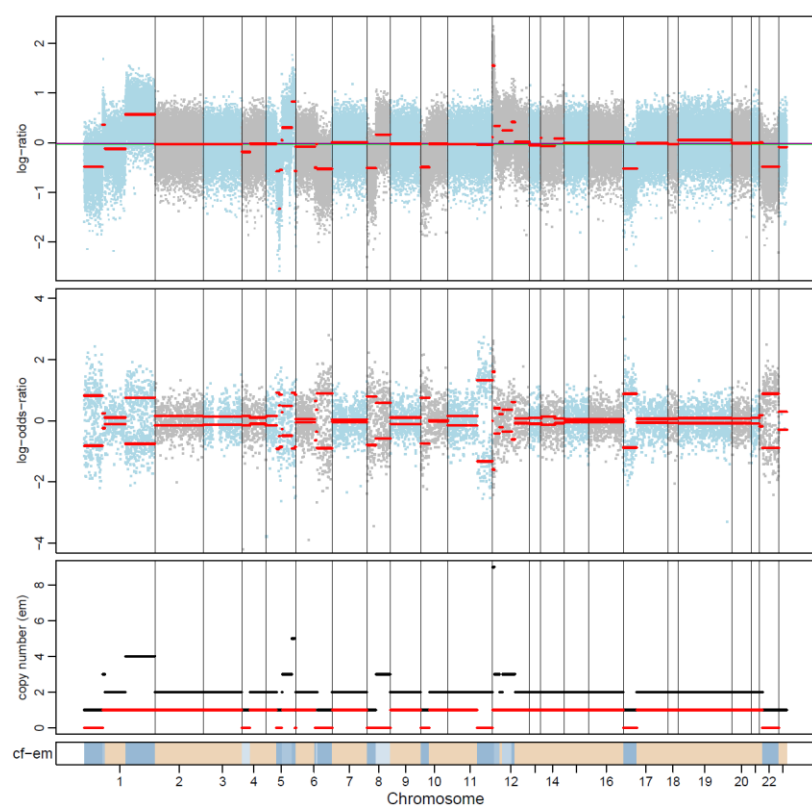
CRC-453-P



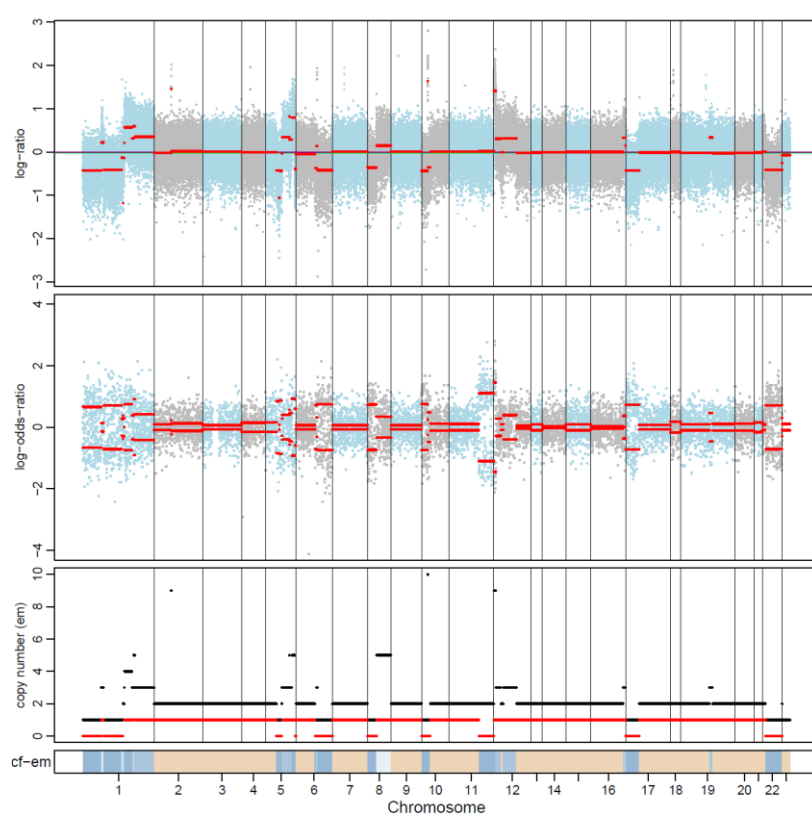
CRC-453-P2



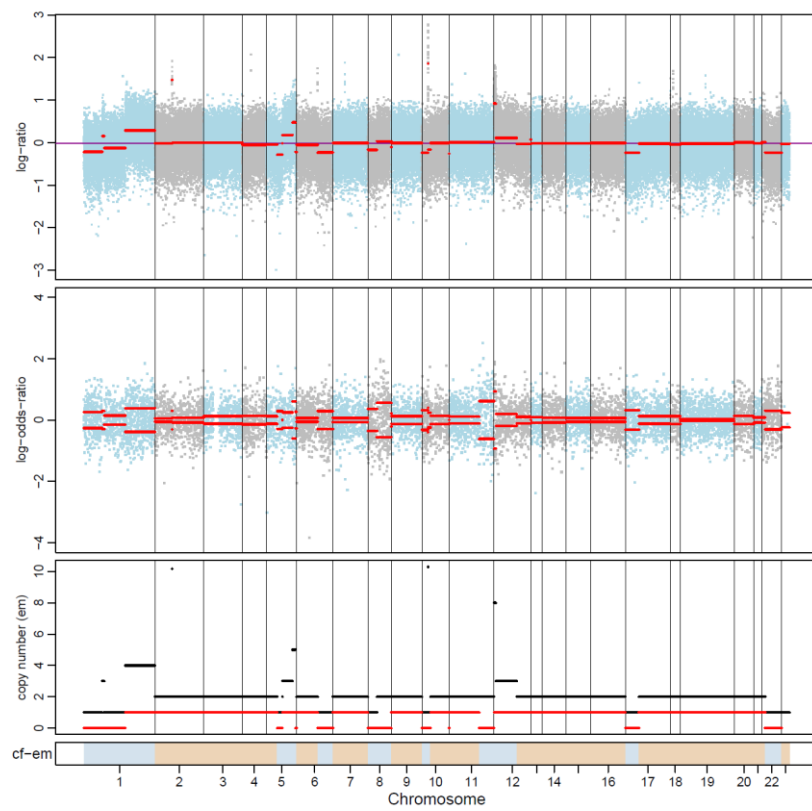
CRC-453-M



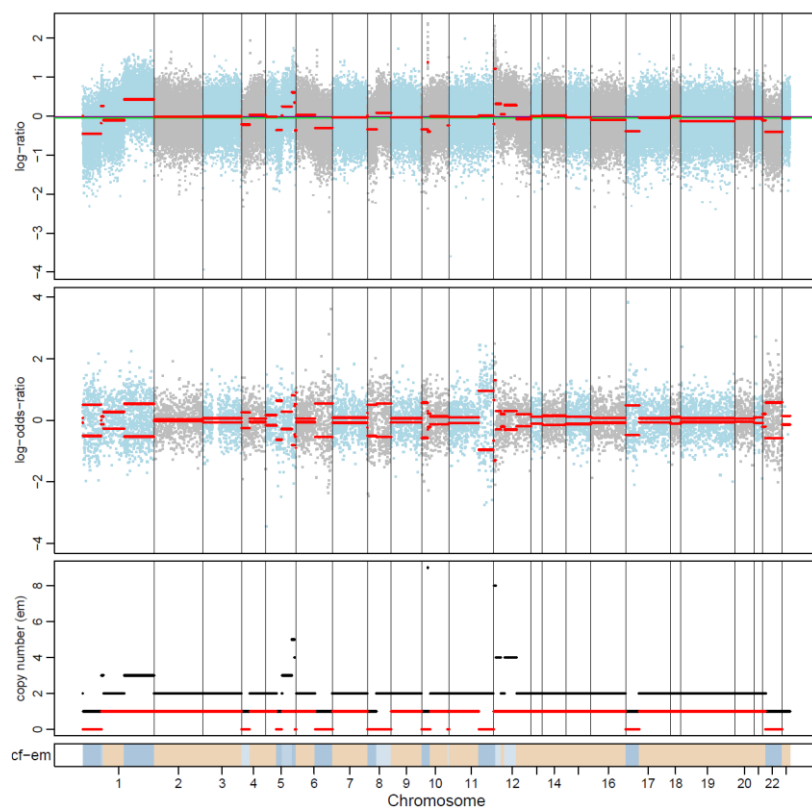
CRC-453-P1



CRC-453-P3

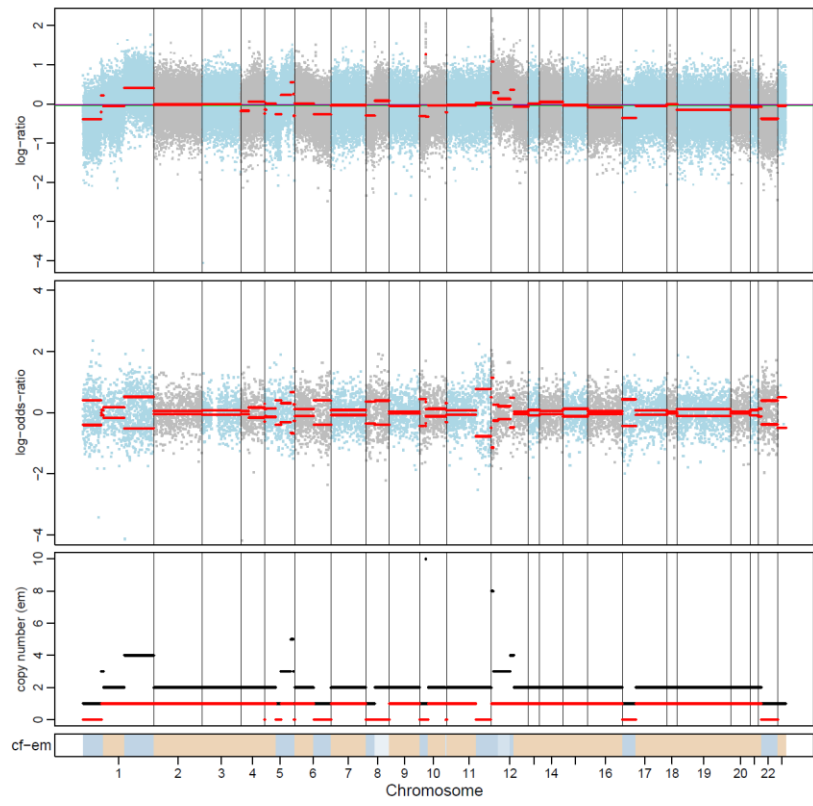


CRC-453-M1

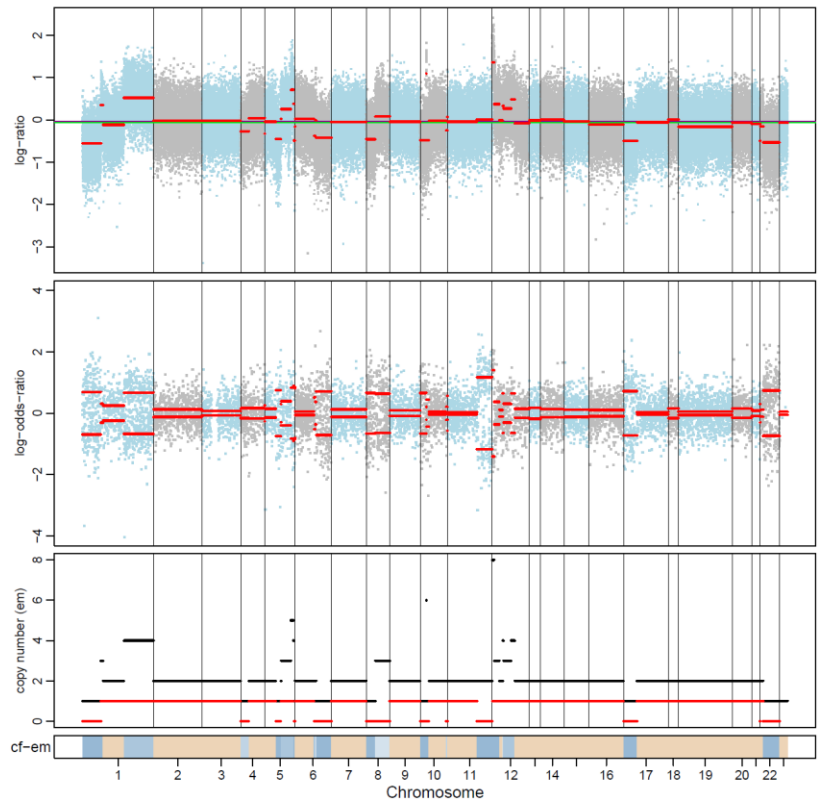




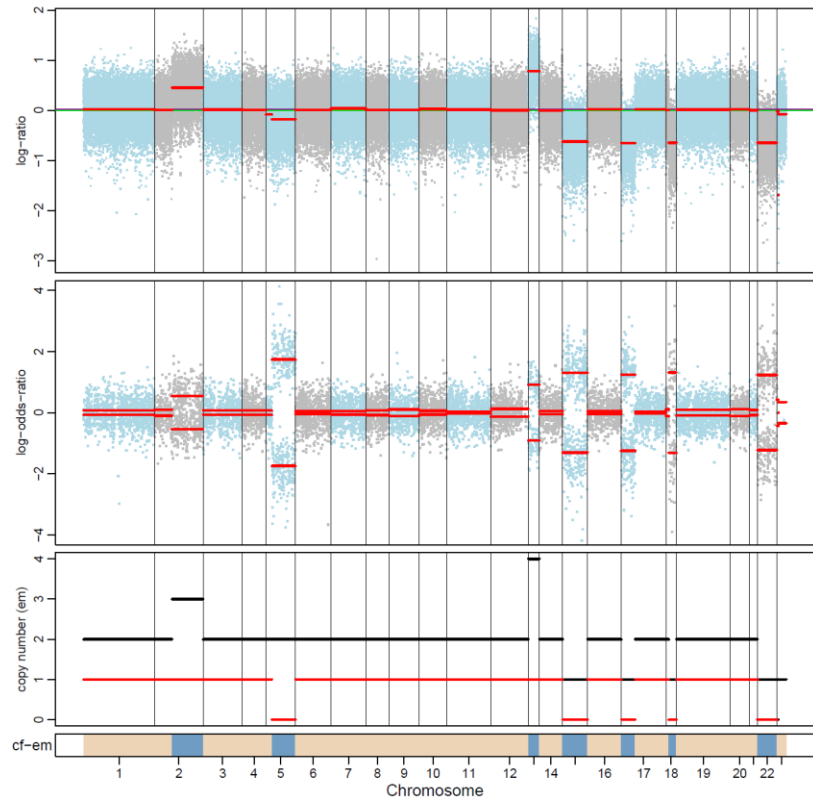
CRC-453-M2



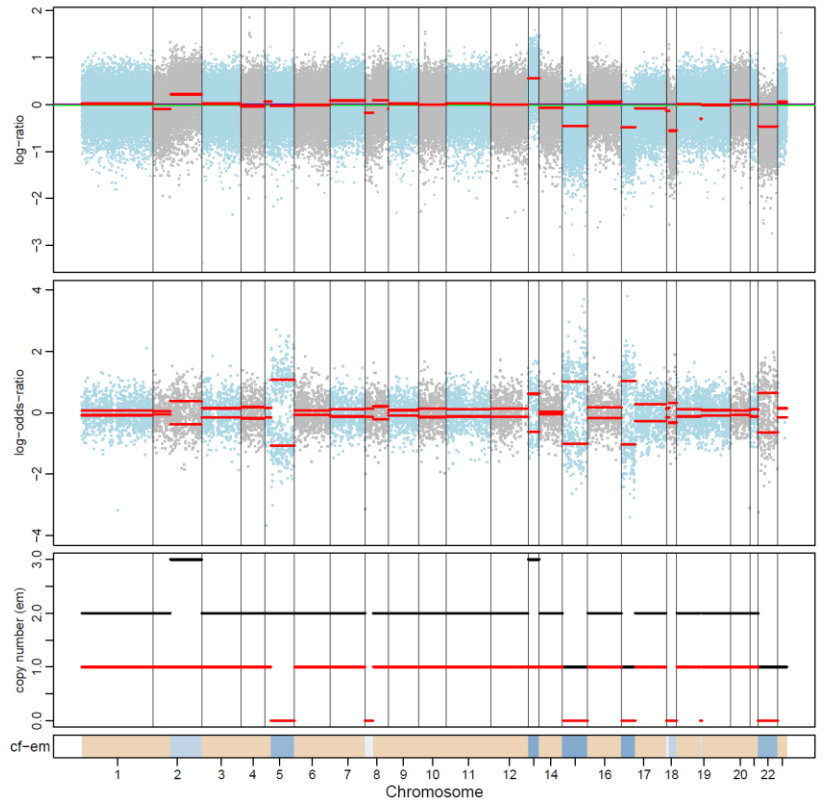
CRC-453-M3



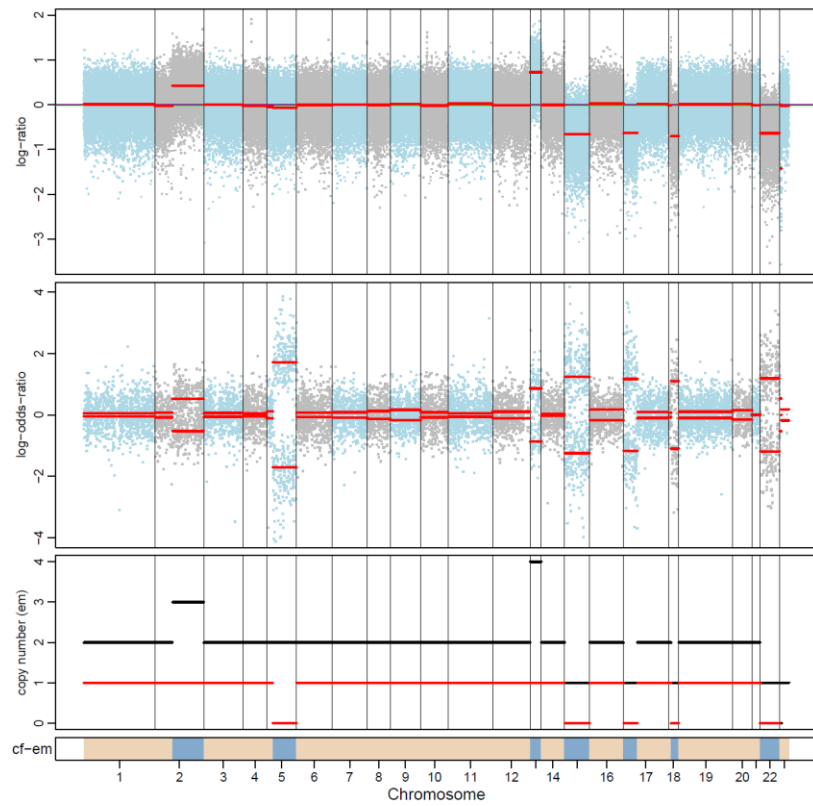
CRC-468-P



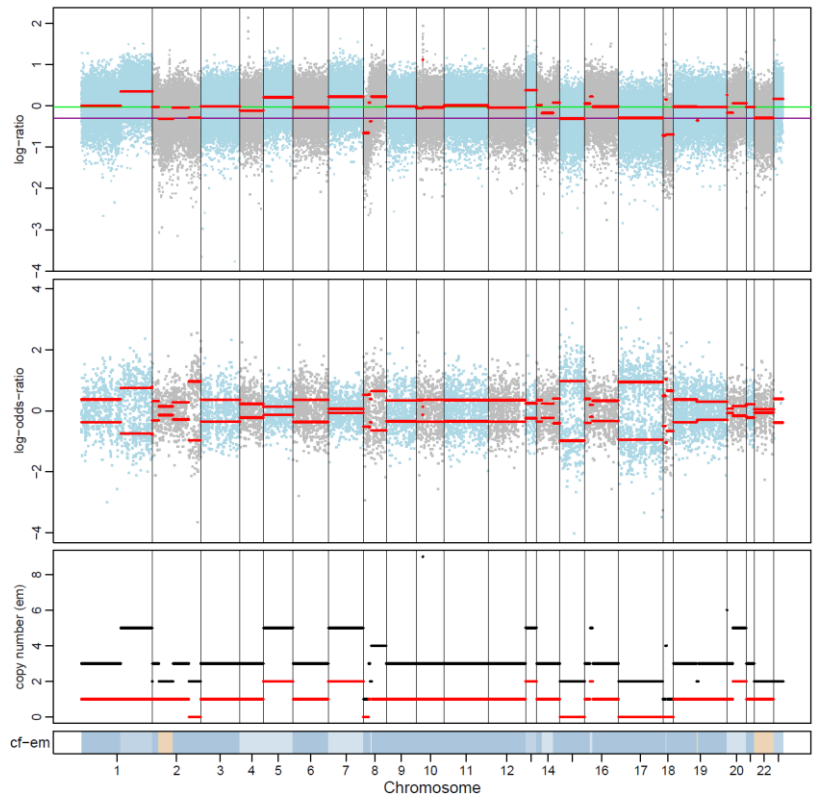
CRC-468-P1



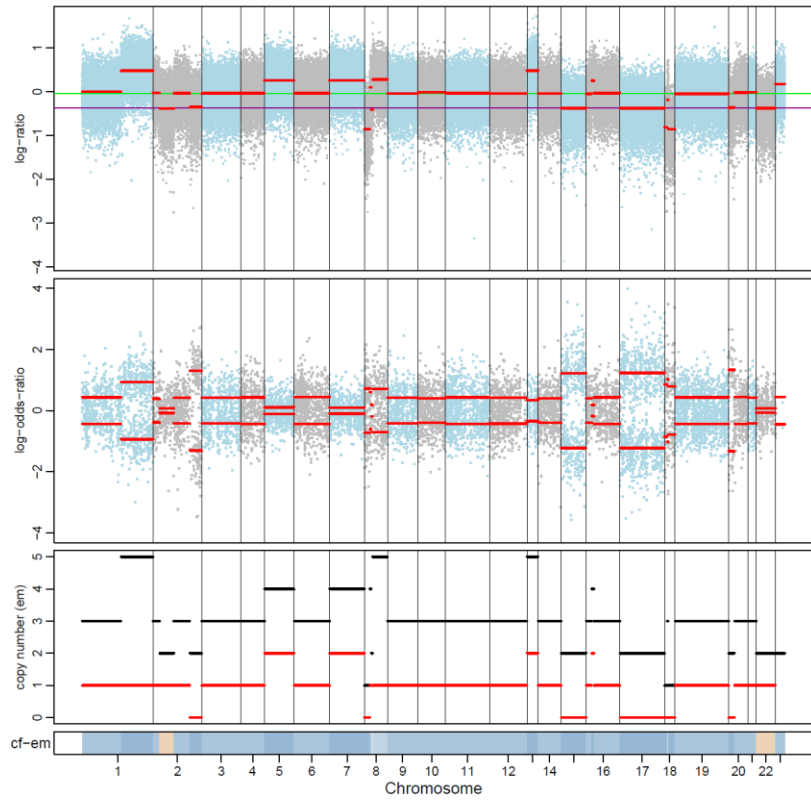
CRC-468-P2



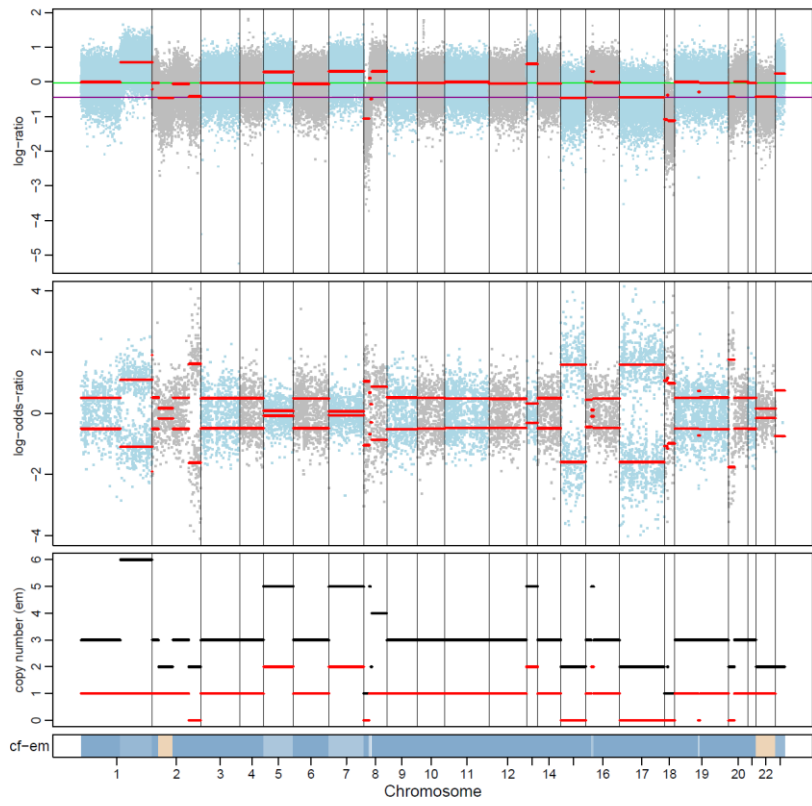
CRC-468-P3



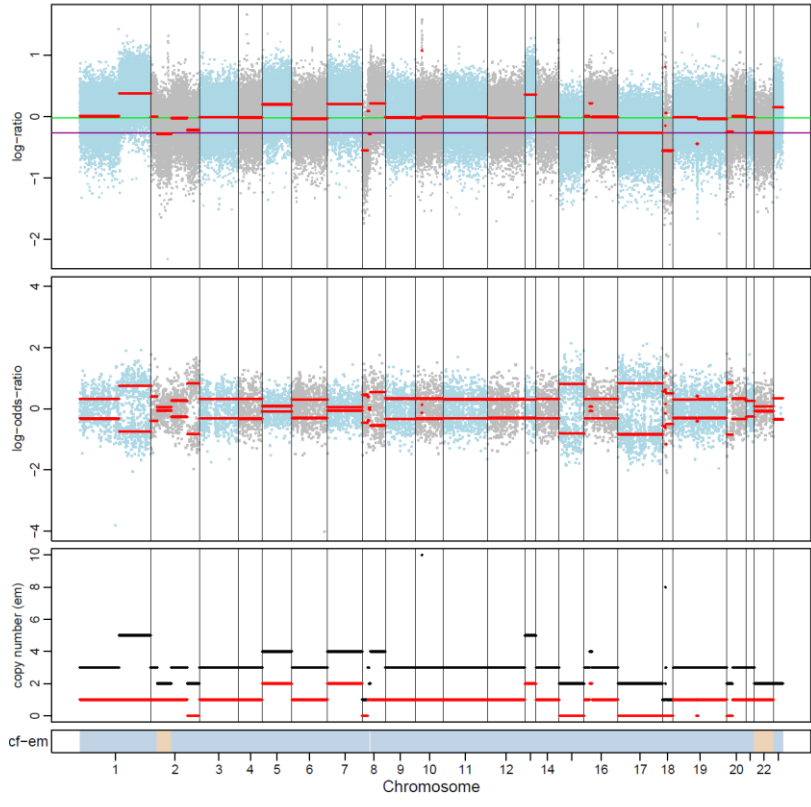
CRC-468-M



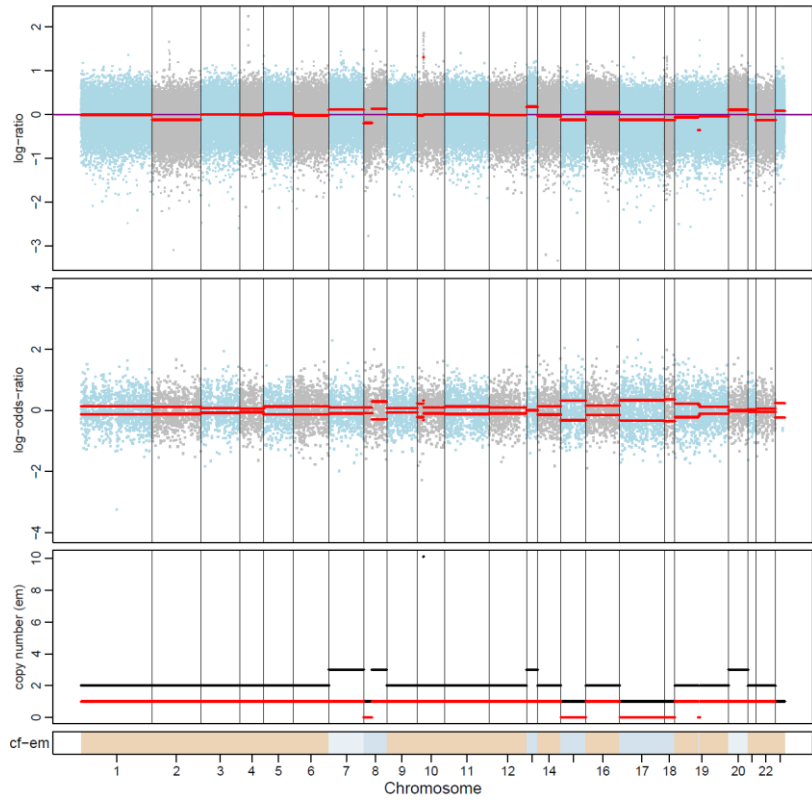
CRC-468-M1



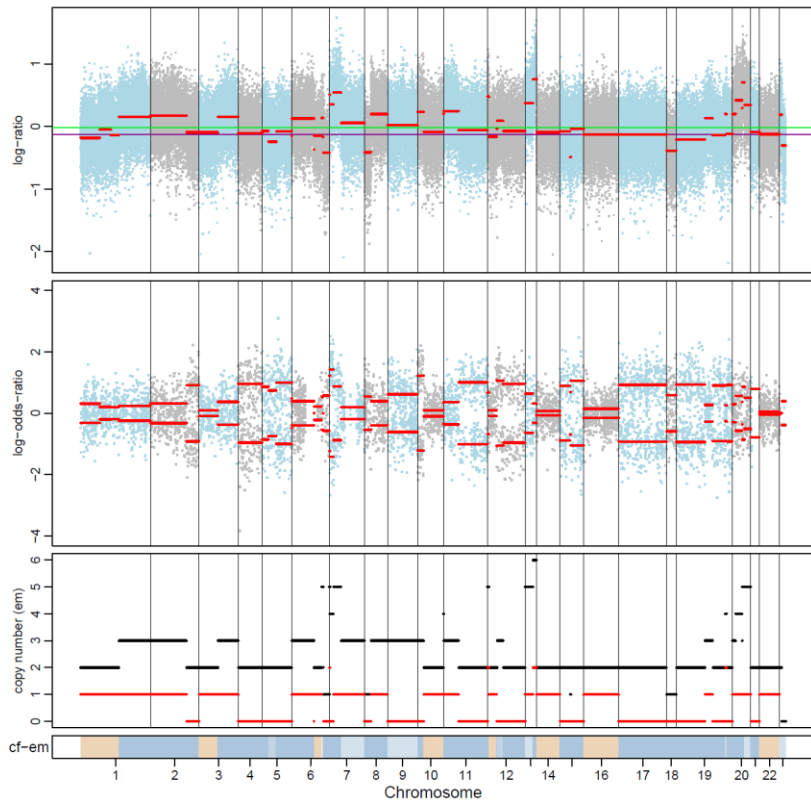
CRC-468-M2



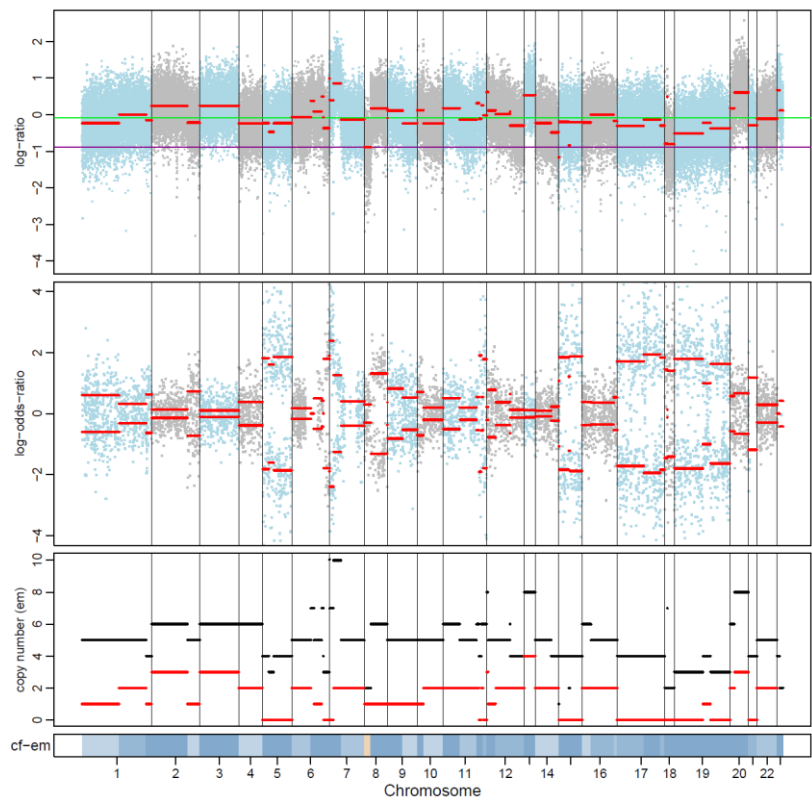
CRC-468-M3



CRC-474-P

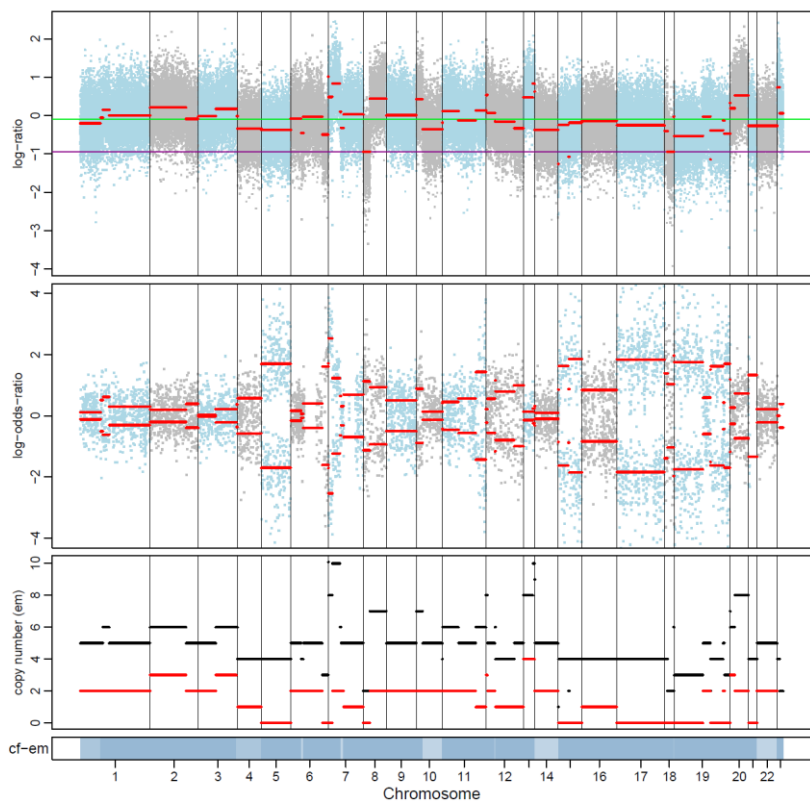


CRC-474-P1

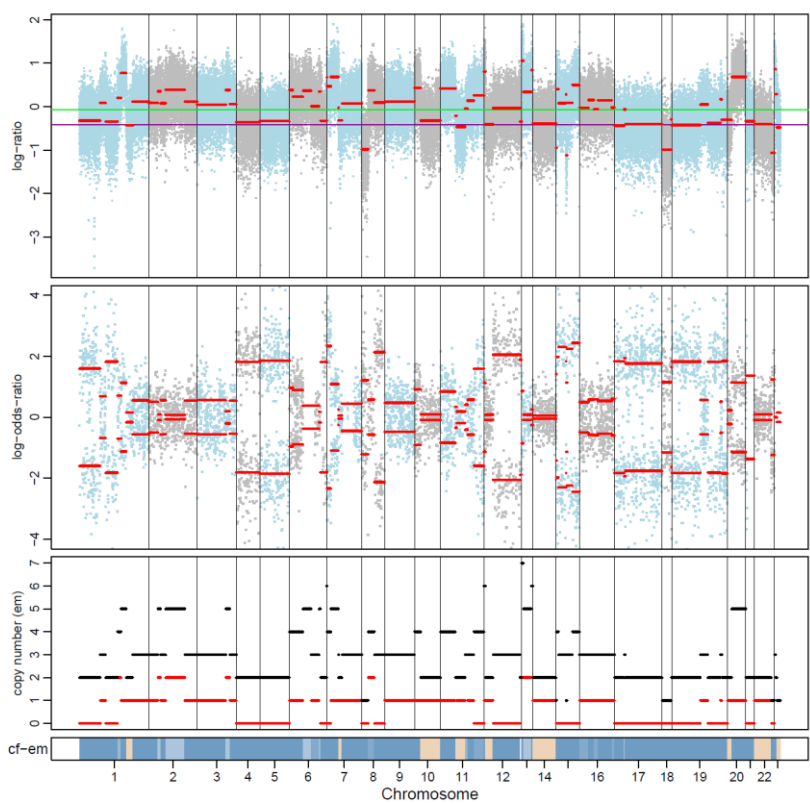




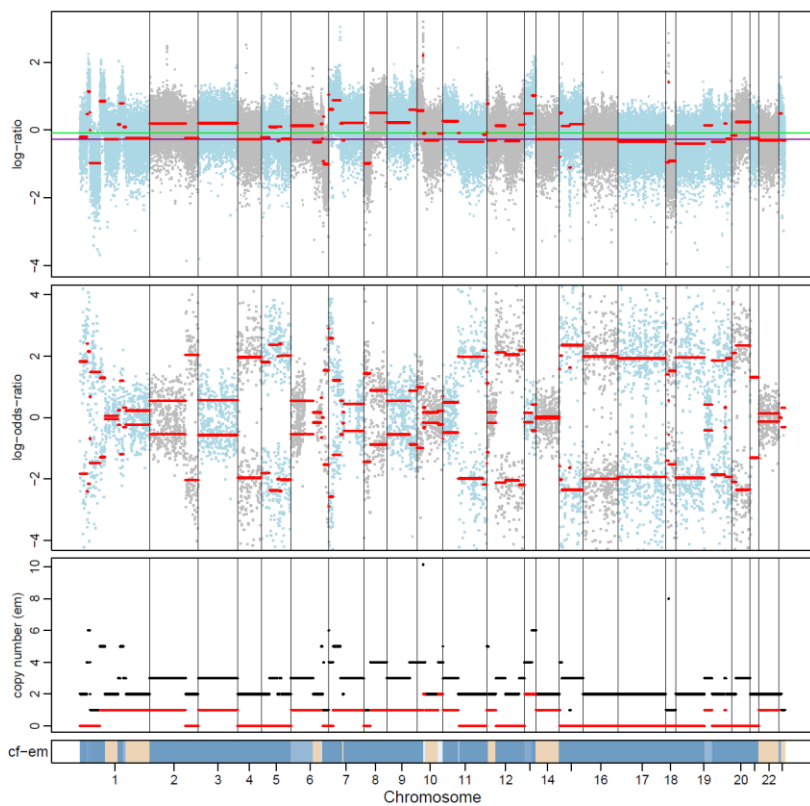
CRC-474-P2



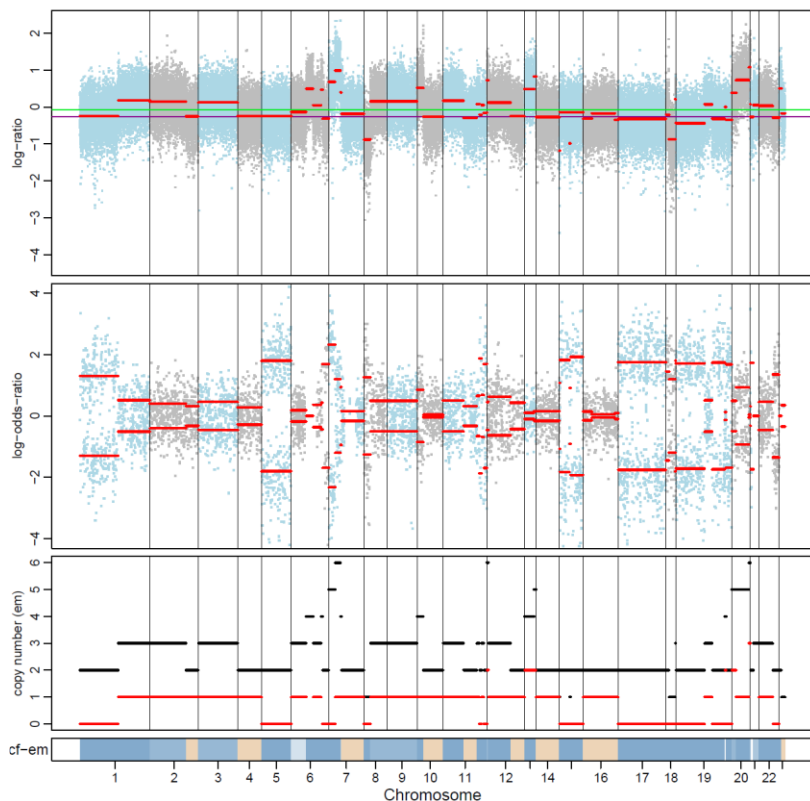
CRC-474-M



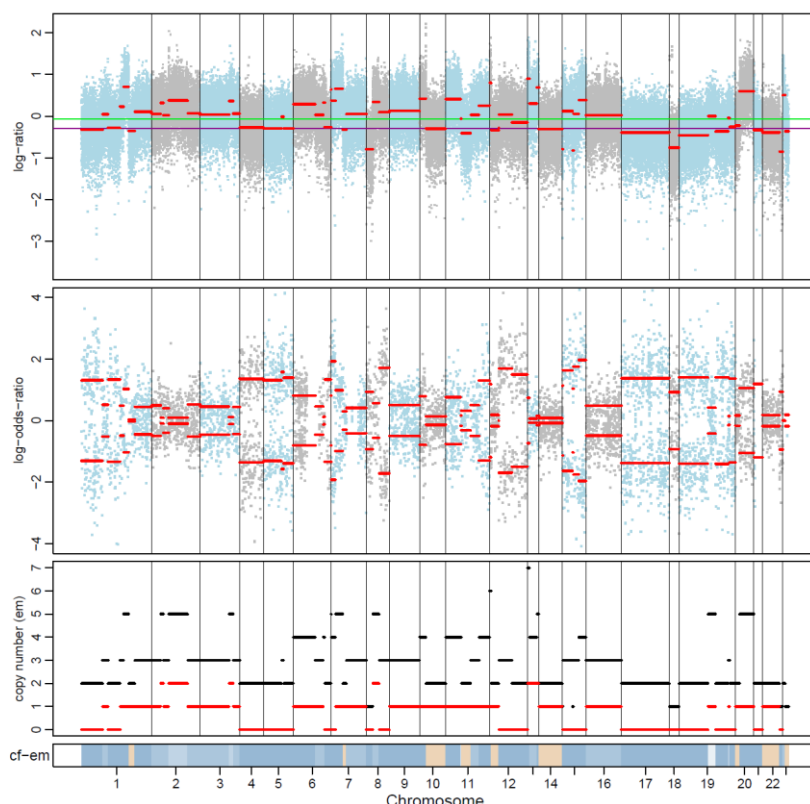
CRC-474-M2



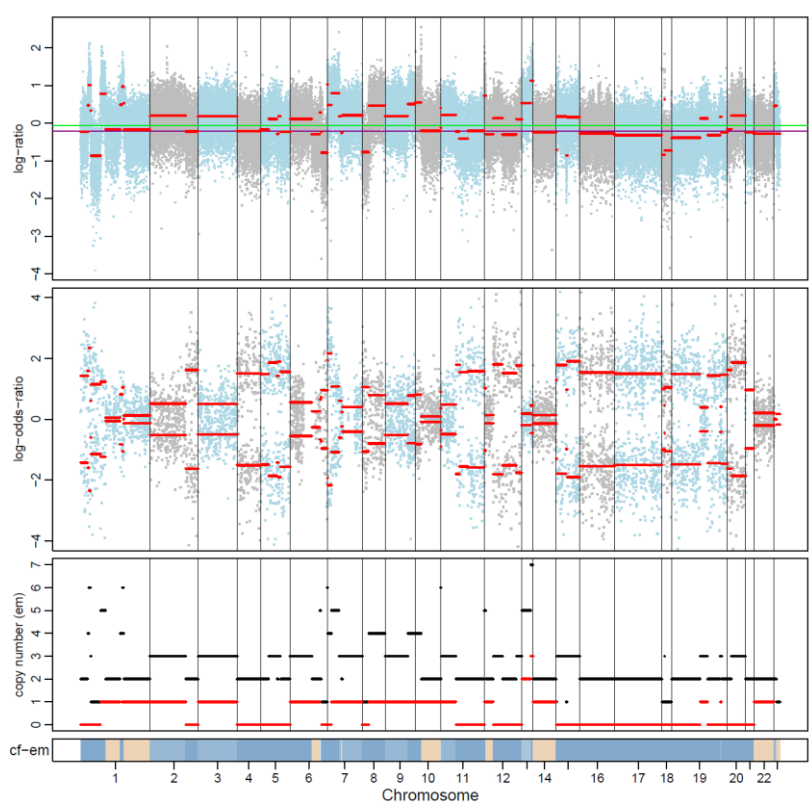
CRC-474-P3



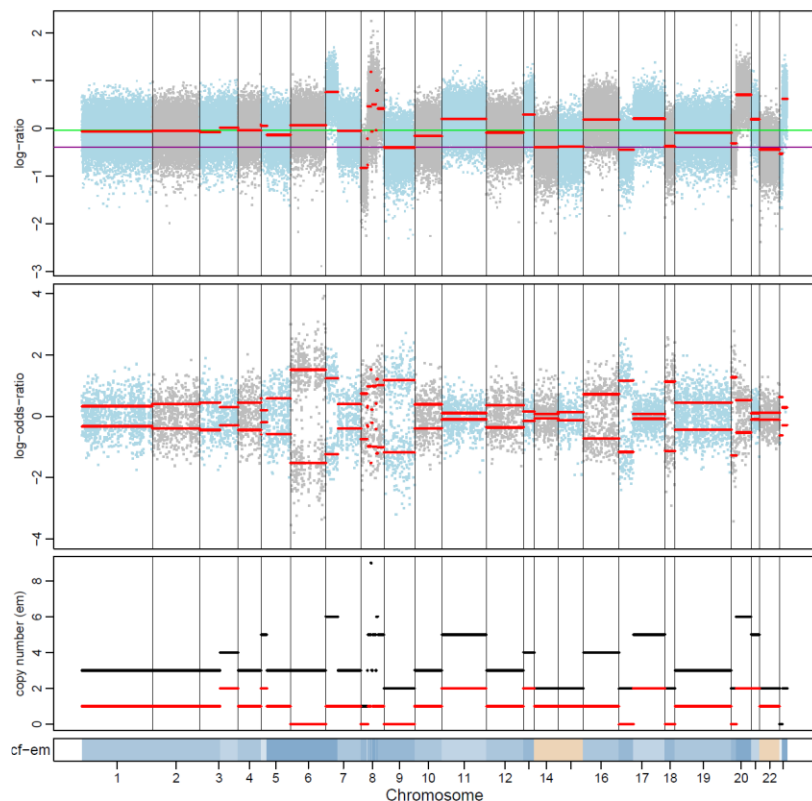
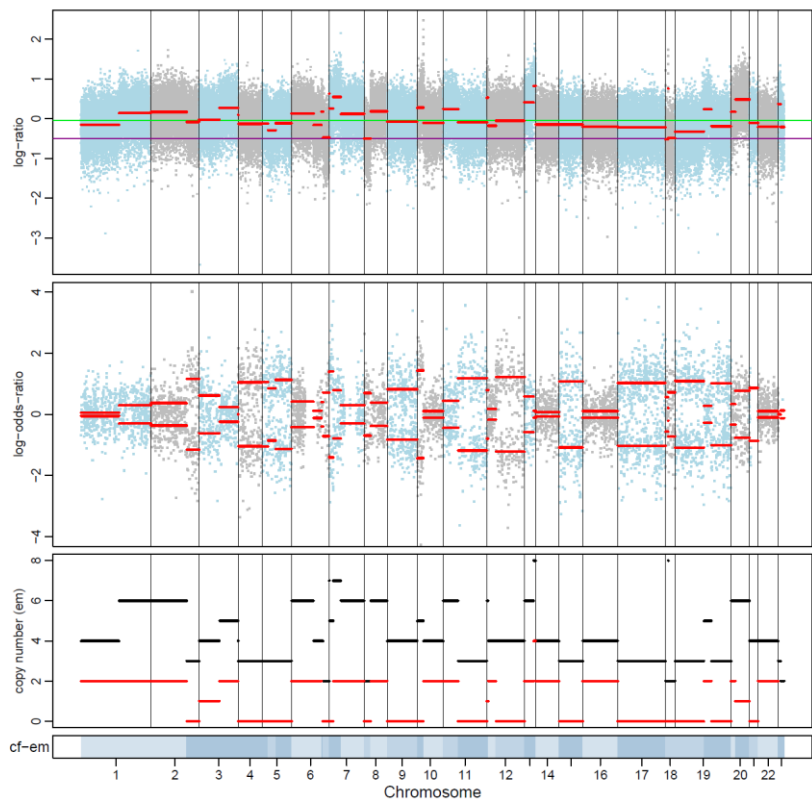
CRC-474-M1



CRC-474-M3

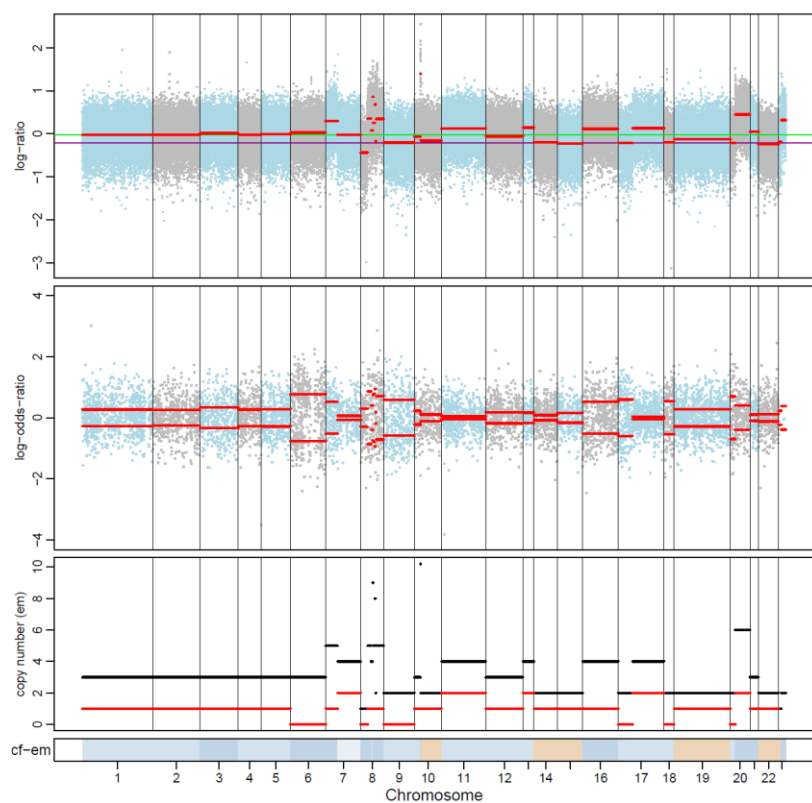
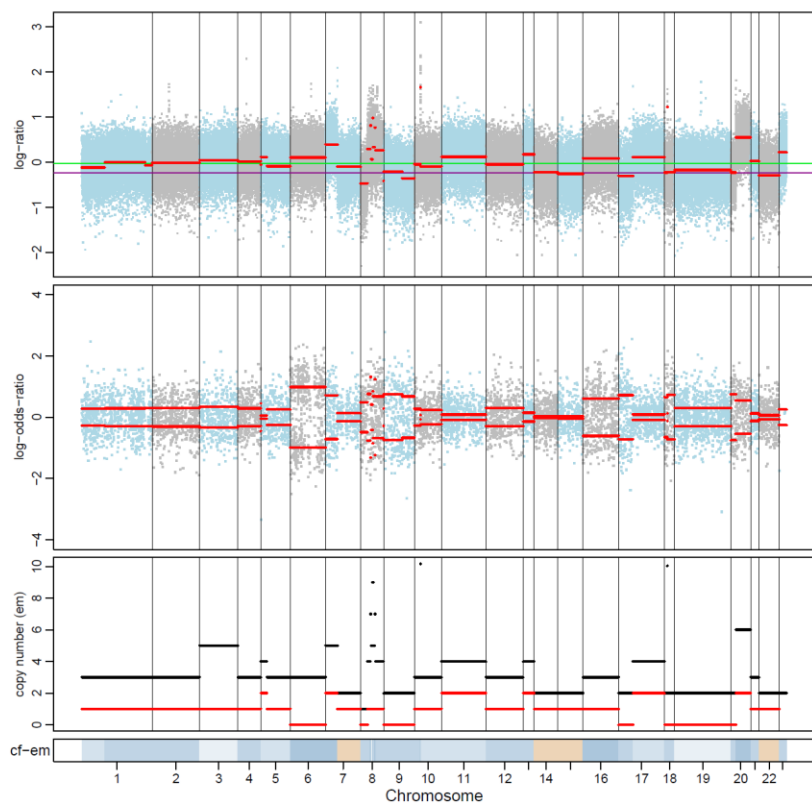


CRC-474-M4



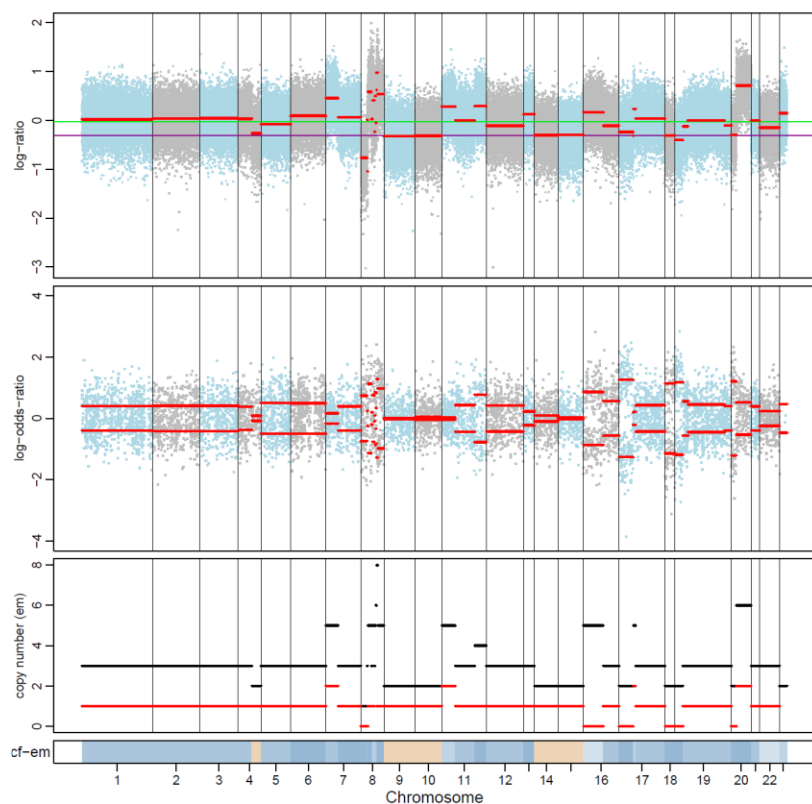
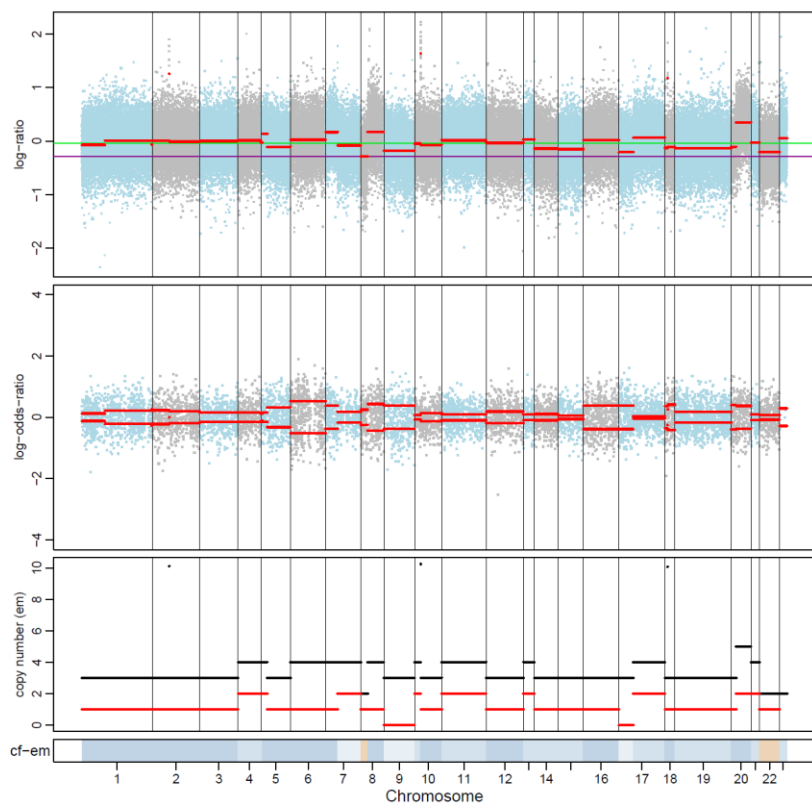
CRC-477-P

CRC-477-P1



CRC-477-P2

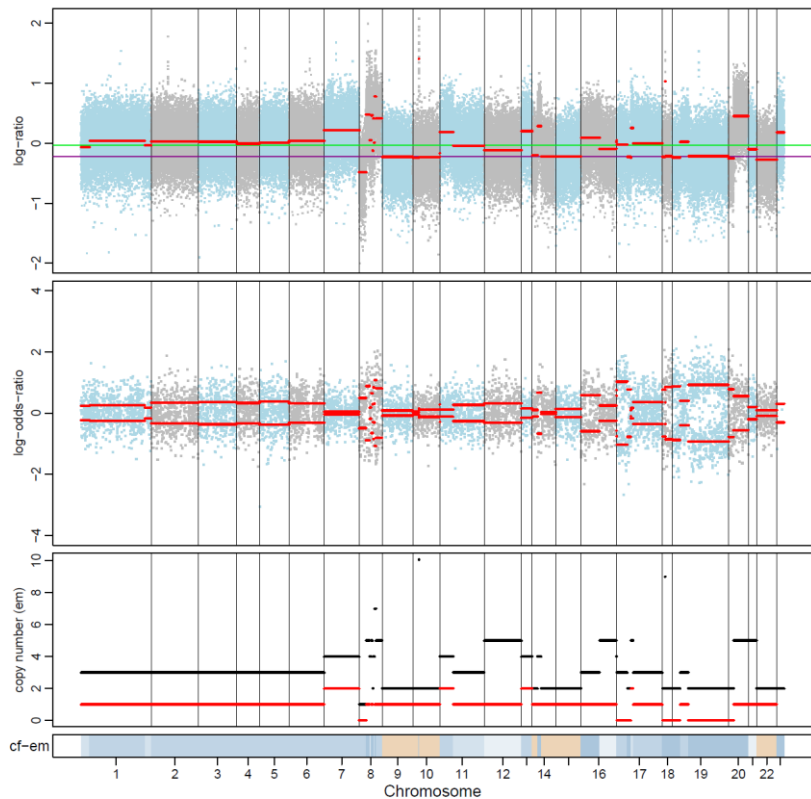
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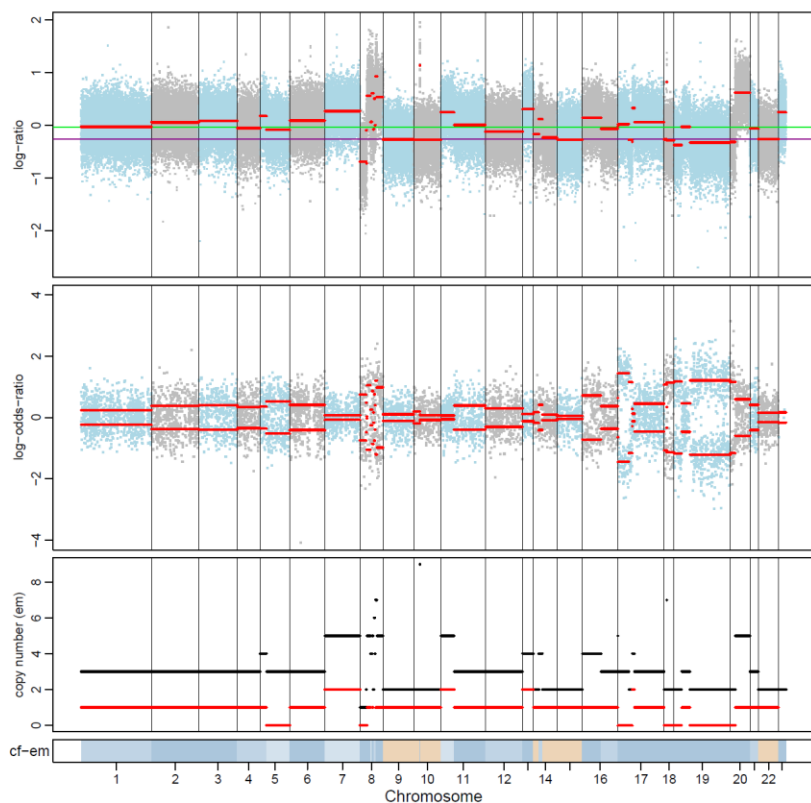
CRC-477-M



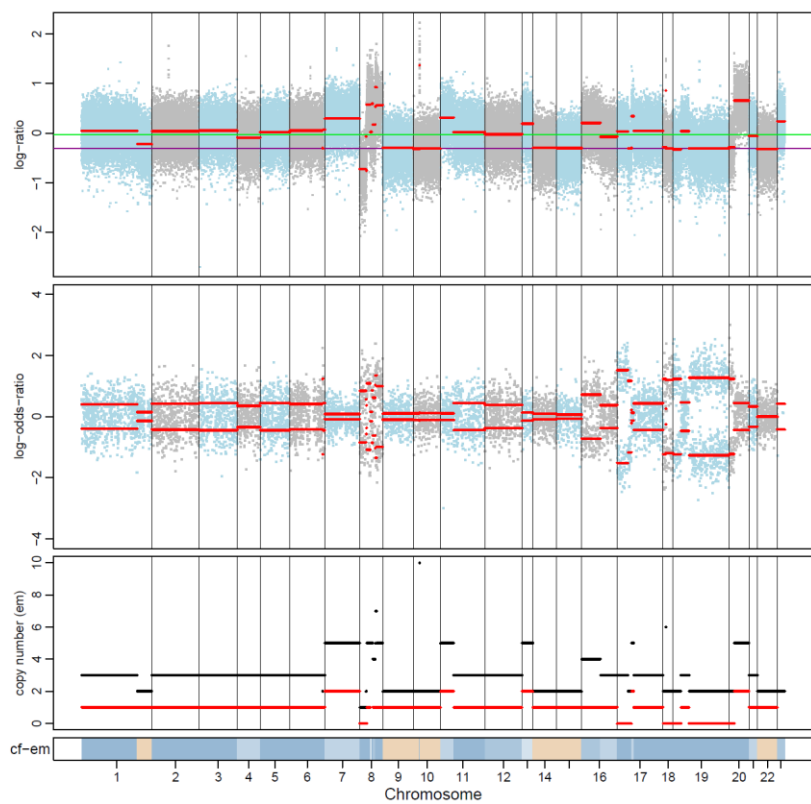
CRC-477-M1



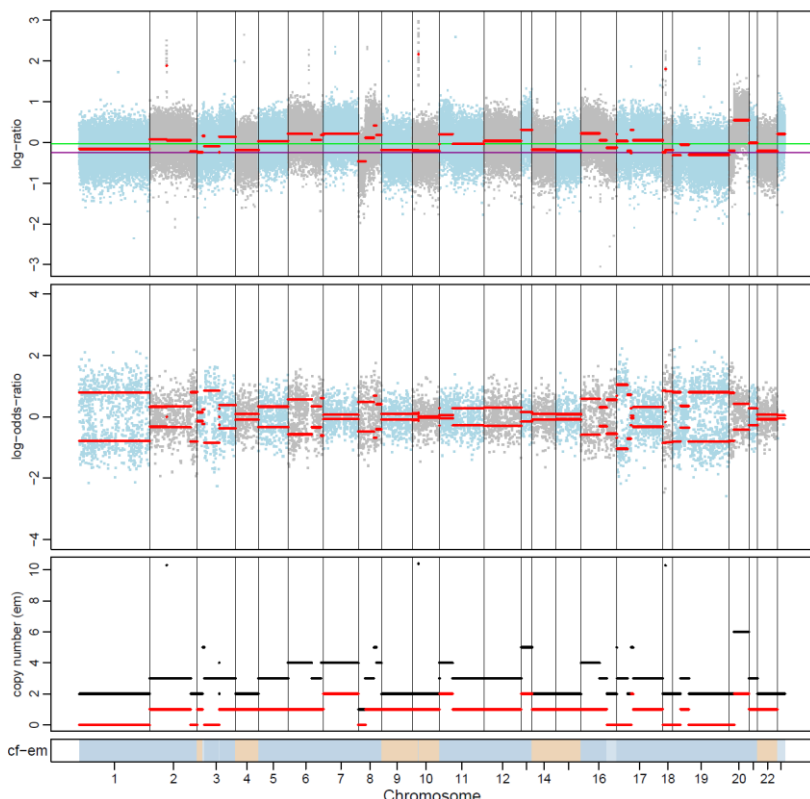
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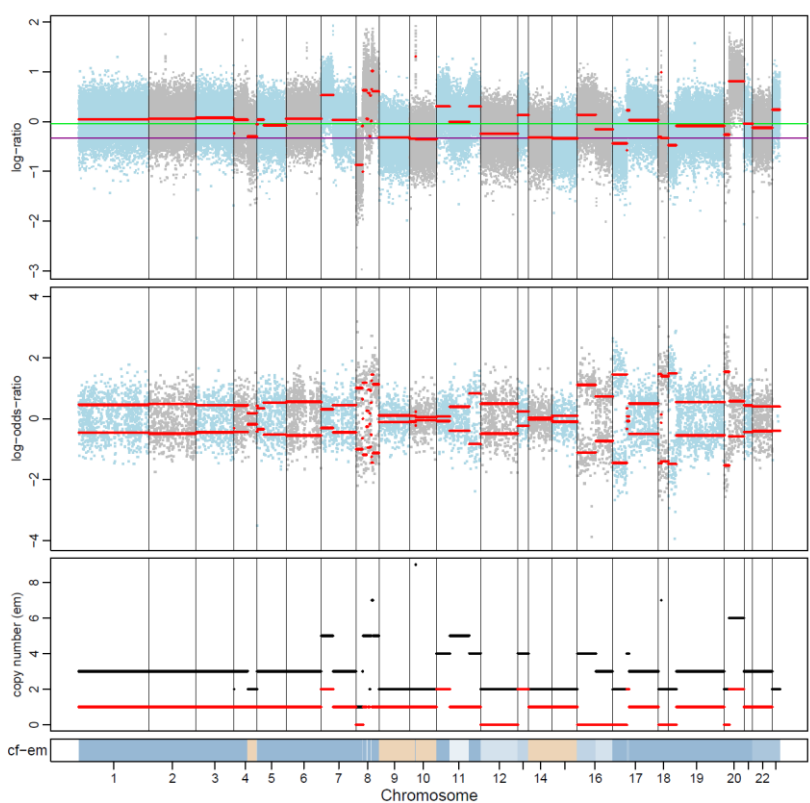
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CRC-477-M2

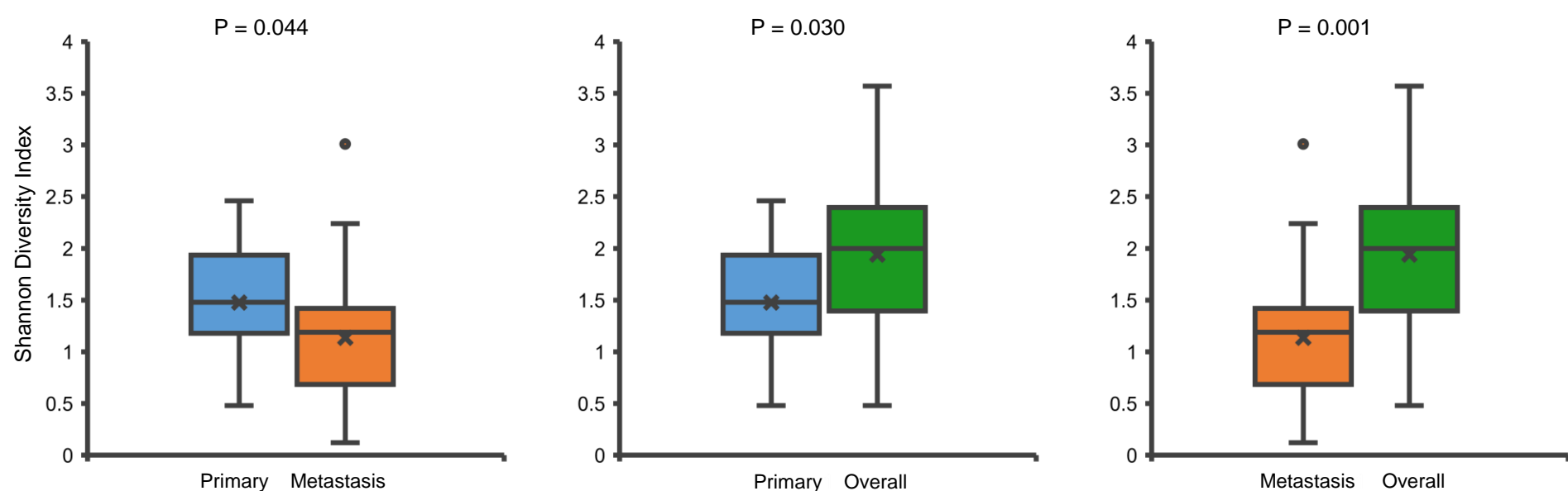


CRC-477-M4

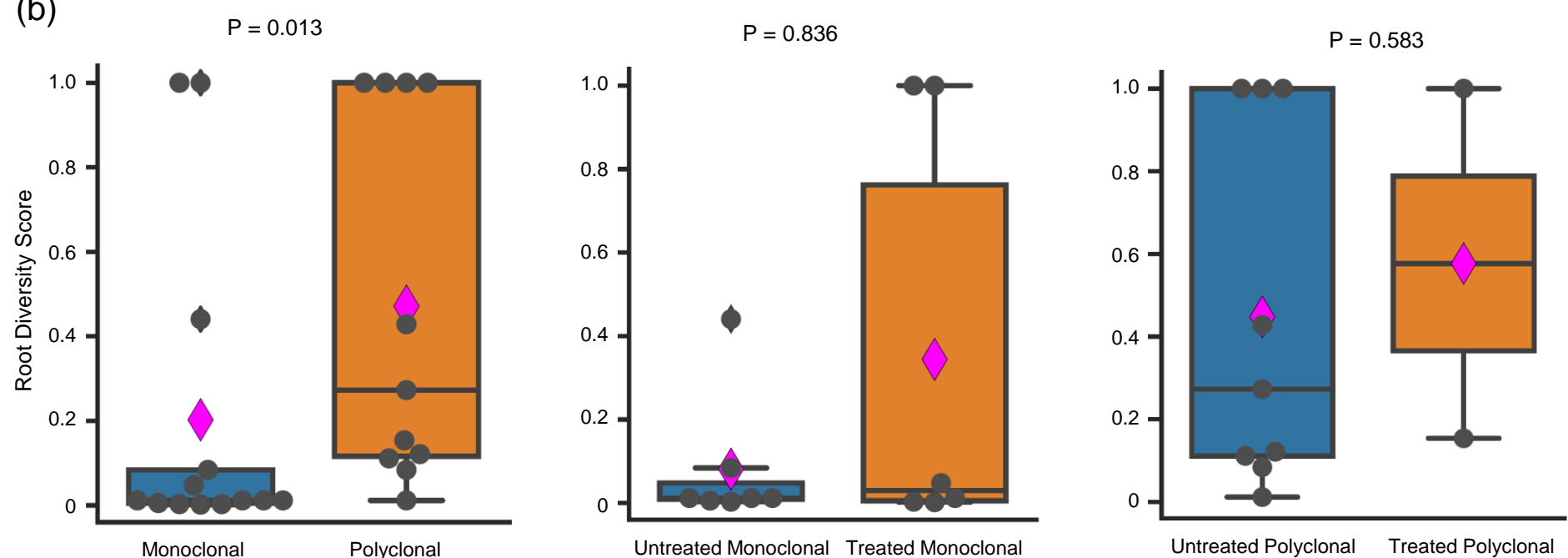




(a)

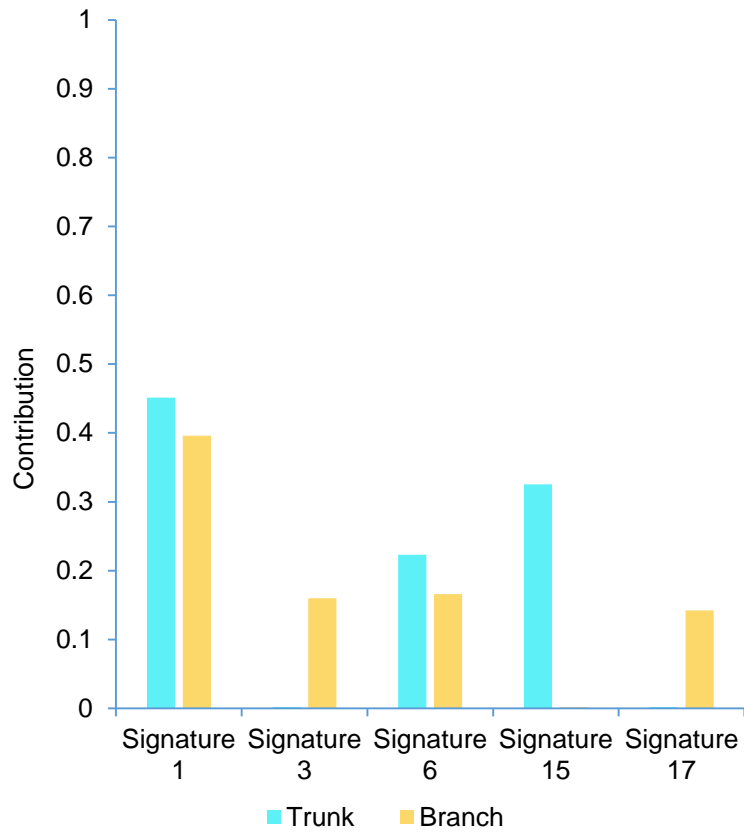


(b)



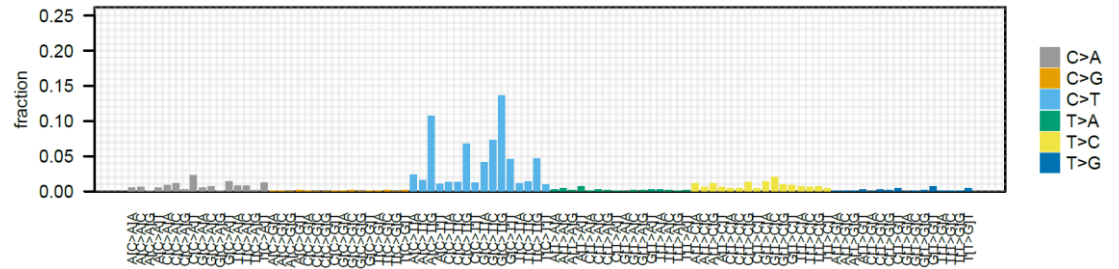
**Figure S2:** Box plot representation of tumour heterogeneity, via (a) Shannon Diversity Index (SDI) (b) Root Diversity Scores (RDS) of 21 samples with multiple sampled regions

(a)



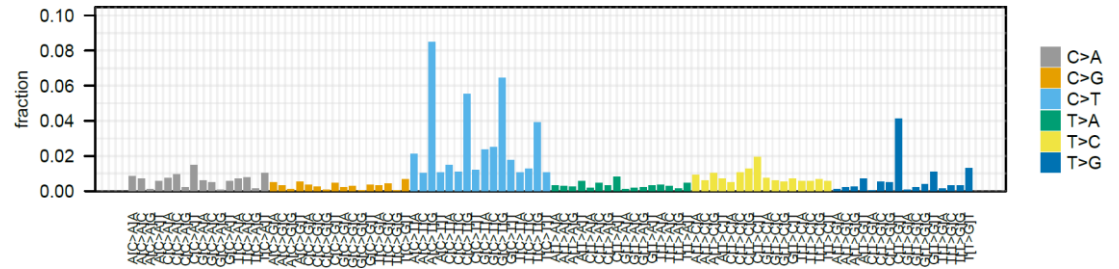
Trunk

Signature.1 : 0.451 & Signature.6 : 0.223 & Signature.15 : 0.326

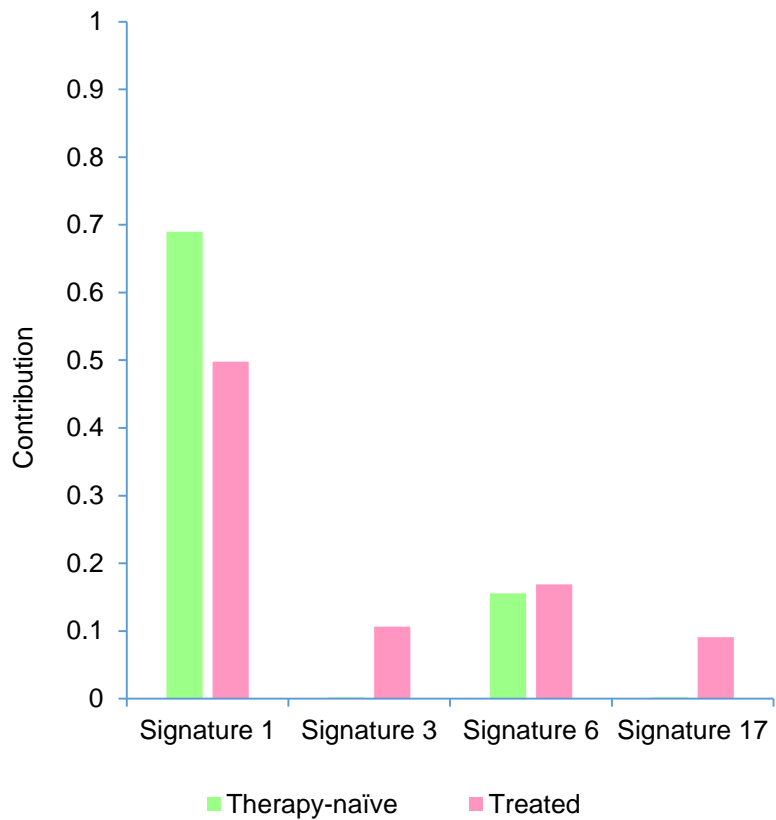


Branch

Signature.1 : 0.396 & Signature.3 : 0.16 & Signature.6 : 0.166 & Signature.17 : 0.142

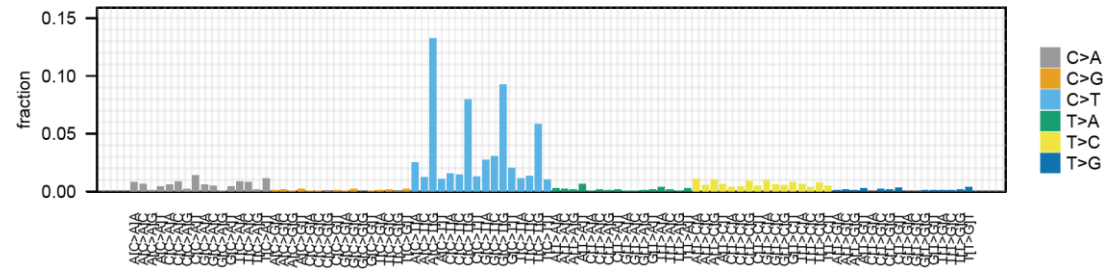


(b)



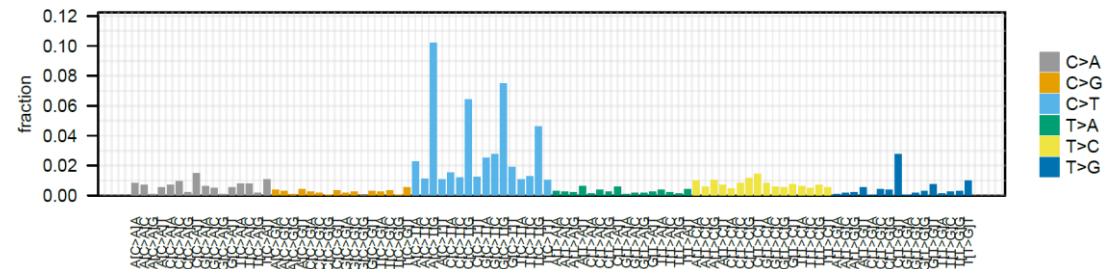
Therapy-naïve

Signature.1 : 0.69 & Signature.6 : 0.156



Treated

Signature.1 : 0.498 & Signature.3 : 0.106 & Signature.6 : 0.169 & Signature.17 : 0.091

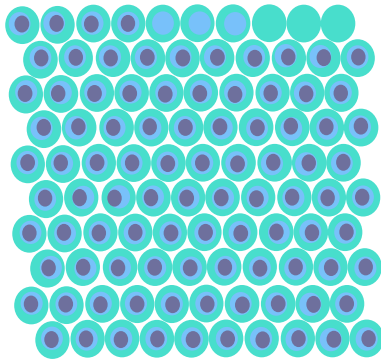
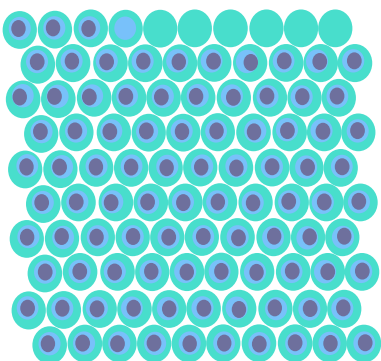
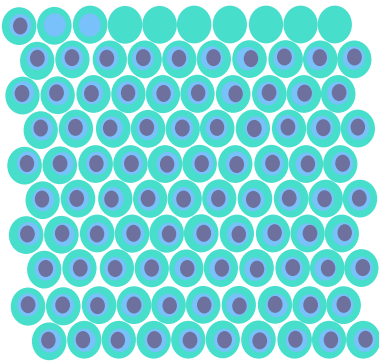
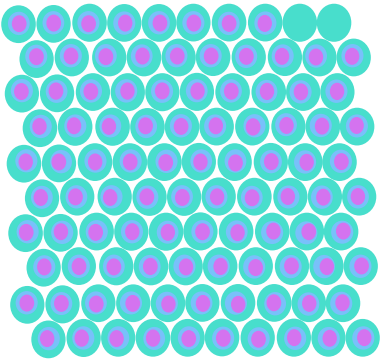
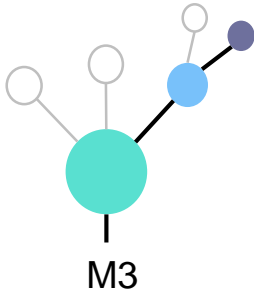
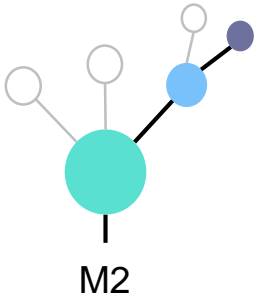
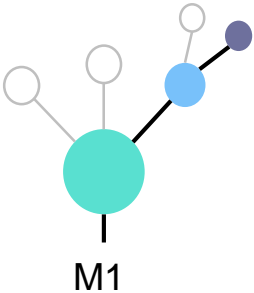
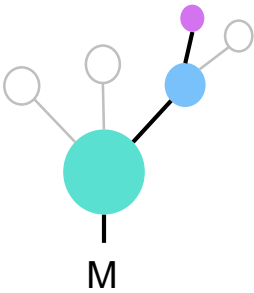
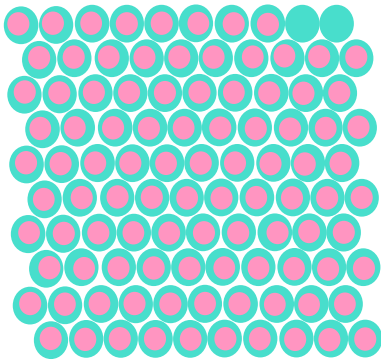
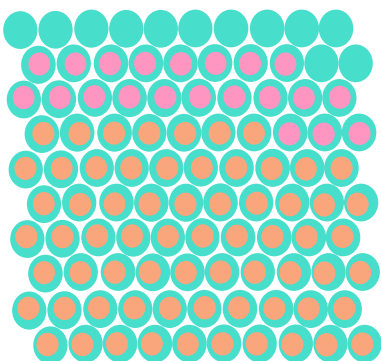
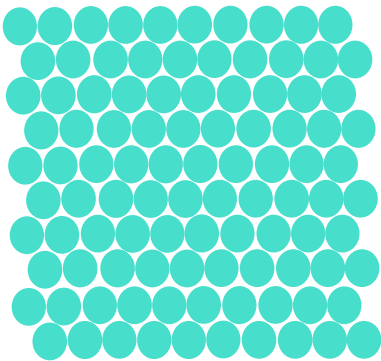
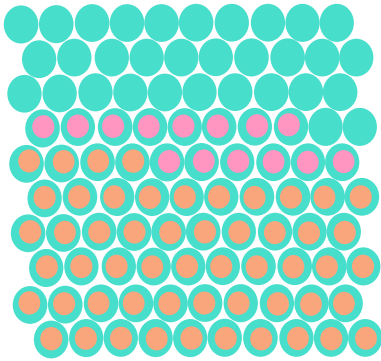
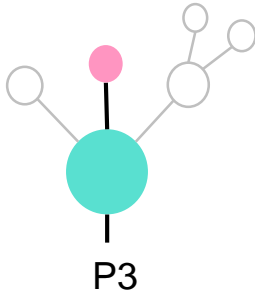
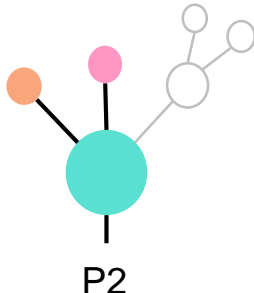
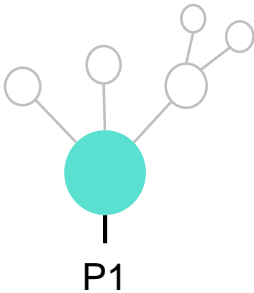
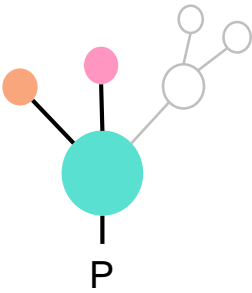
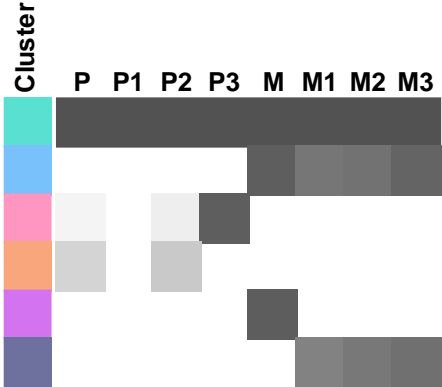
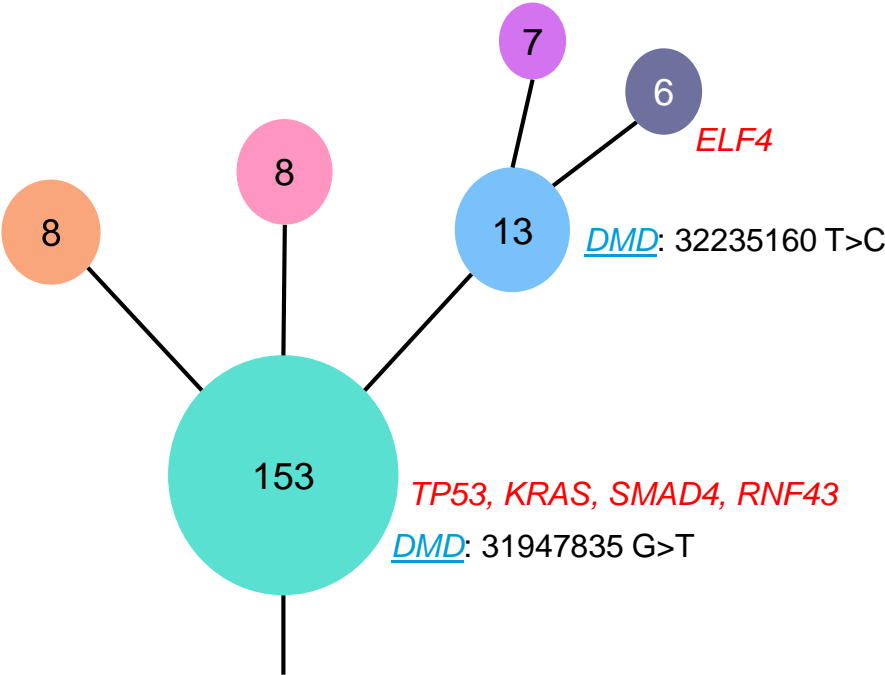
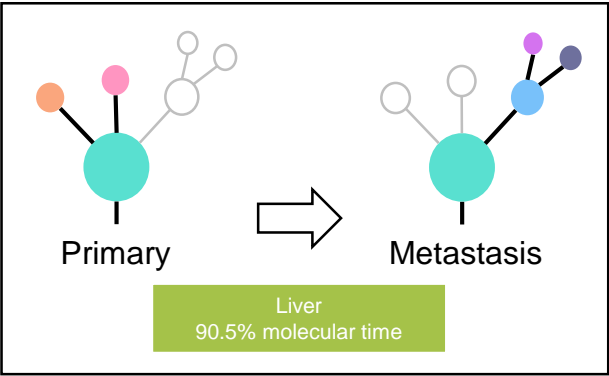


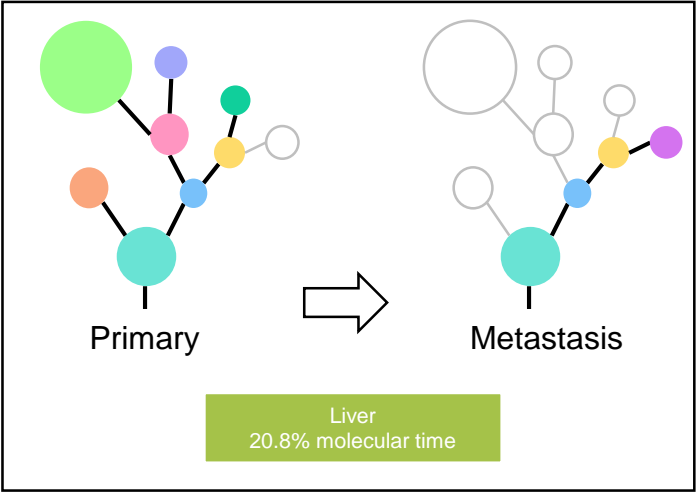
**Figure S3:** Contribution of all mutational signatures, from the 30 published COSMIC mutational signatures, across the metastatic CRC cohort for (a) Trunk and branch single nucleotide base mutations; and single nucleotide base mutations in (b) Therapy-naïve and treated cases. The raw plots have also been included. Signature 1 relates to age at diagnosis; Signature 3 is associated with defective DNA homologous repair; Signatures 6 and 15 are related to defective DNA mismatch repair; and Signature 17 is partially related to 5-fluorouracil and capecitabine chemotherapy

## Figure S4: Phylogenetic trees.

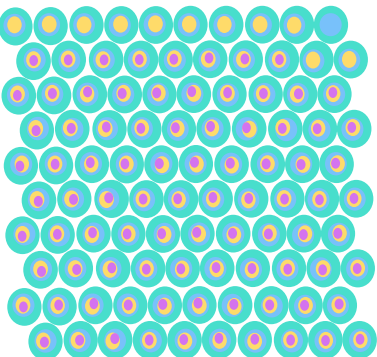
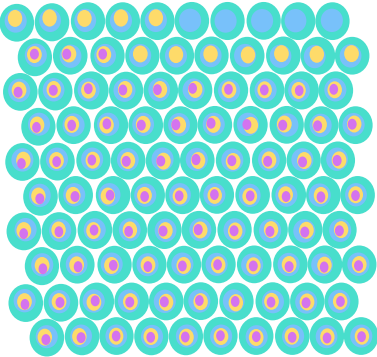
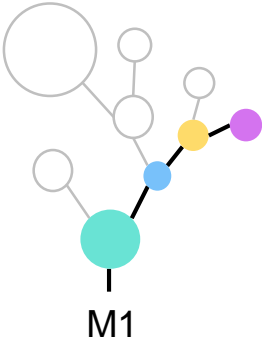
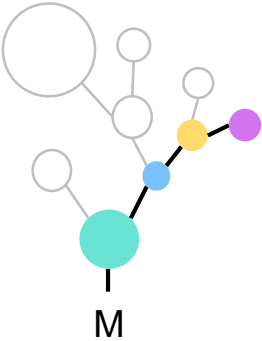
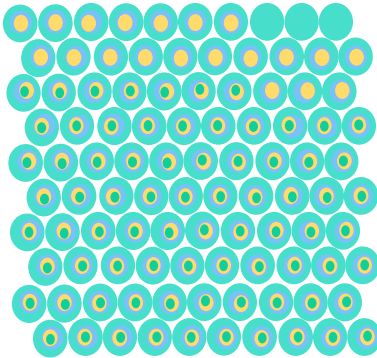
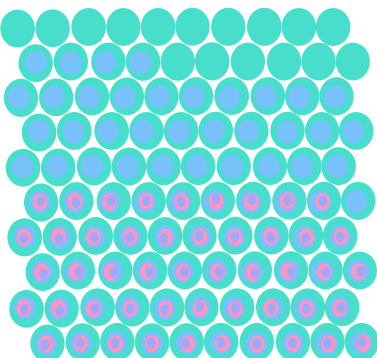
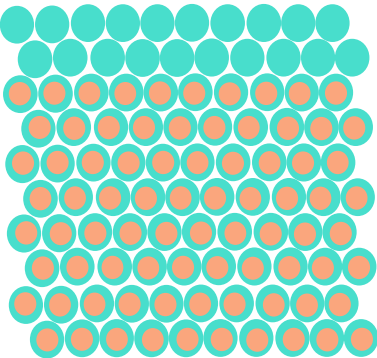
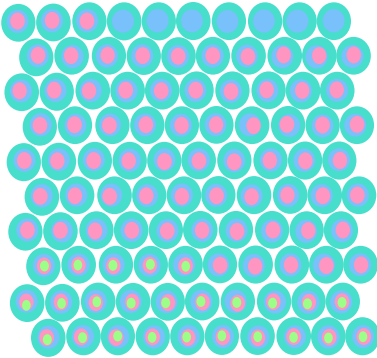
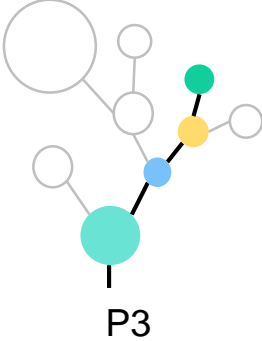
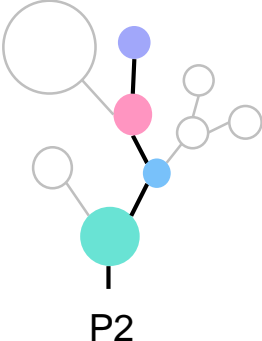
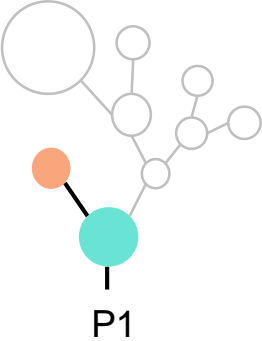
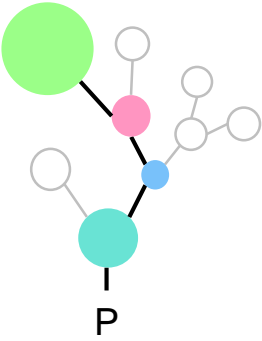
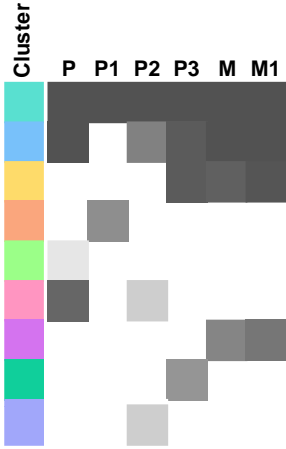
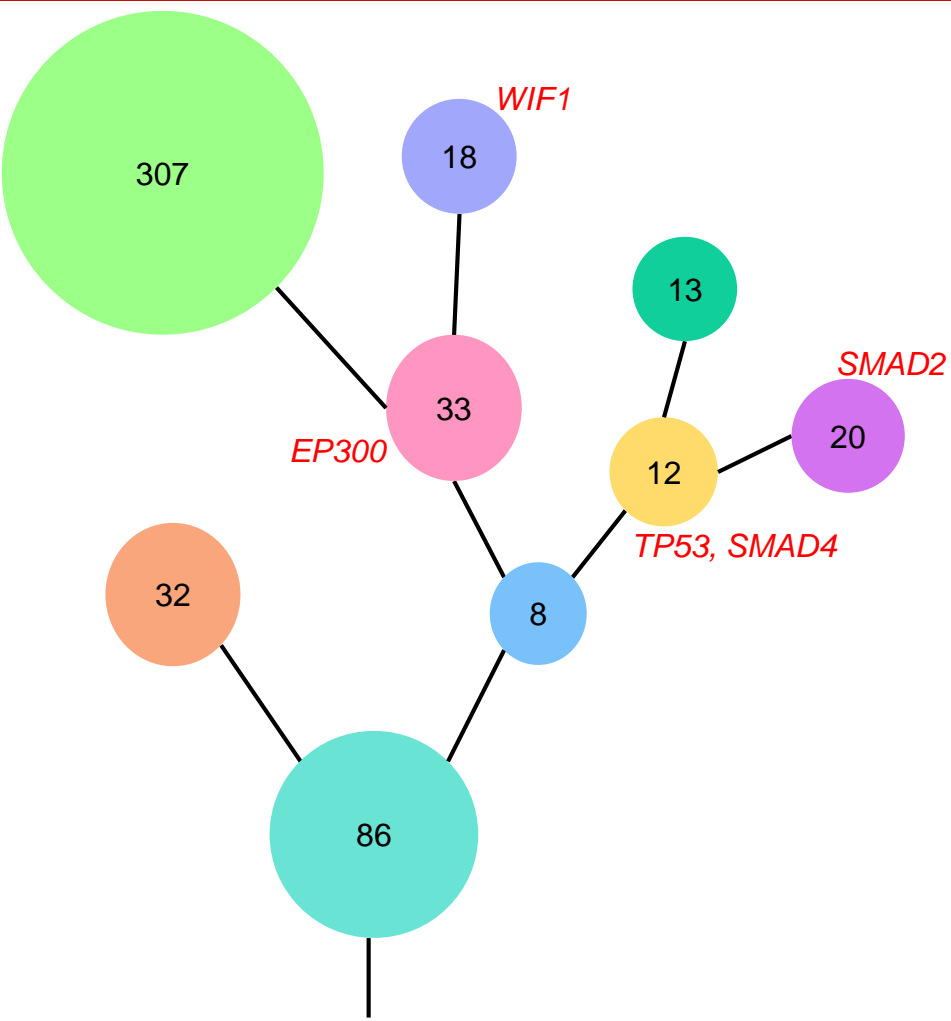
Phylogenetic trees for 30 colorectal cancer tumors with metastasis. For each sample only the optimal tree derived using LICHeE (Lineage Inference for Cancer Heterogeneity and Evolution) is presented. Driver genes are highlighted in red; non-driver cancer gene events are denoted in blue and non-cancer events in black. Parallel events converging at a particular gene have been underlined. The middle top pane shows the complete phylogenetic tree as constructed based on mutation clusters, with primary and metastatic phylogenetic trees, with metastatic site and %final molecular time at primary tumour, shown separately in a black box. Different colored nodes represent distinct clones, with the number of mutations contributing to the cluster displayed inside each node. Below are the phylogenetic trees shown for each region, where clusters not found in a given region have been represented as grey empty nodes. “P”, represents regions from primary tumors; “LN-M”, represents tumor tissue from lymph node metastases; “M”, represents metastatic tumor tissue. Beneath each regional phylogenetic tree, a grid of a 100 representative cells shows the mutational clusters present via coinciding cluster colors.

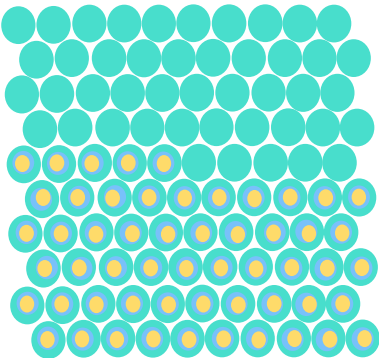
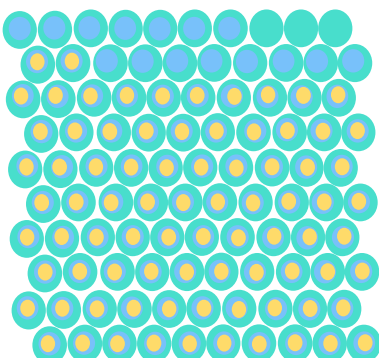
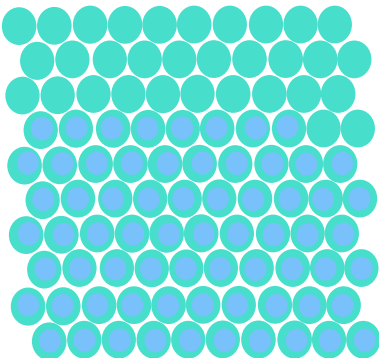
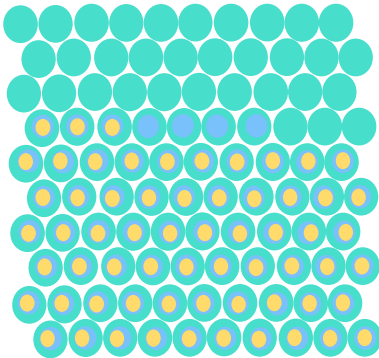
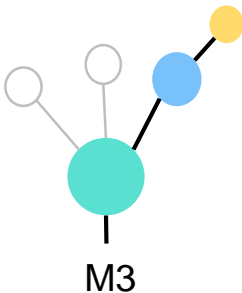
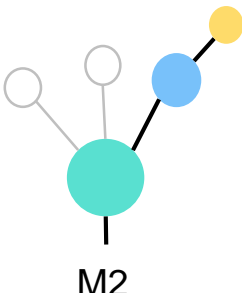
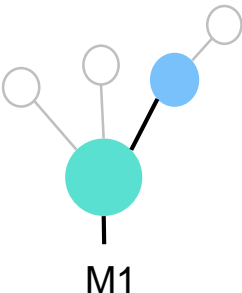
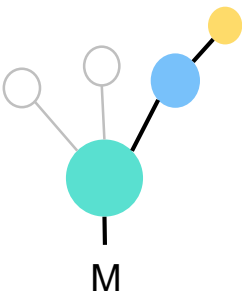
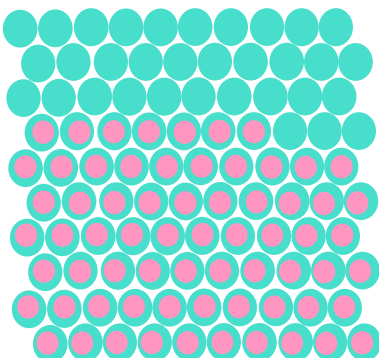
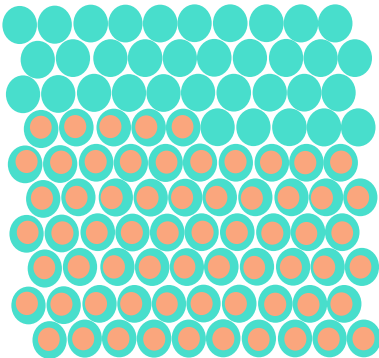
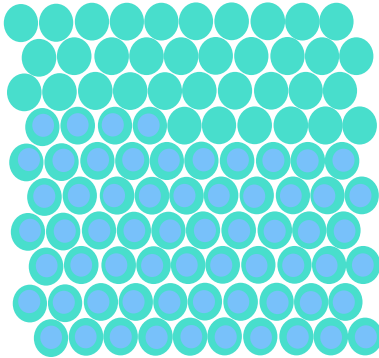
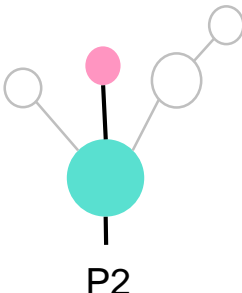
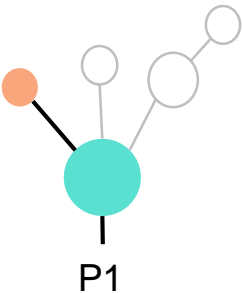
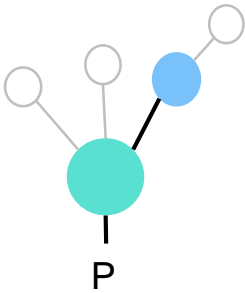
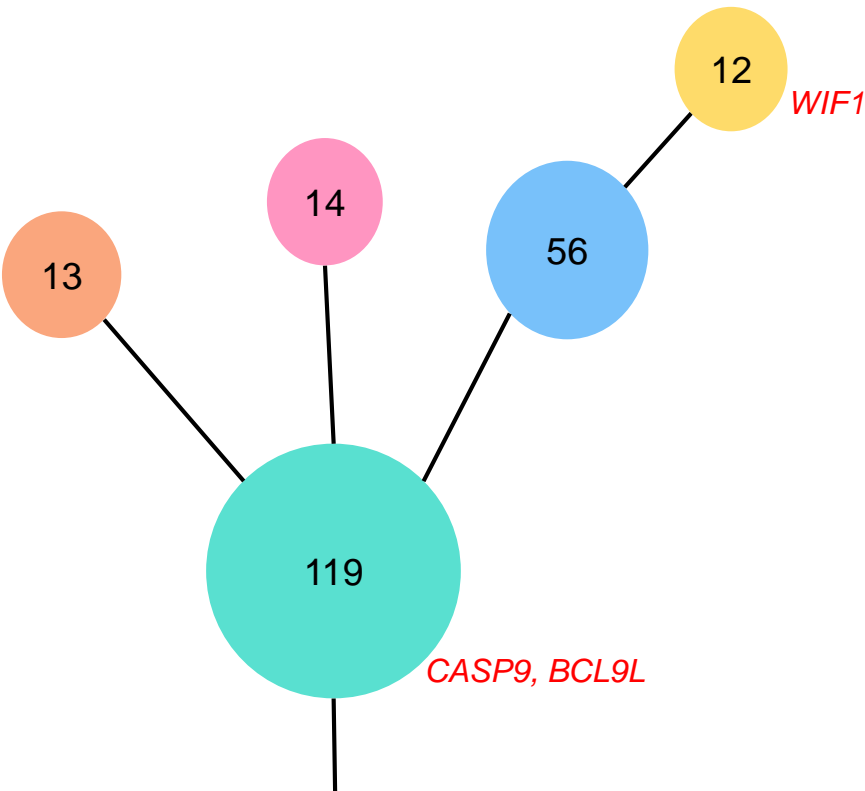
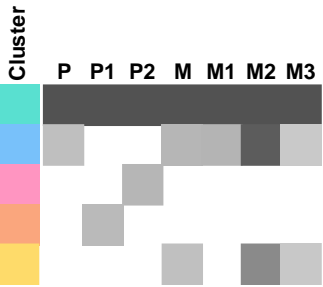
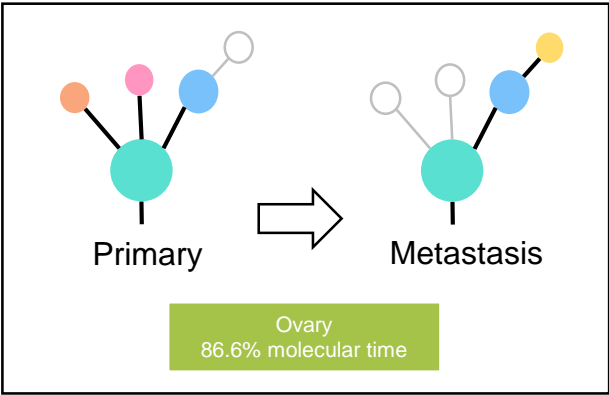




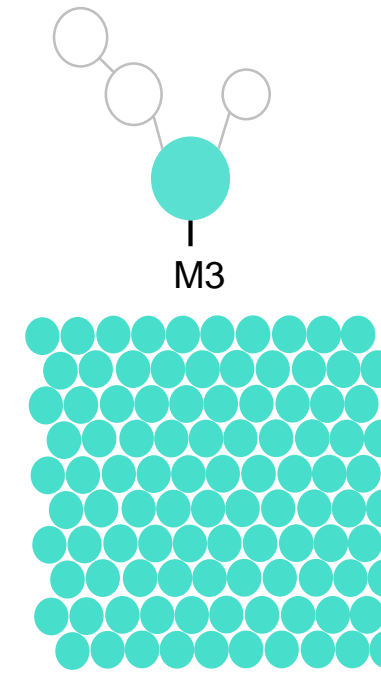
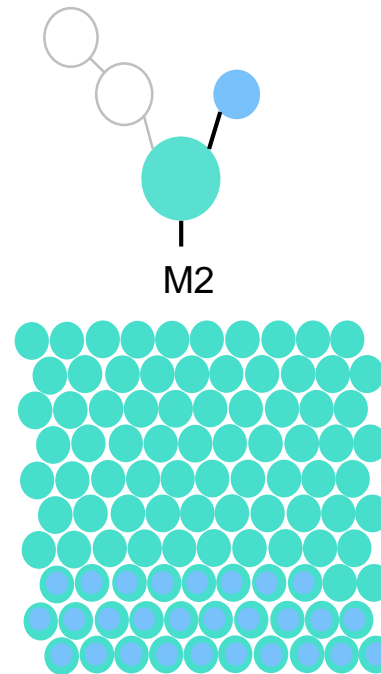
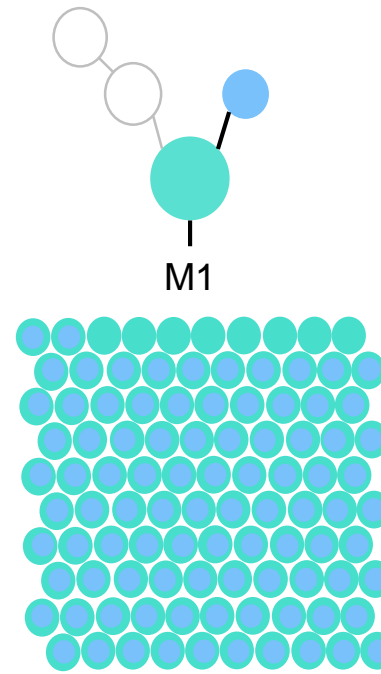
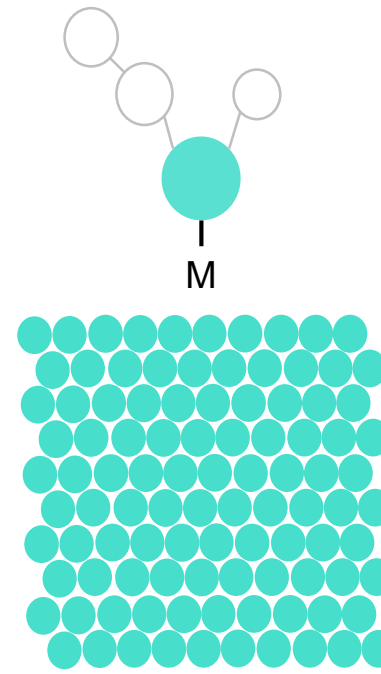
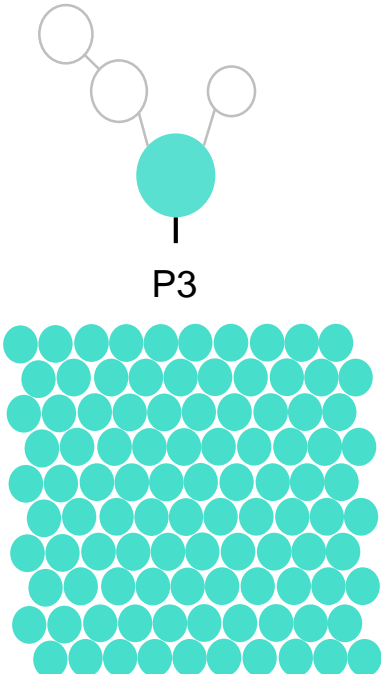
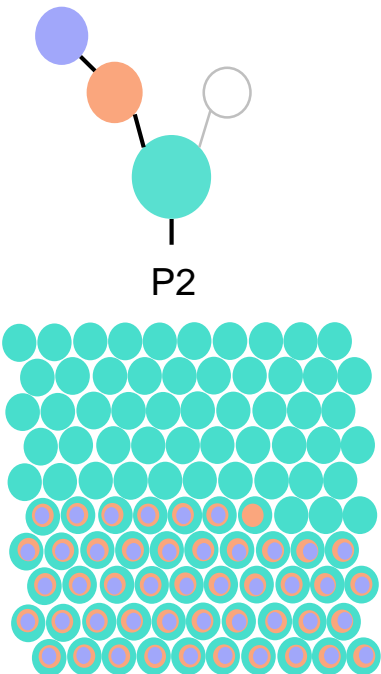
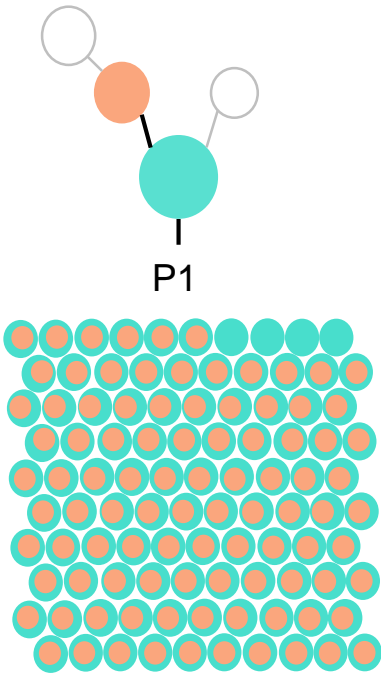
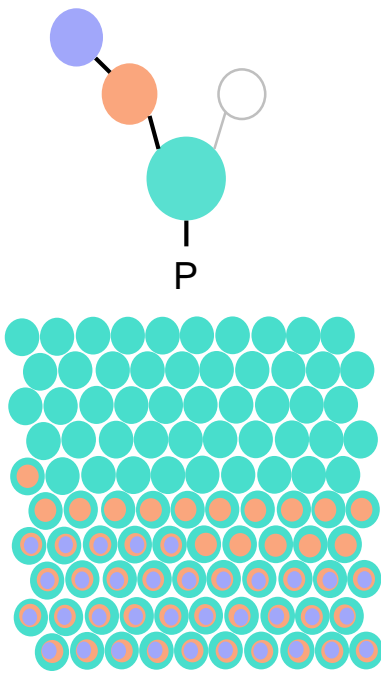
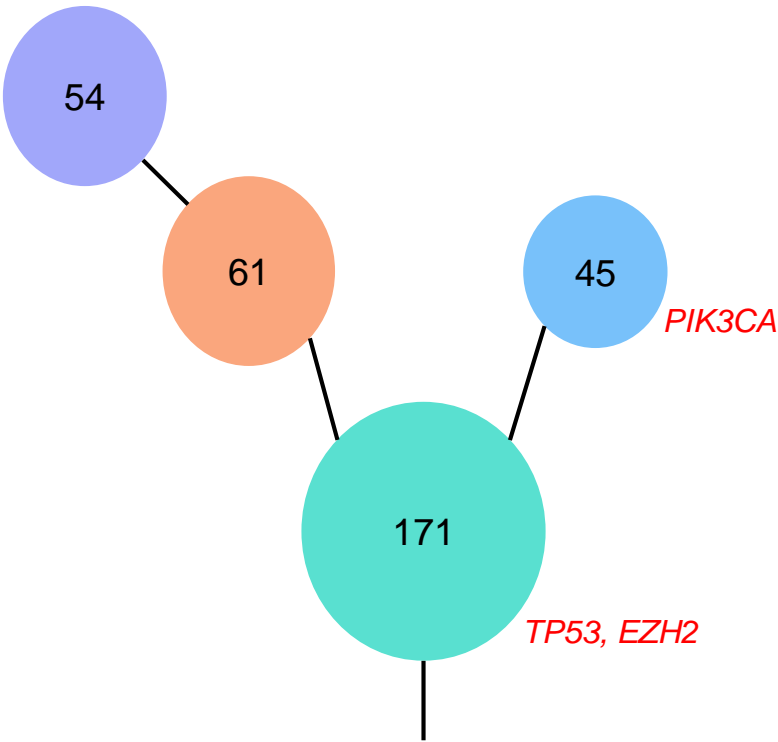
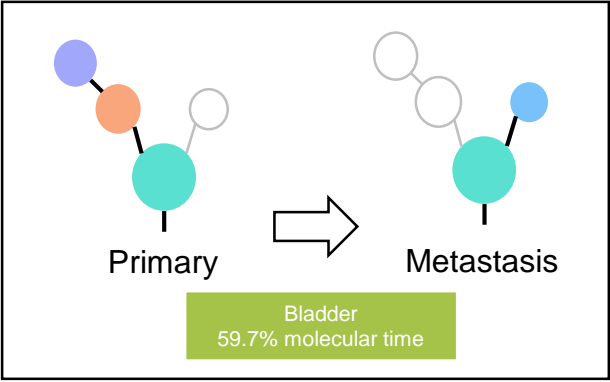


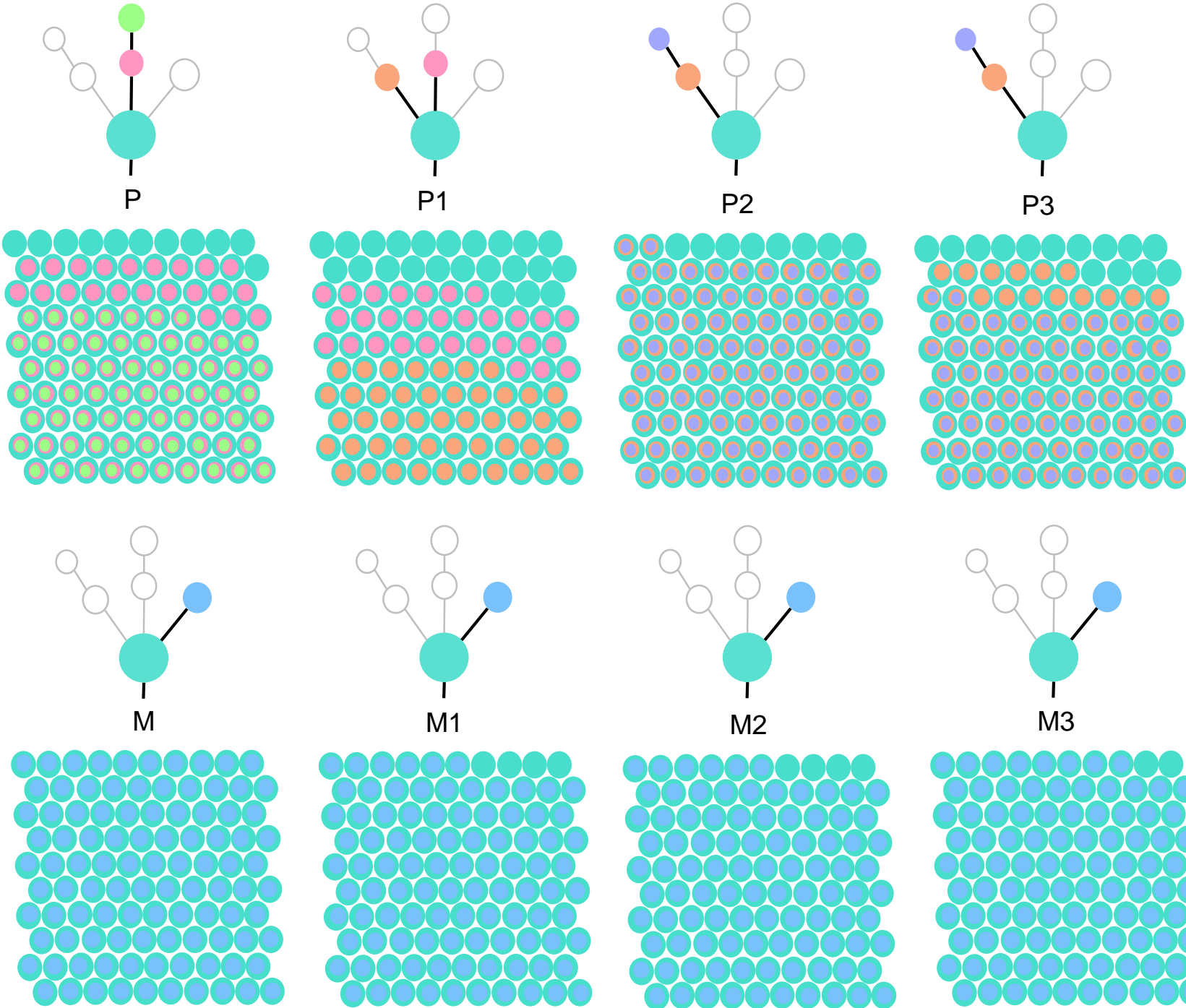
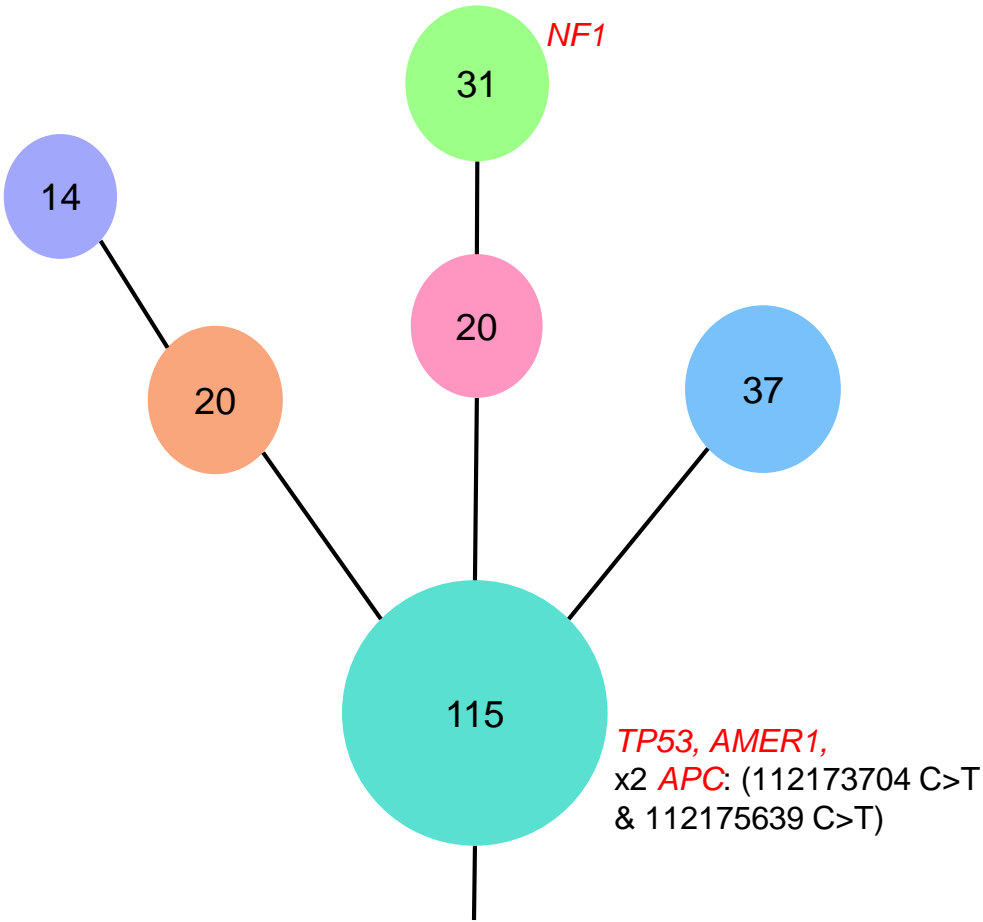
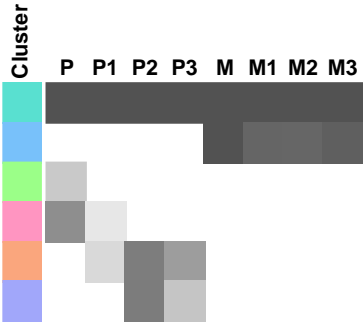
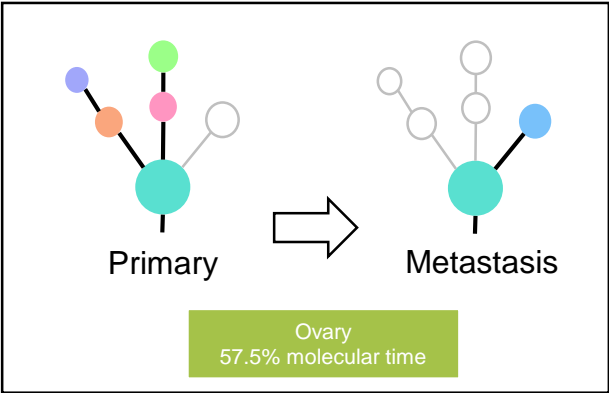
NRG1, BRCA1,  
MED12, APC

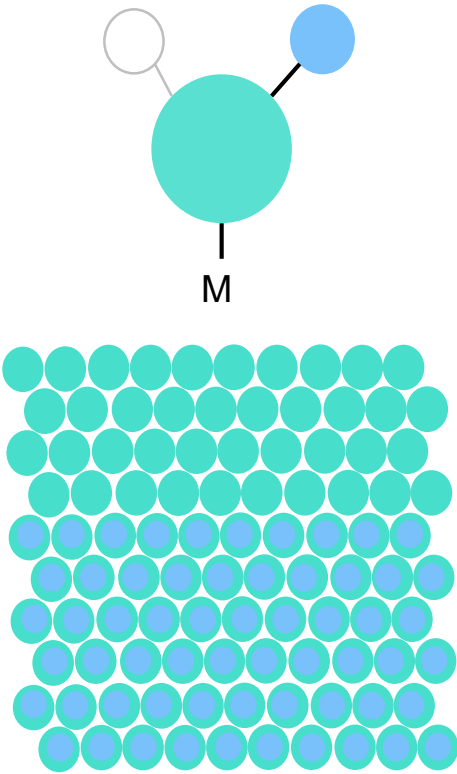
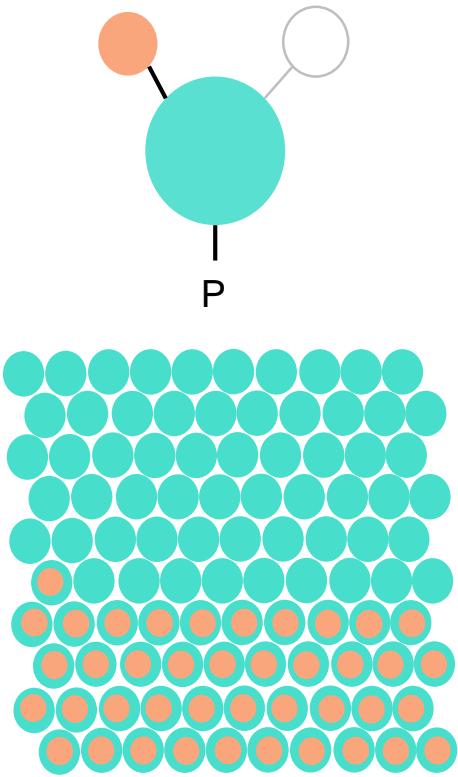
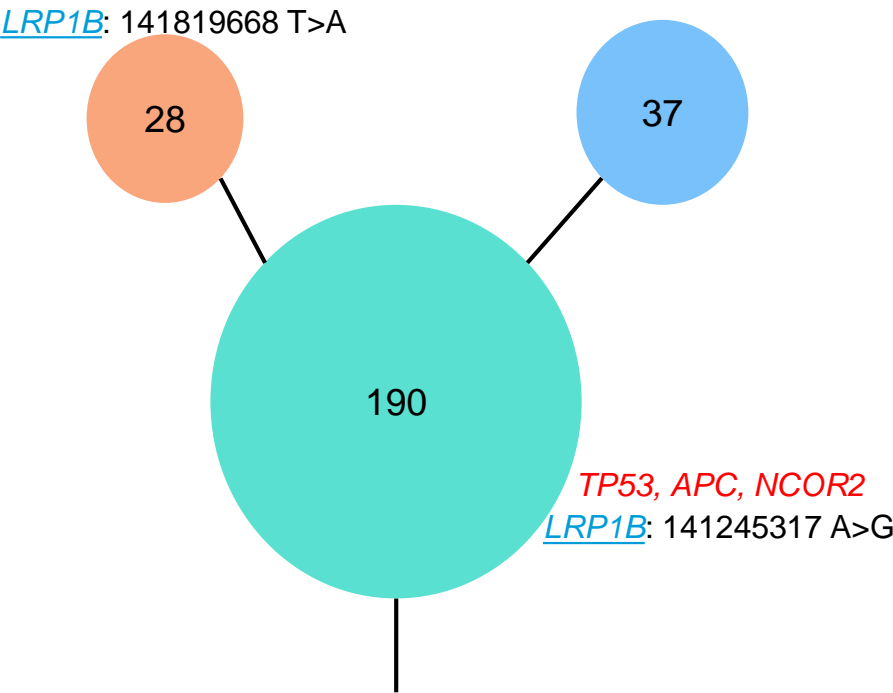
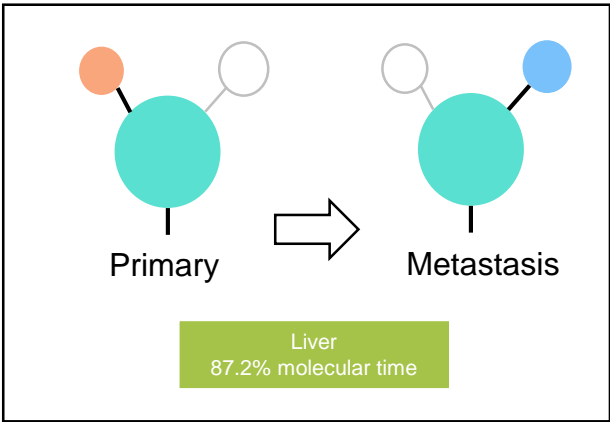




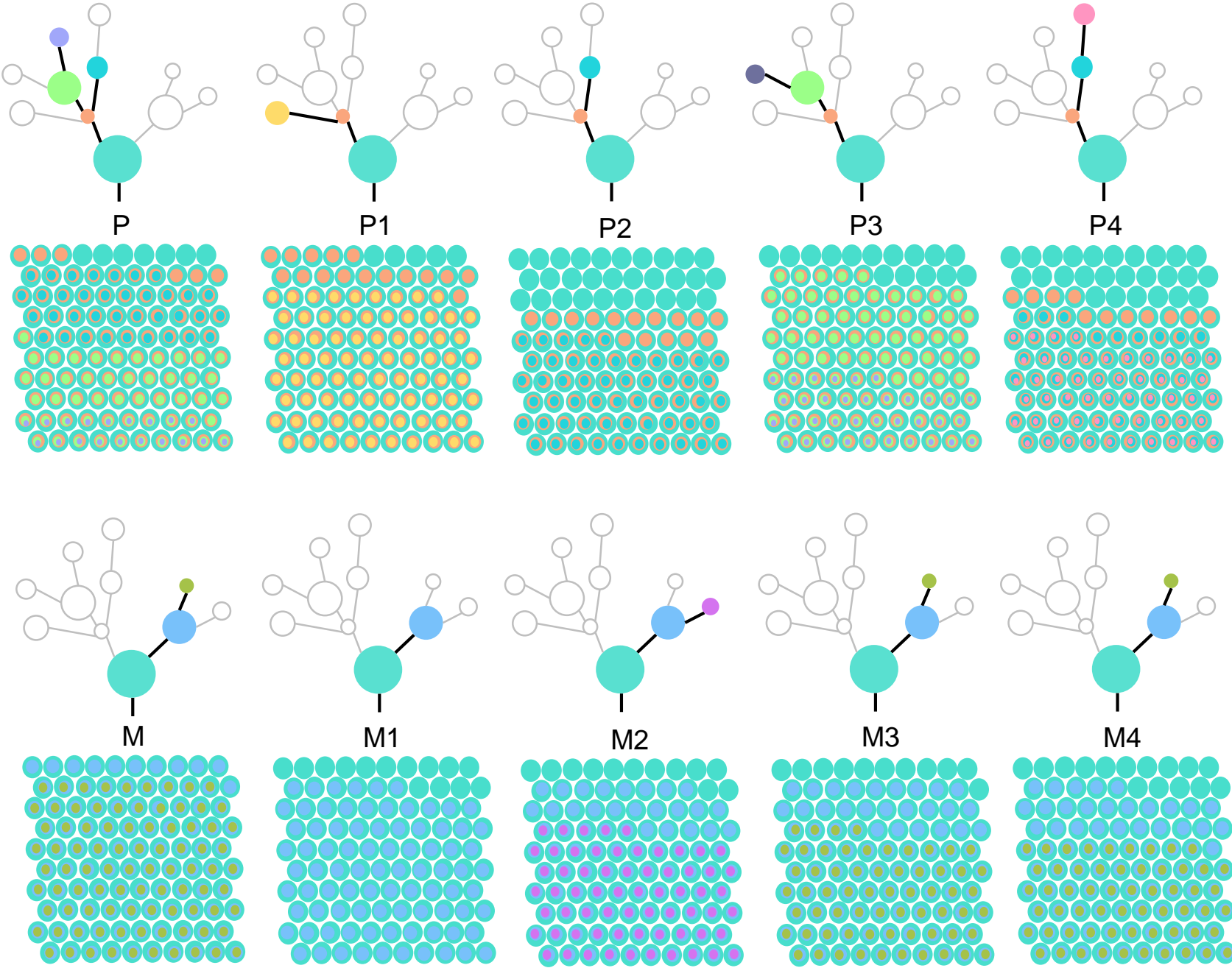
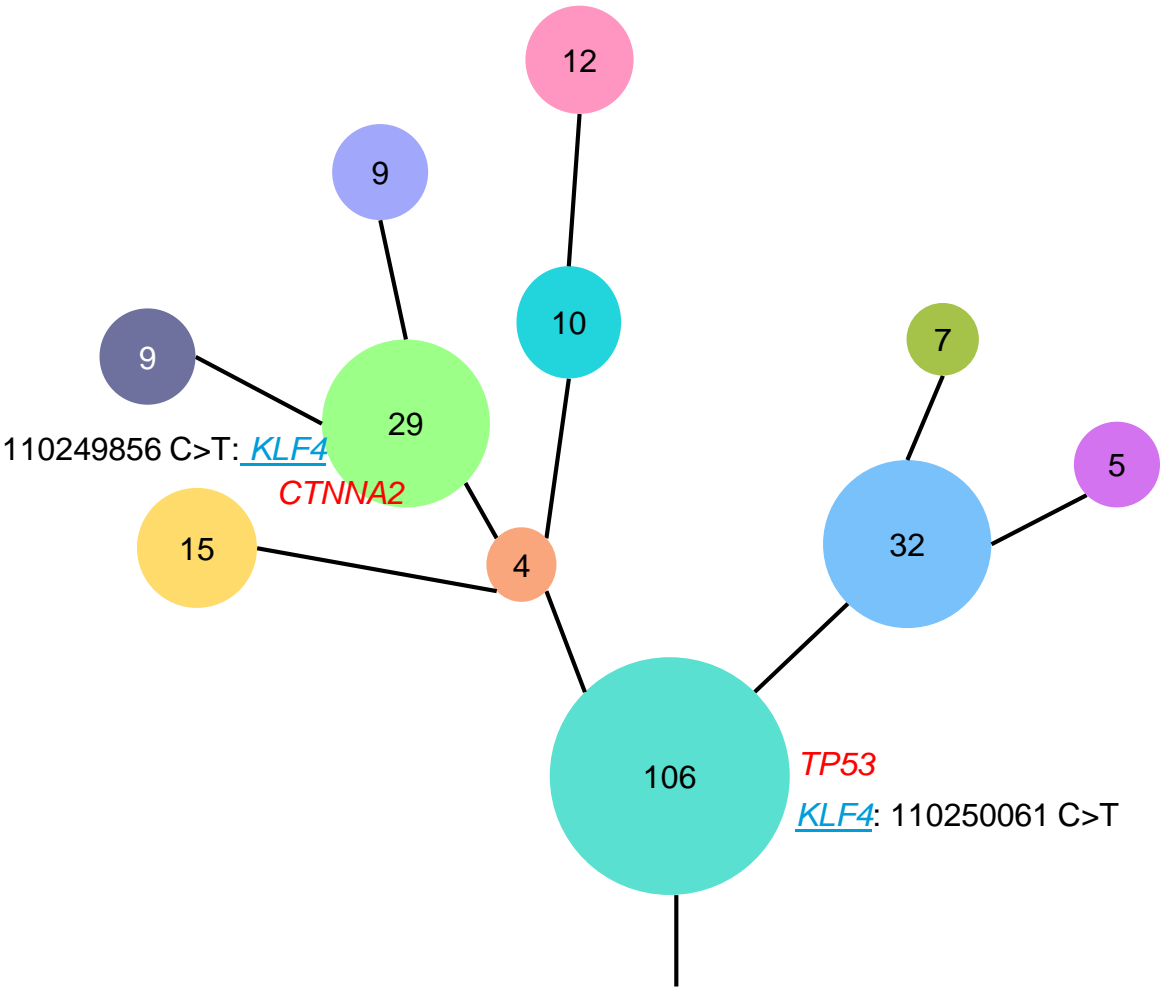
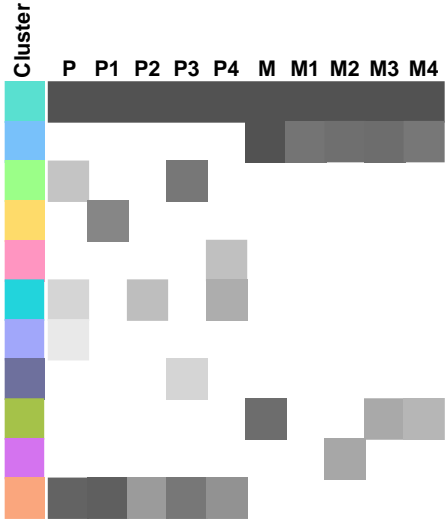
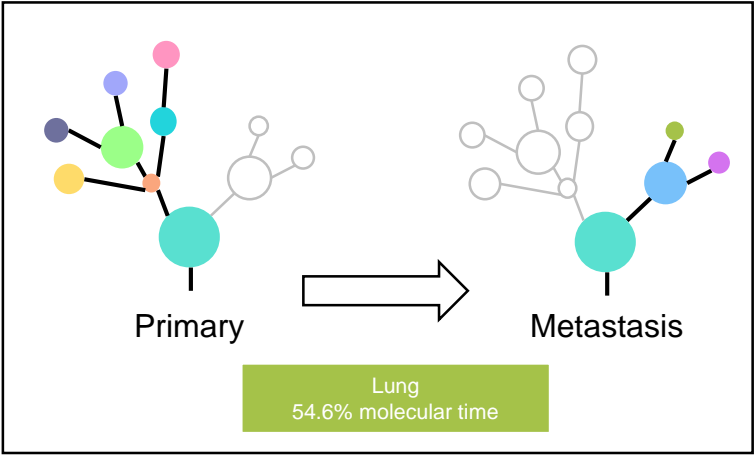


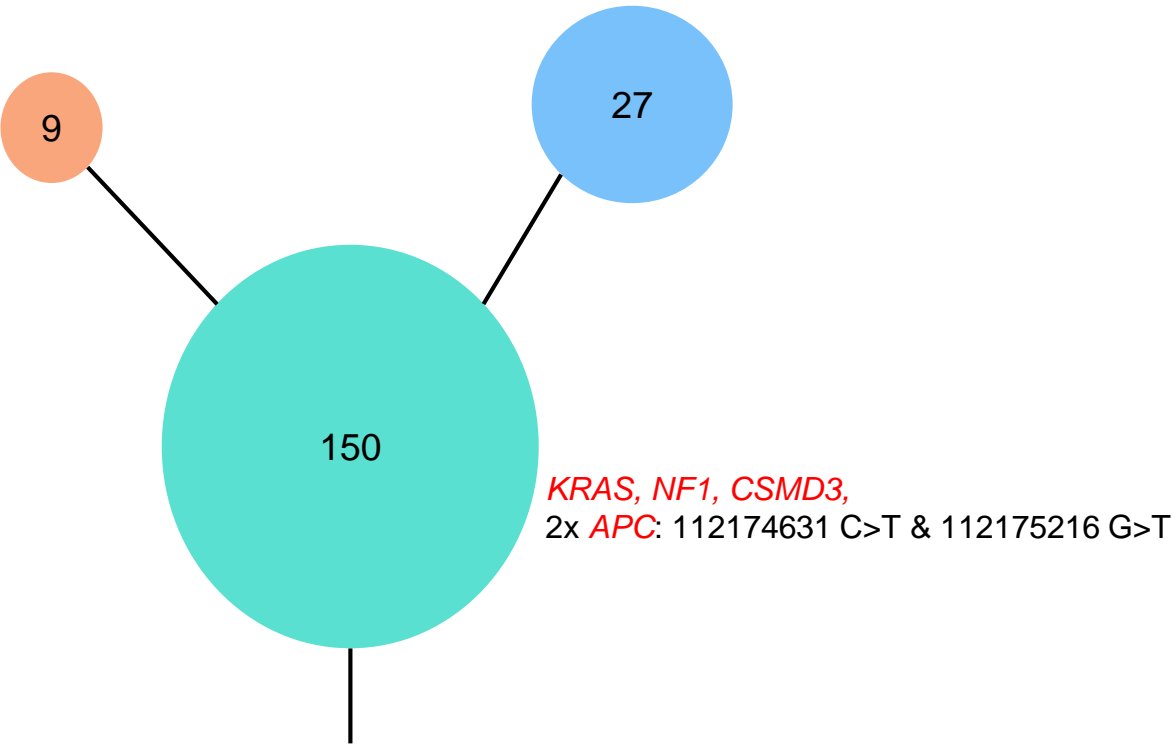
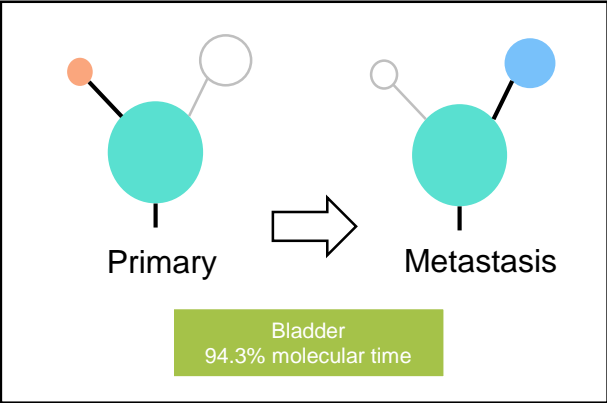




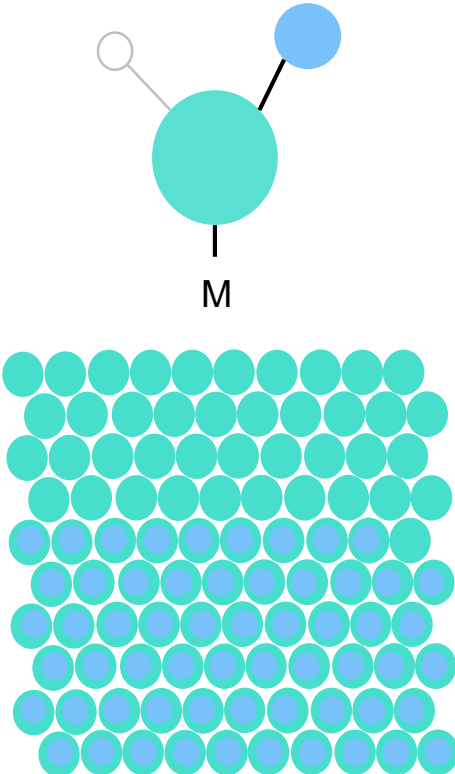
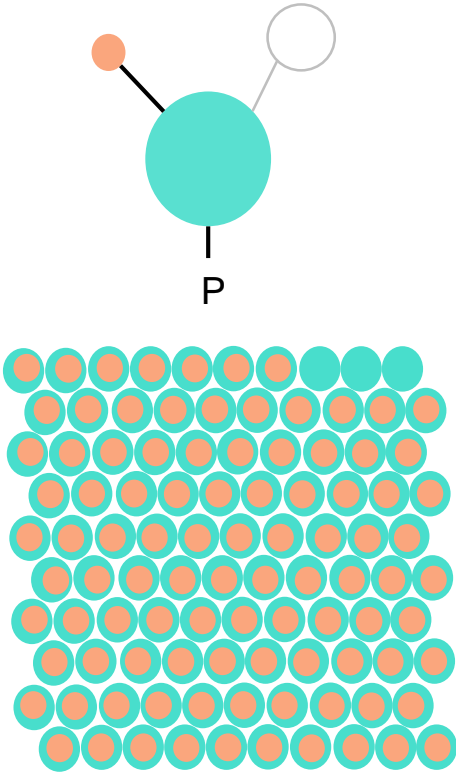


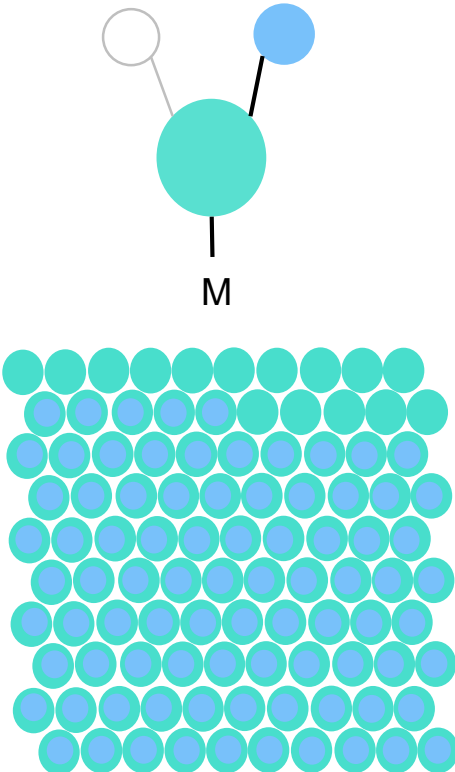
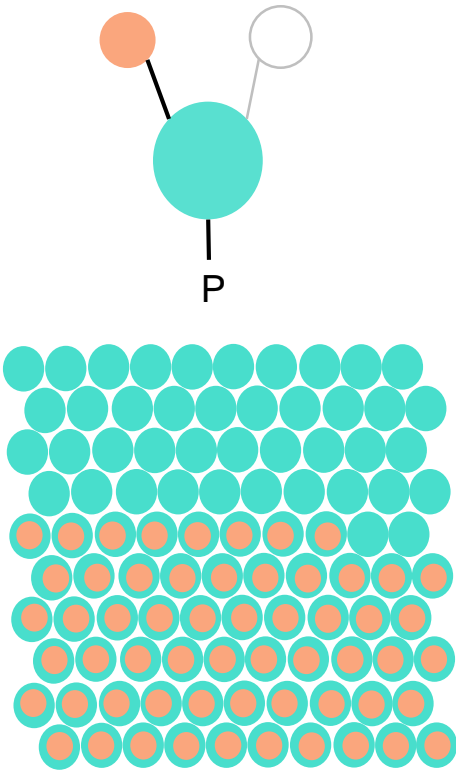
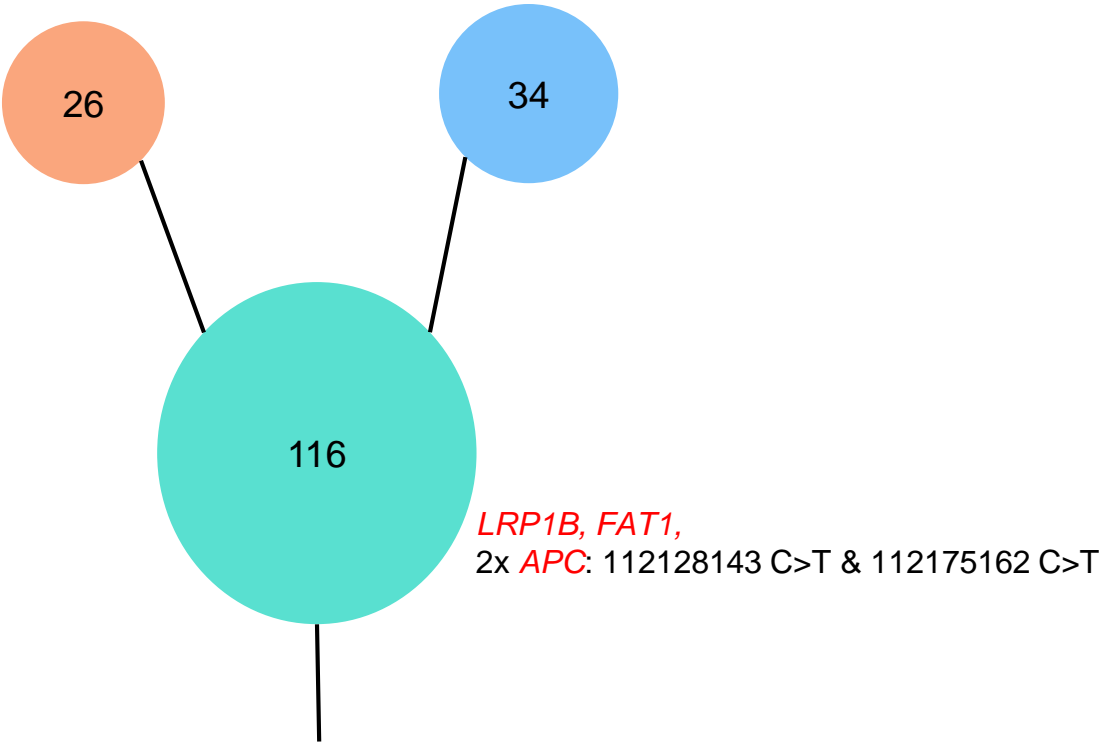
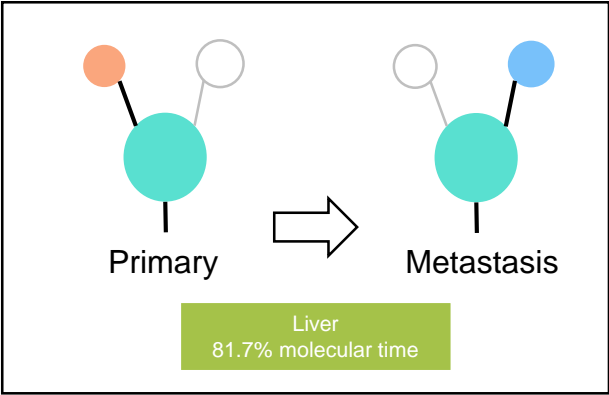




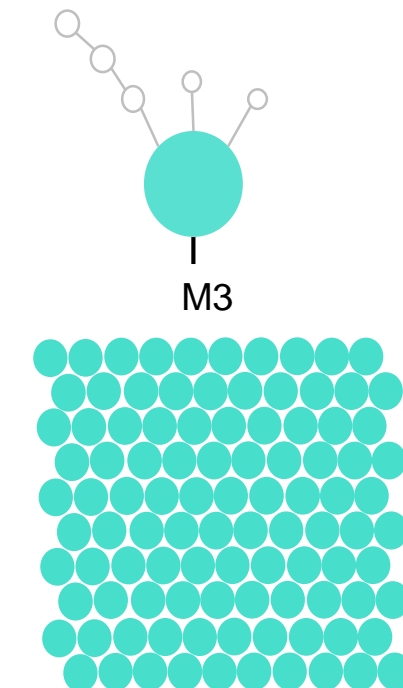
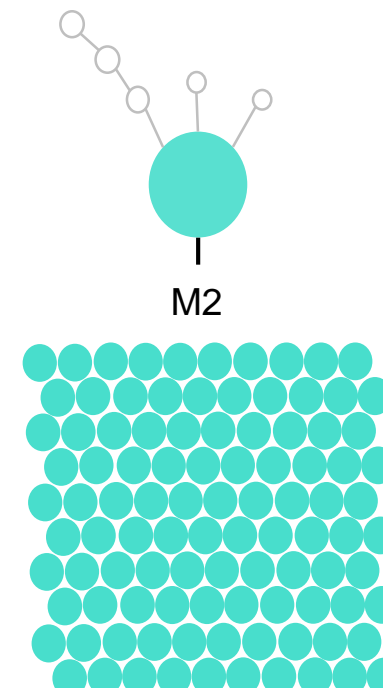
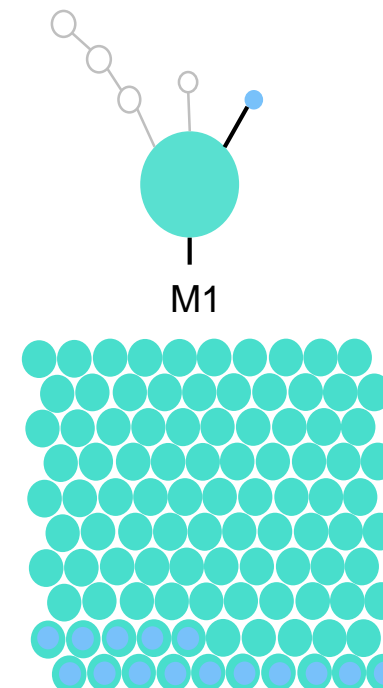
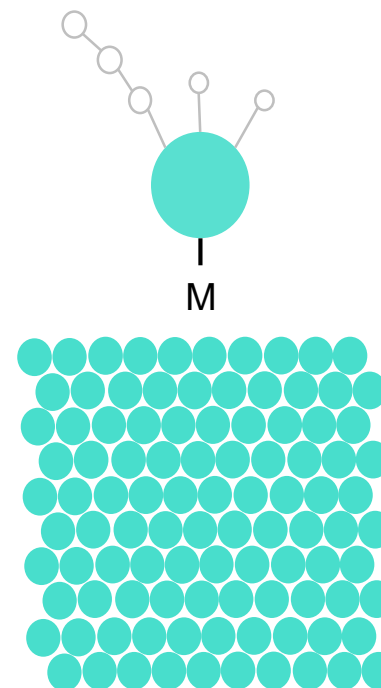
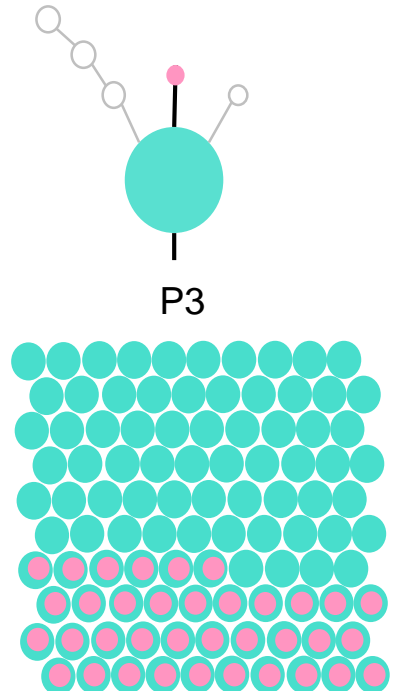
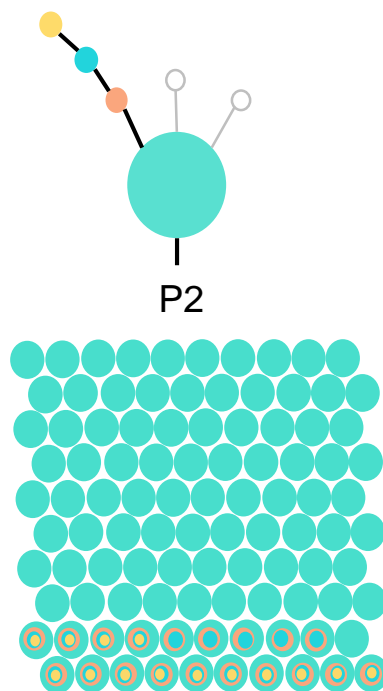
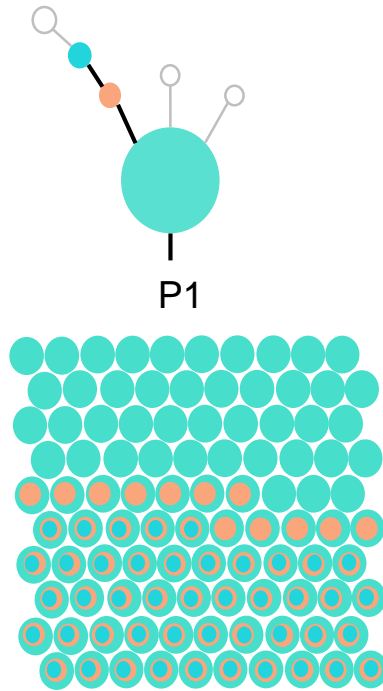
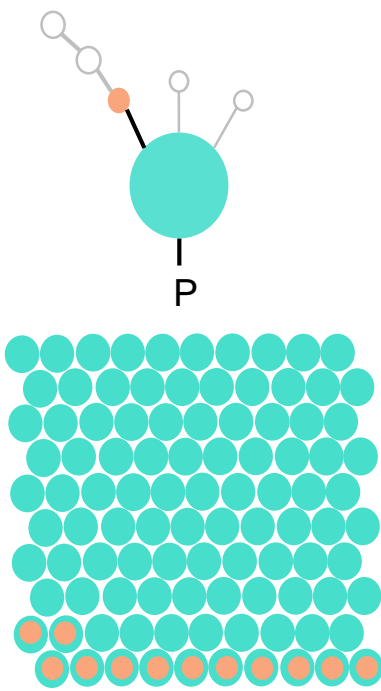
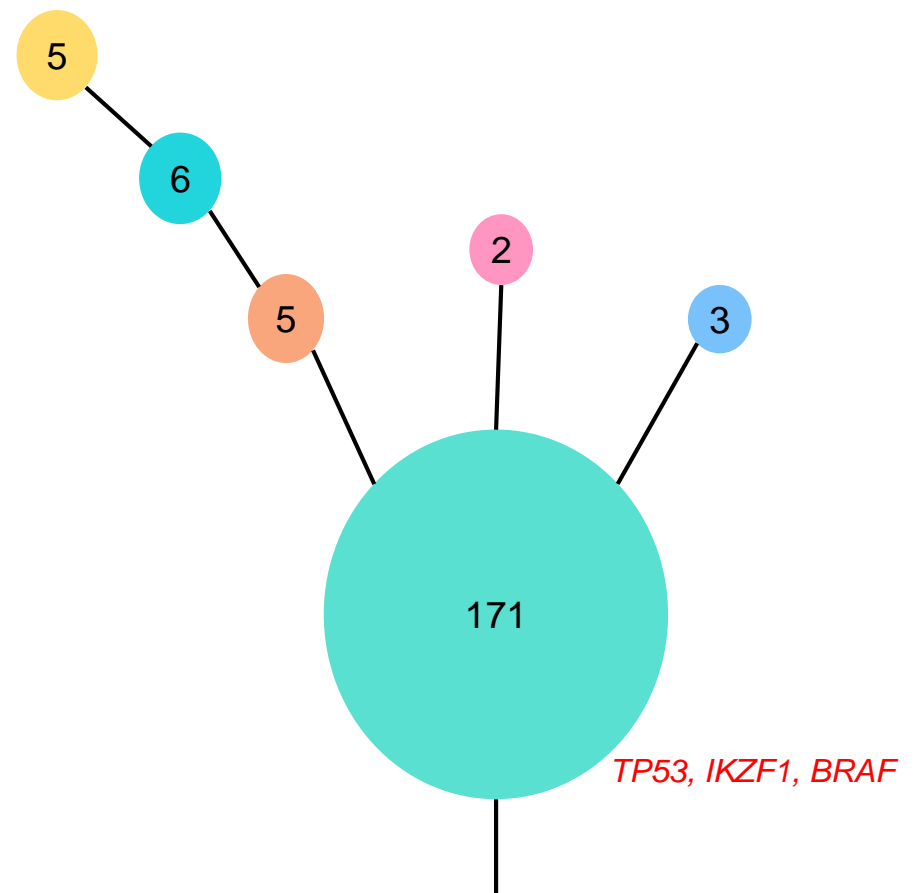
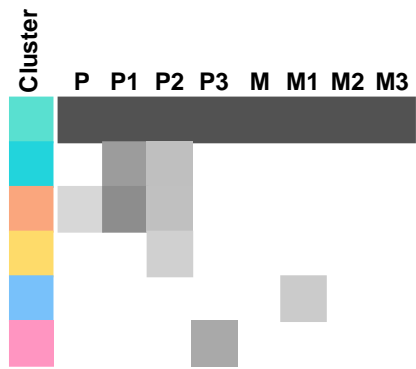
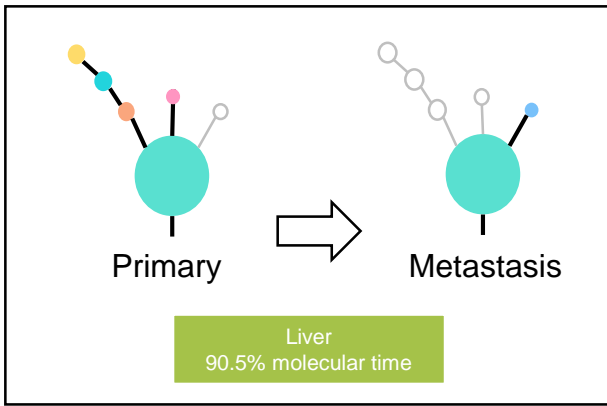


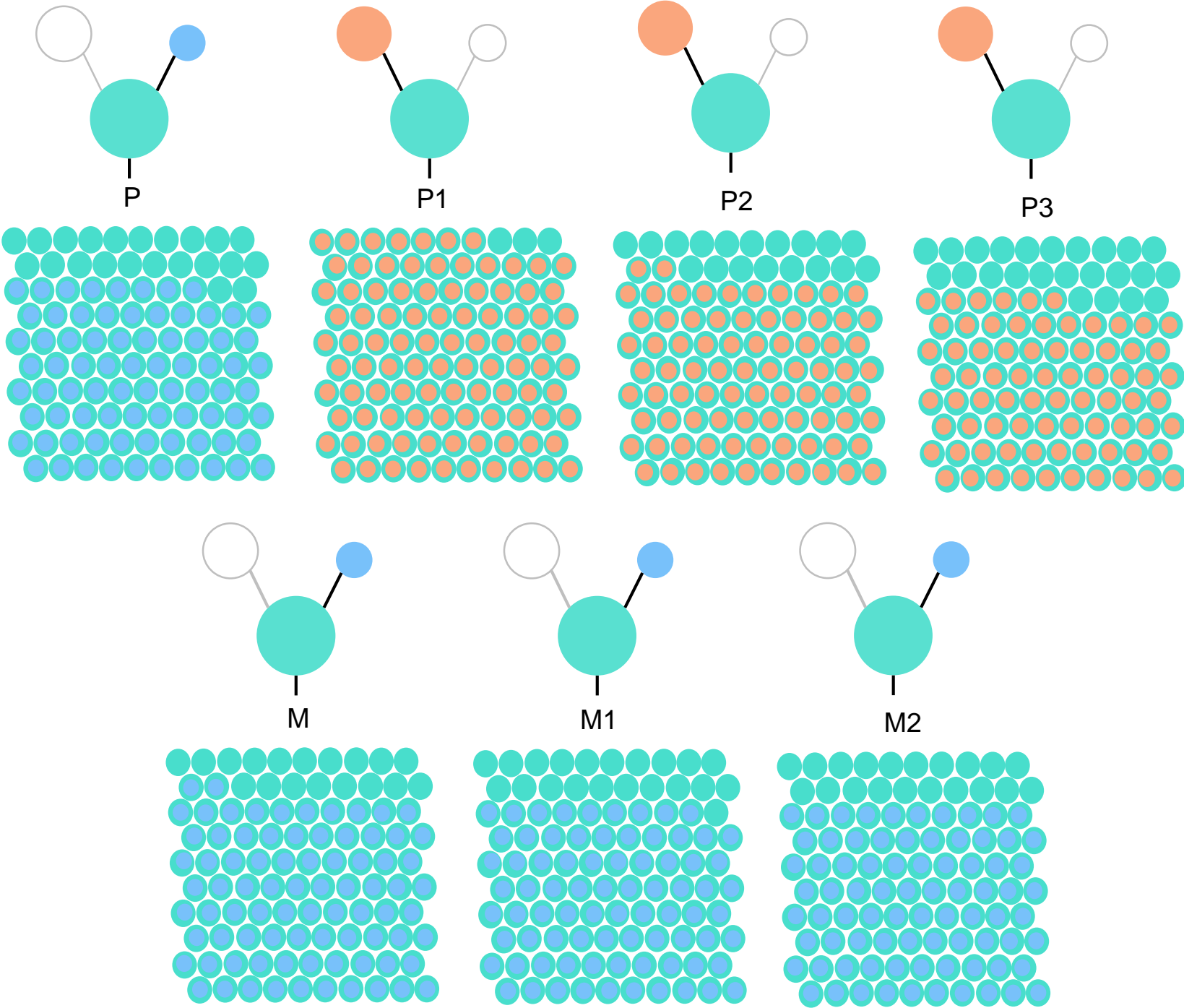
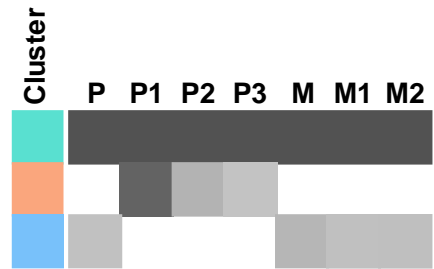
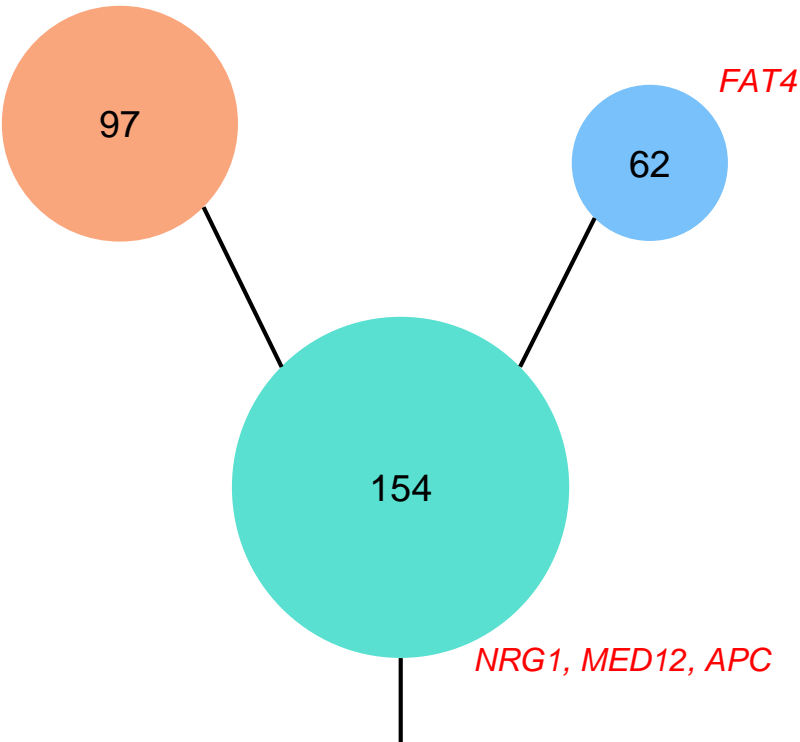
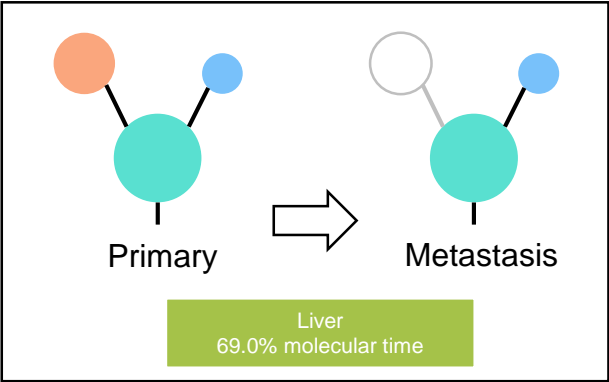
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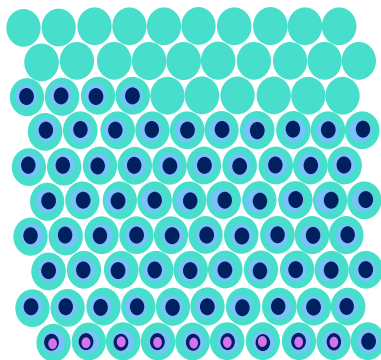
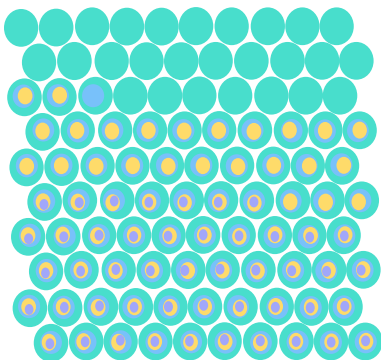
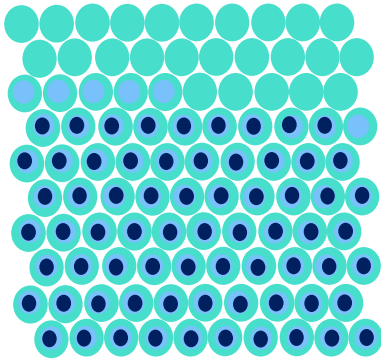
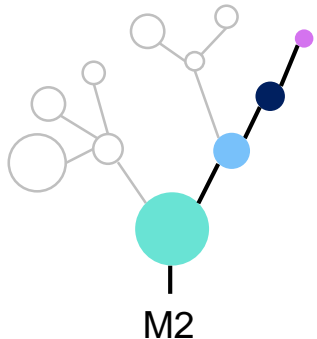
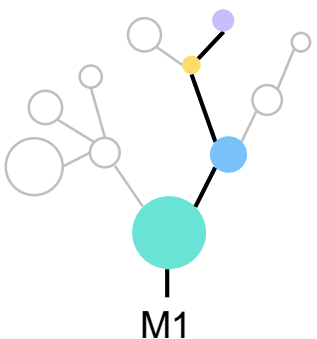
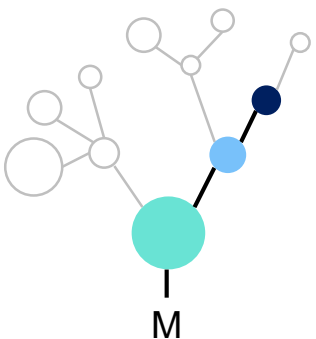
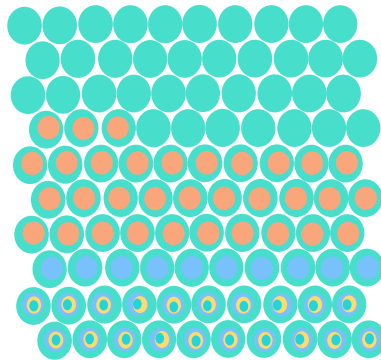
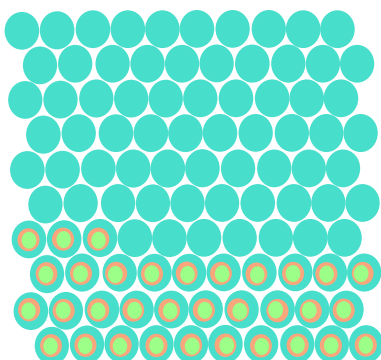
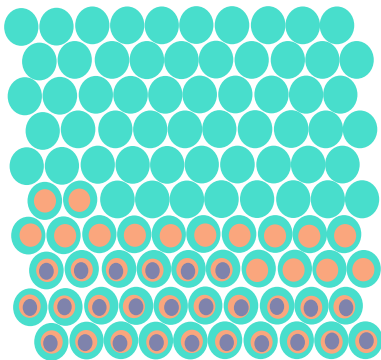
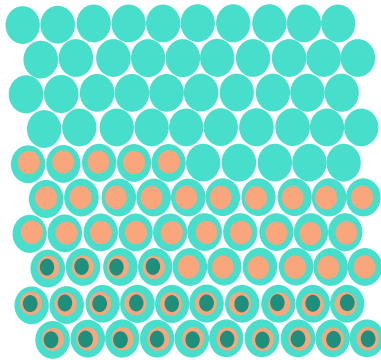
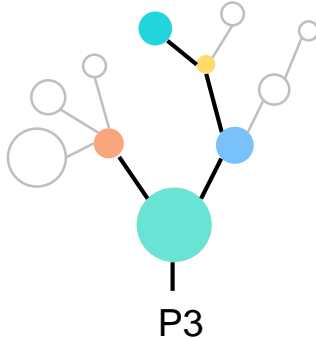
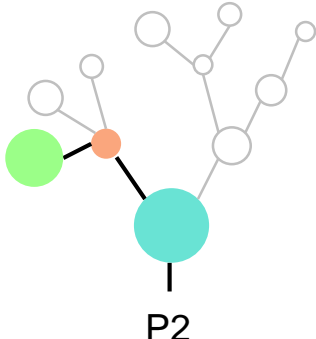
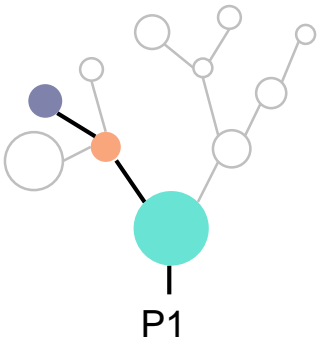
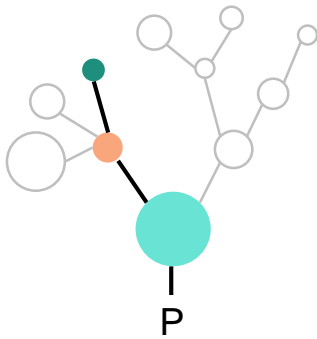
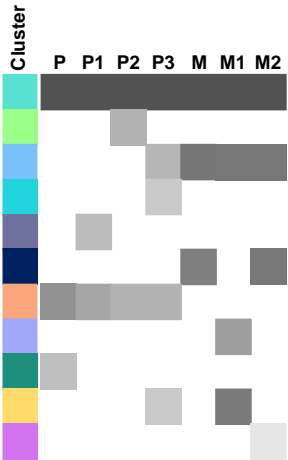
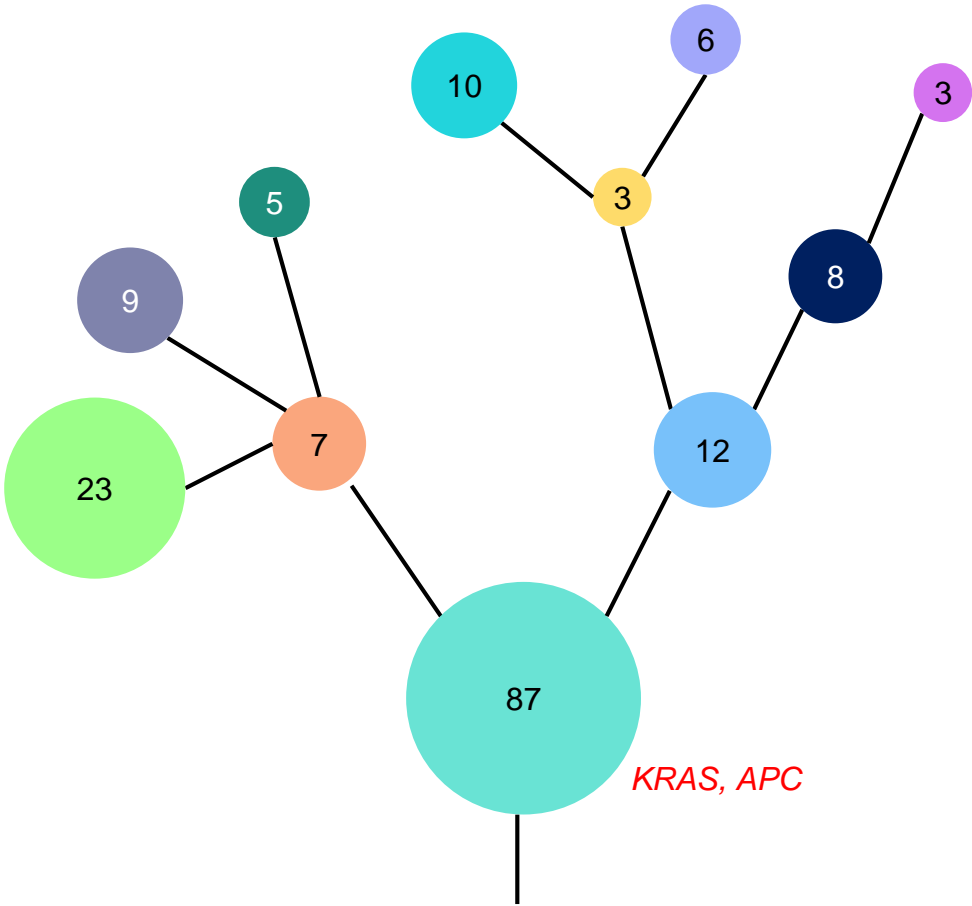
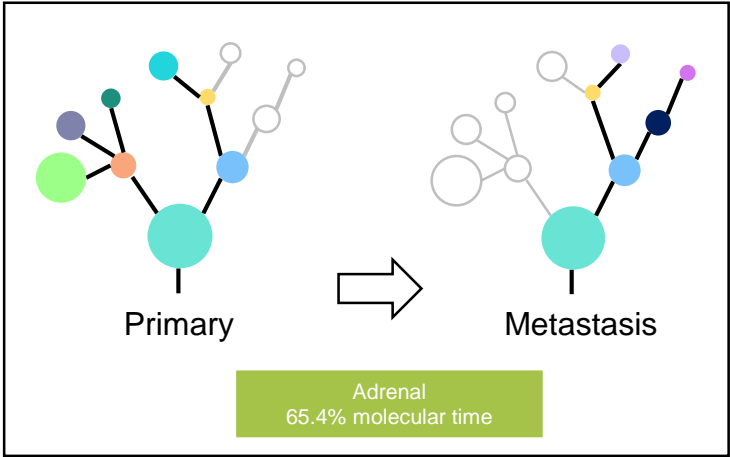




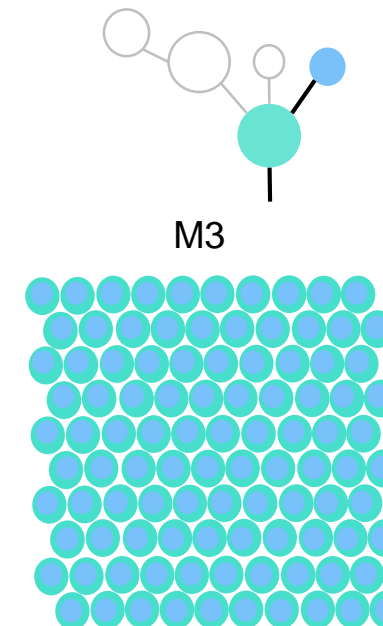
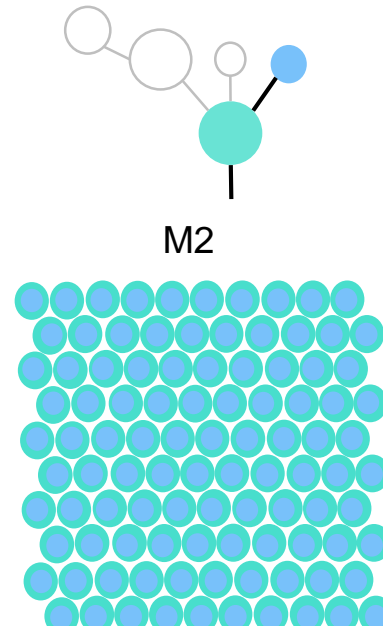
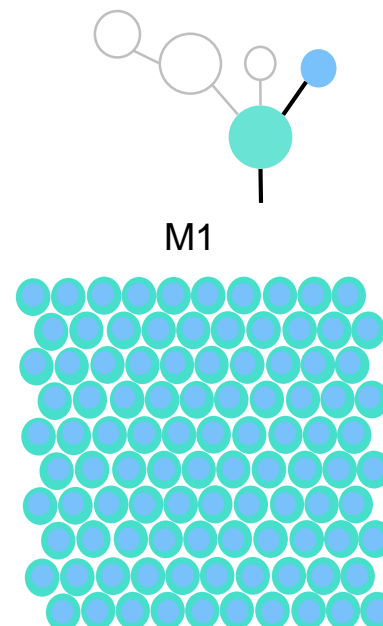
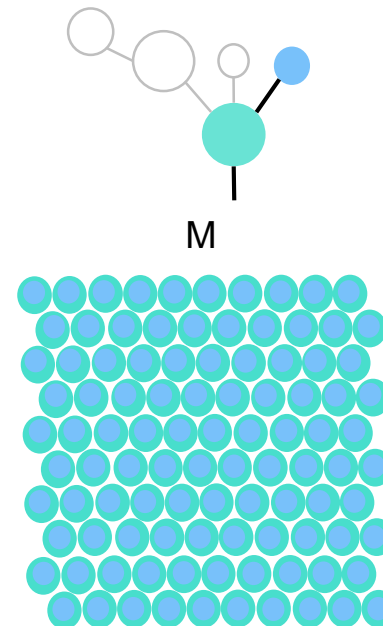
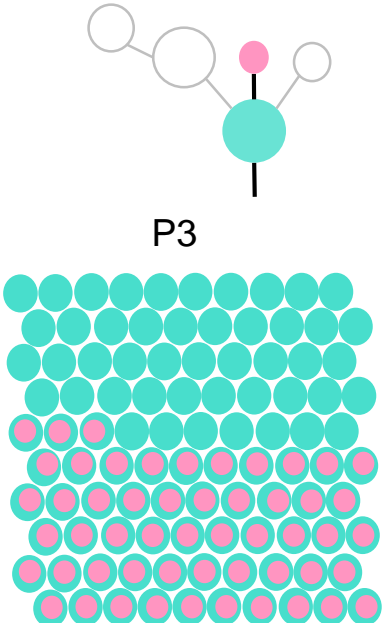
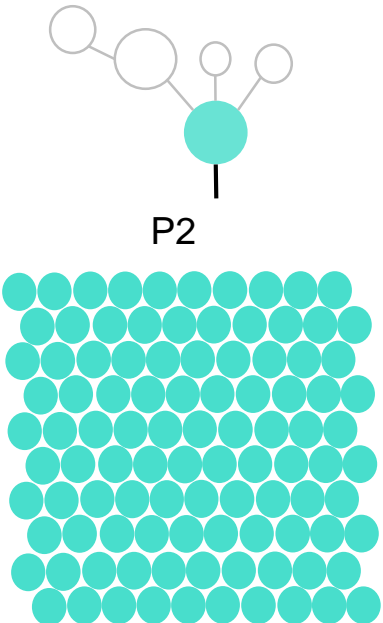
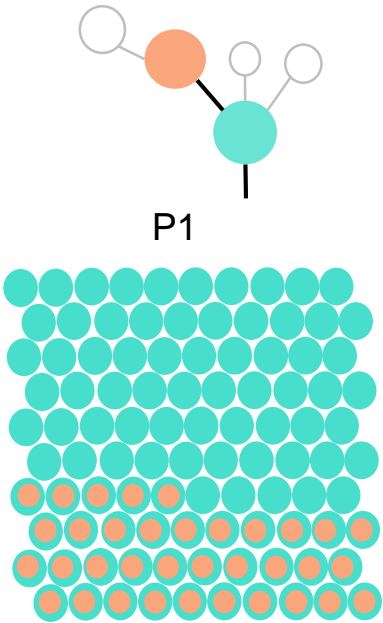
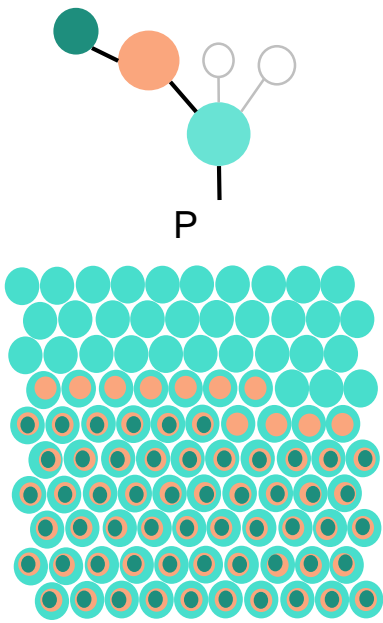
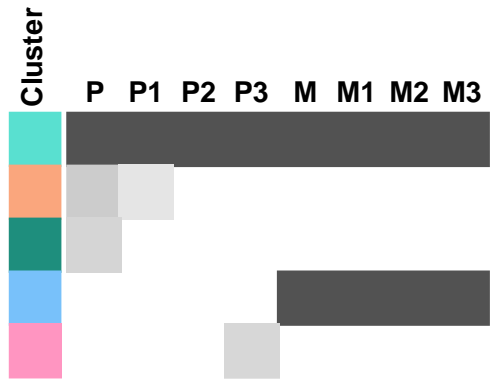
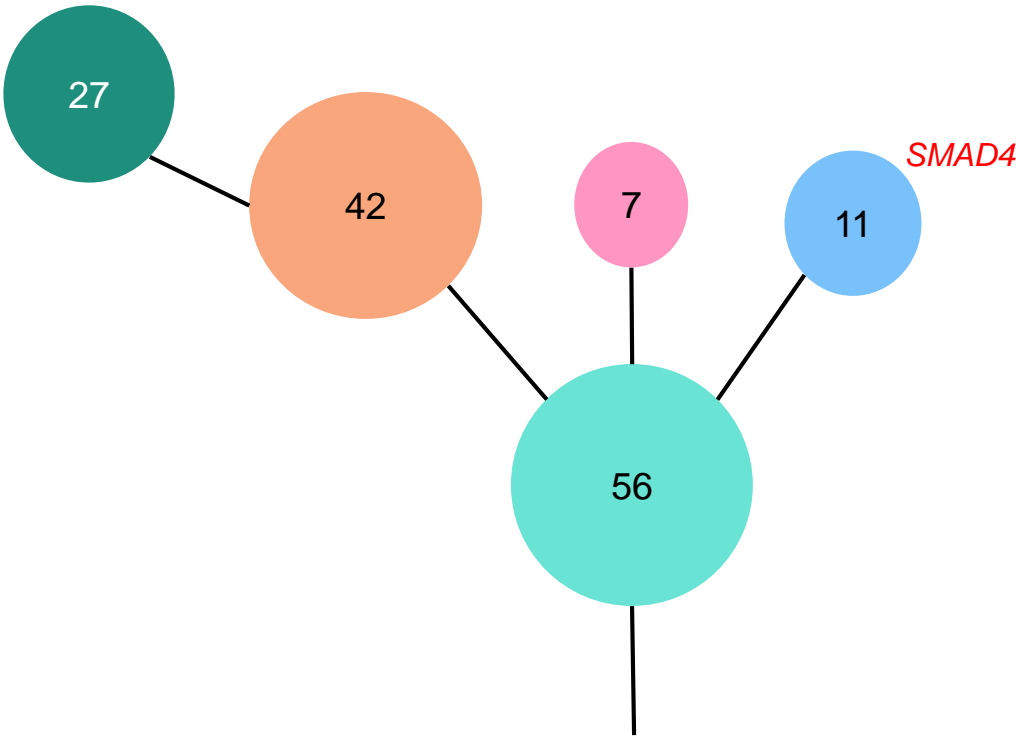
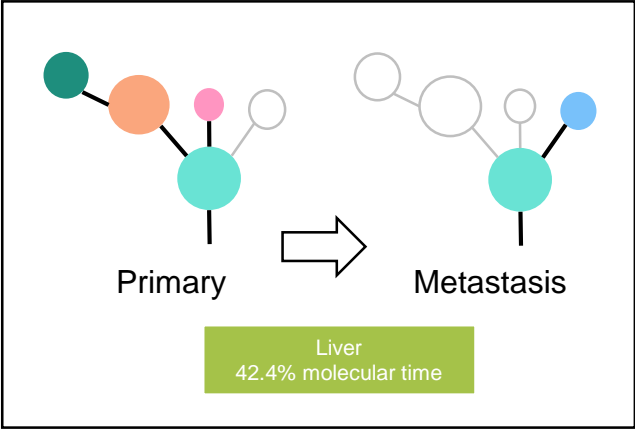


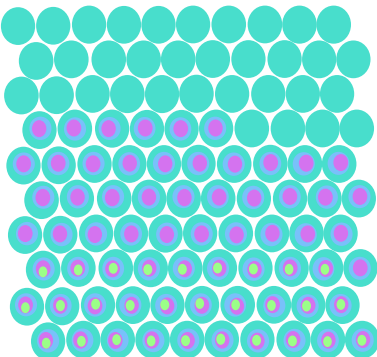
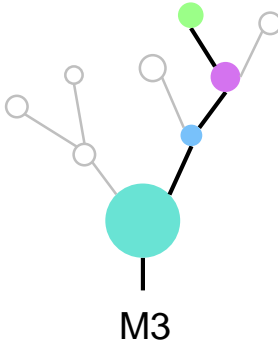
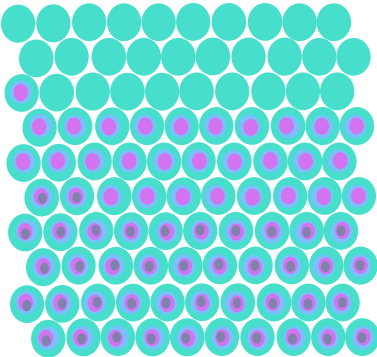
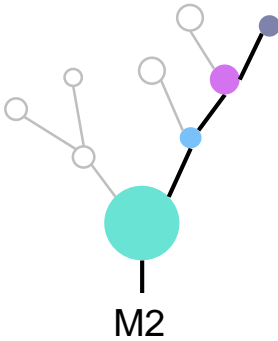
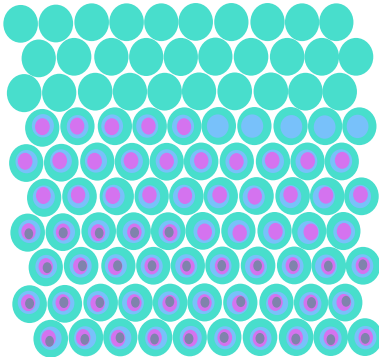
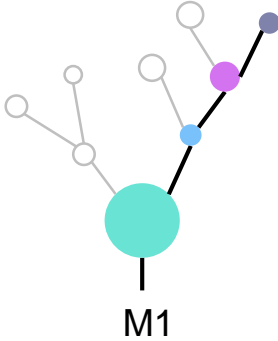
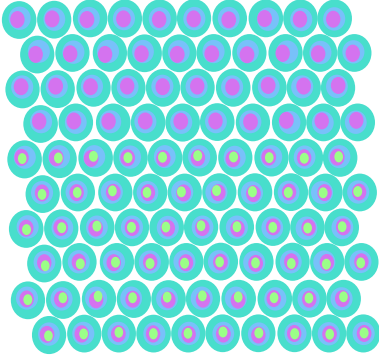
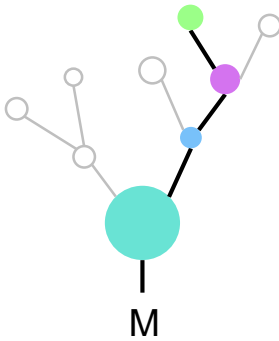
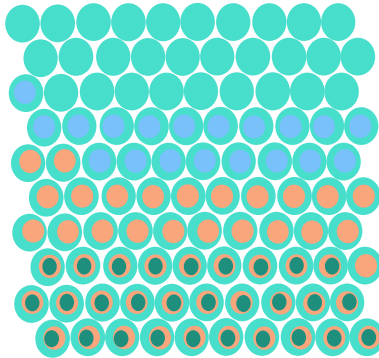
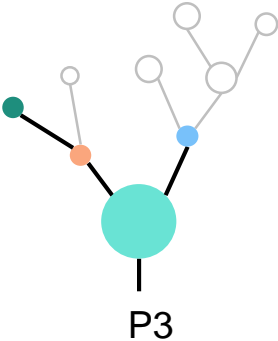
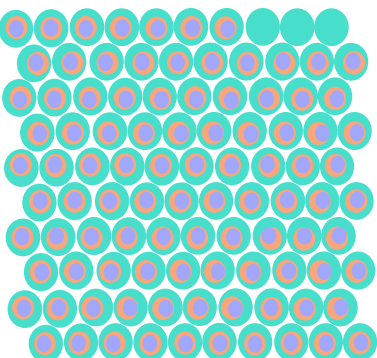
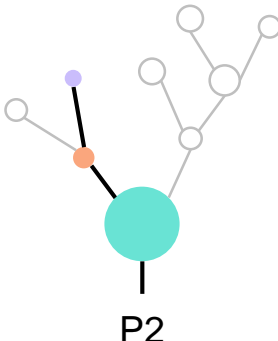
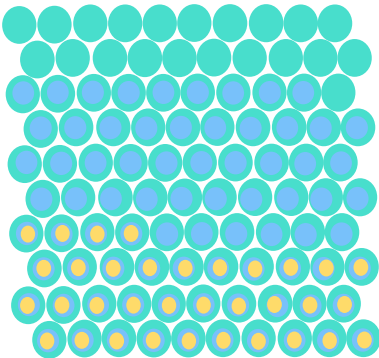
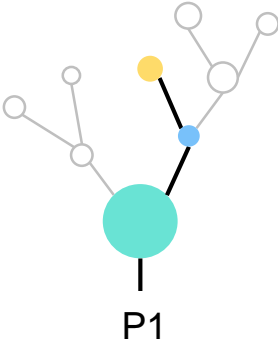
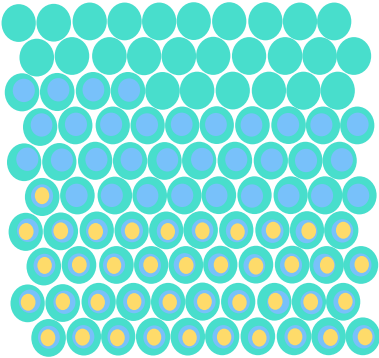
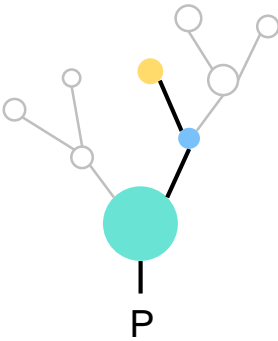
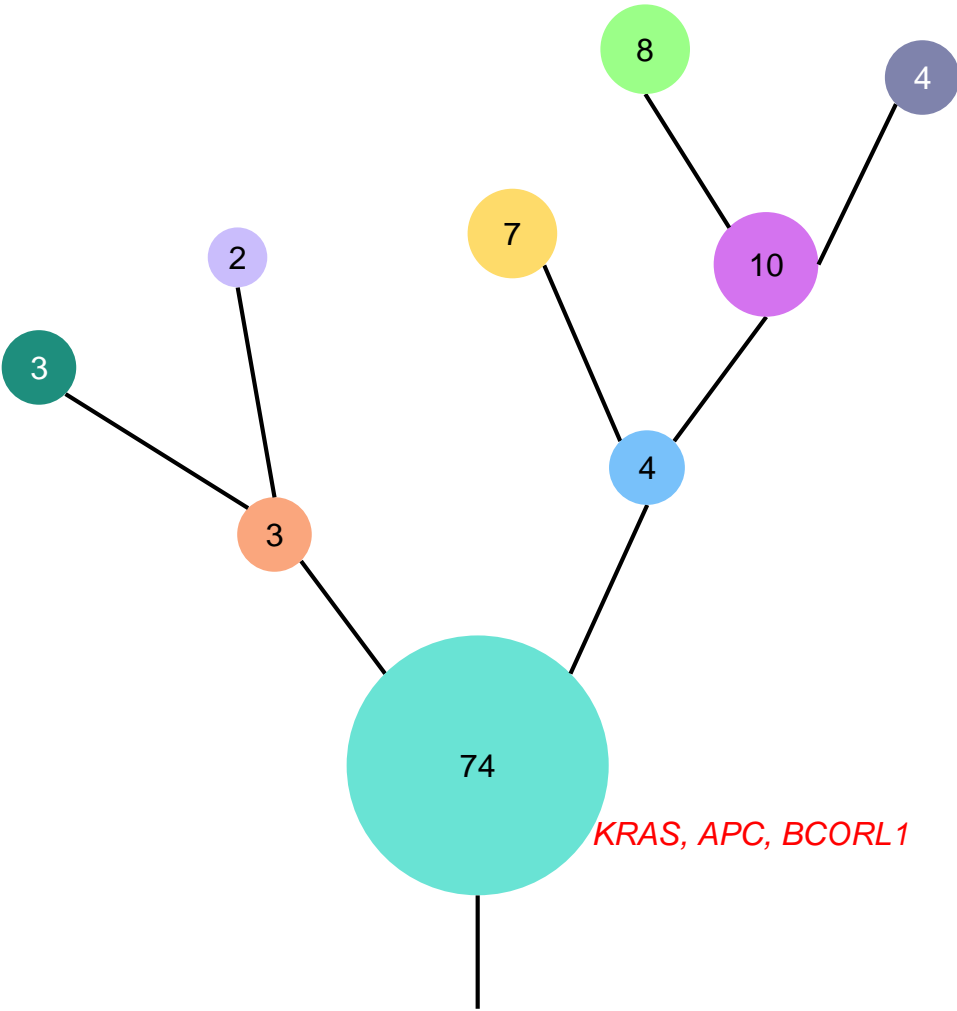
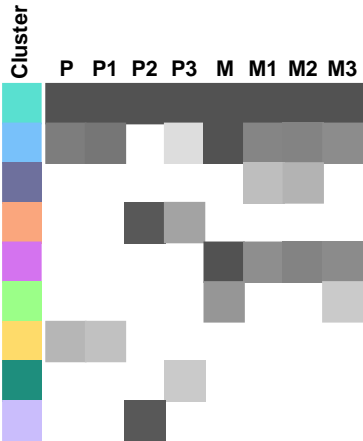
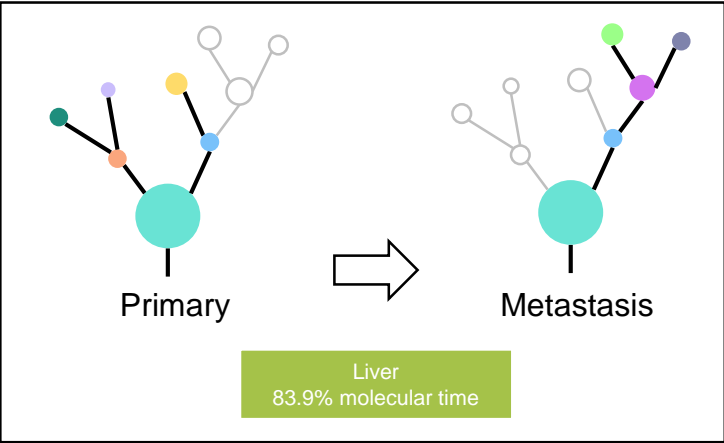


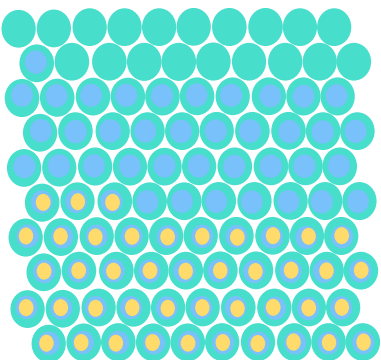
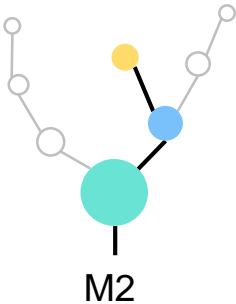
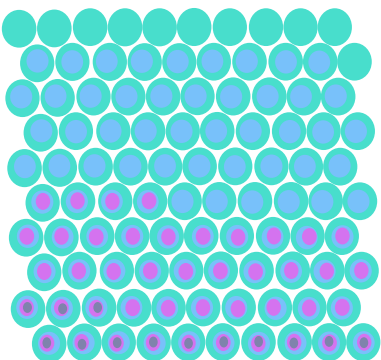
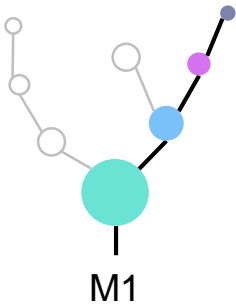
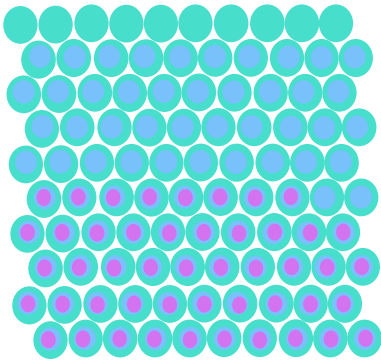
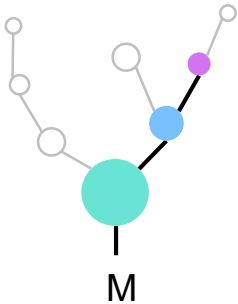
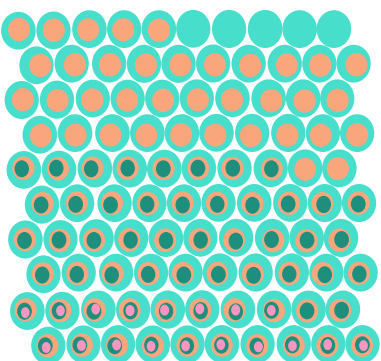
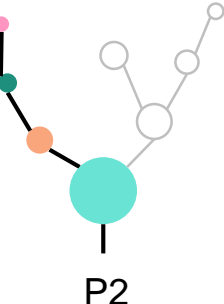
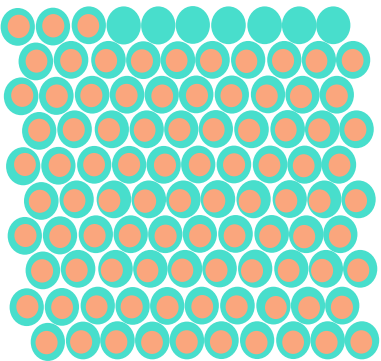
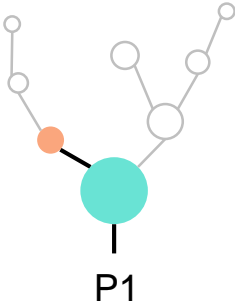
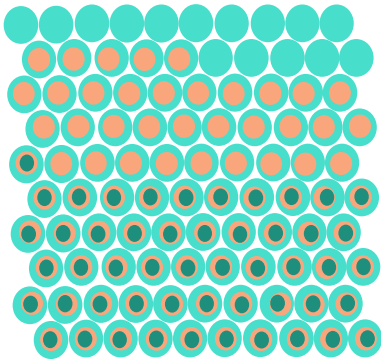
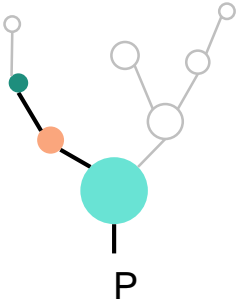
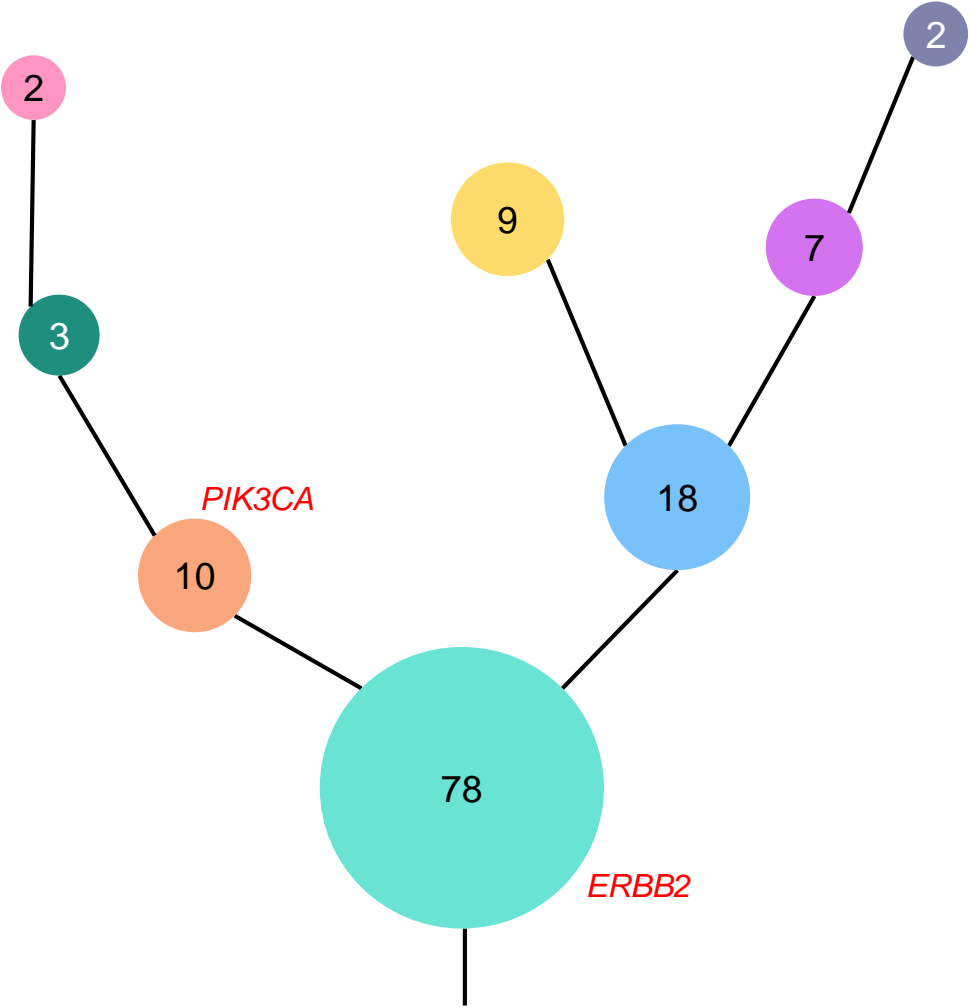
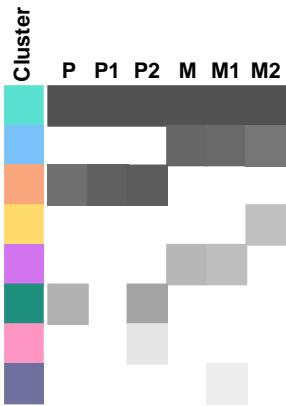
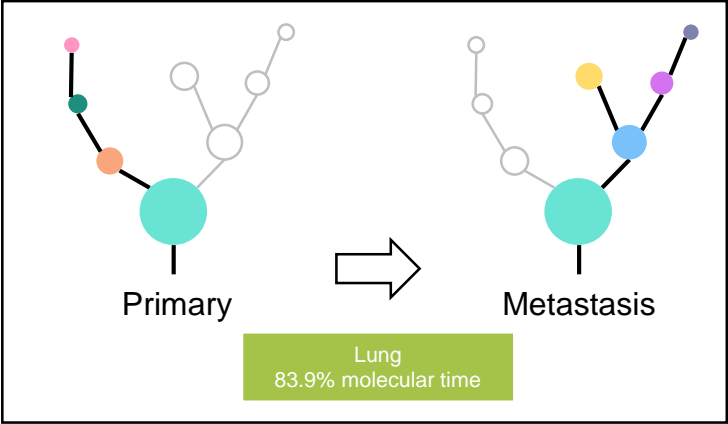




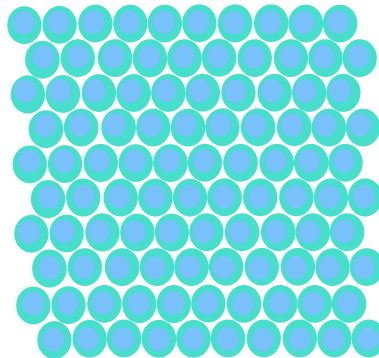
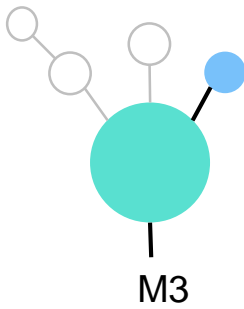
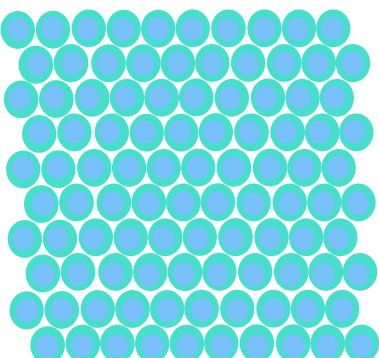
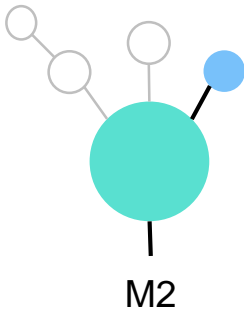
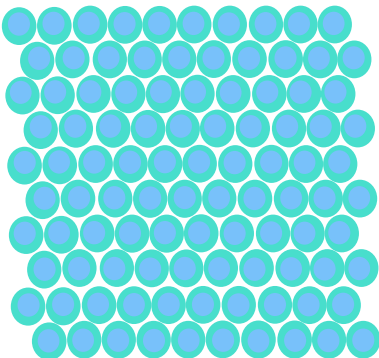
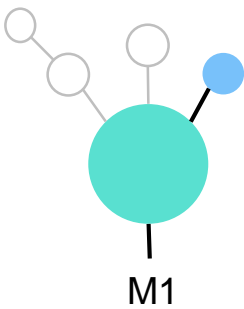
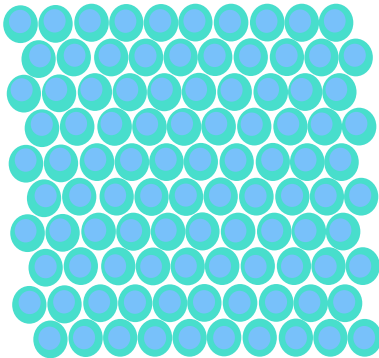
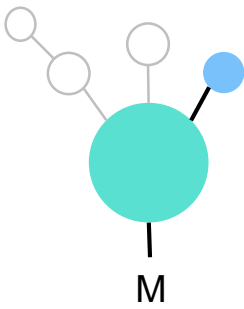
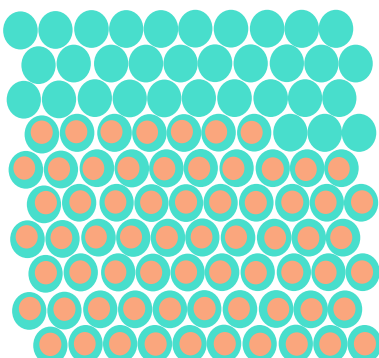
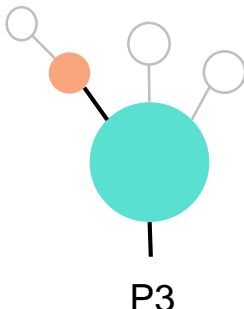
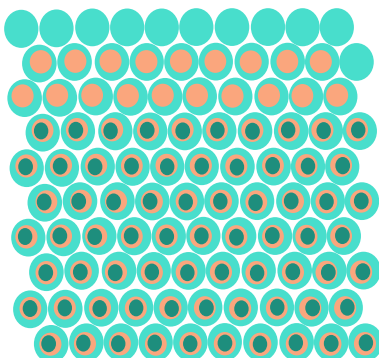
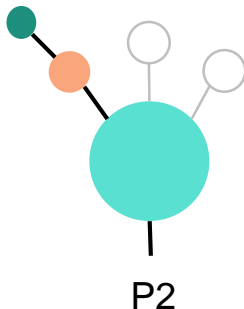
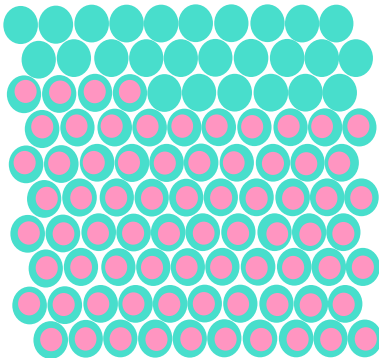
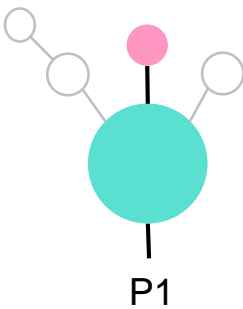
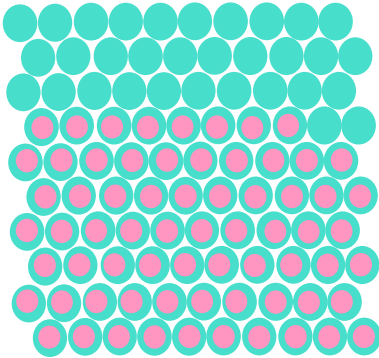
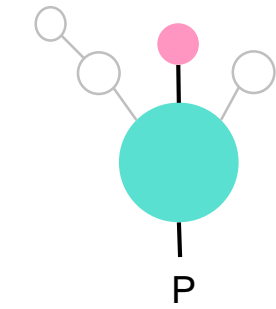
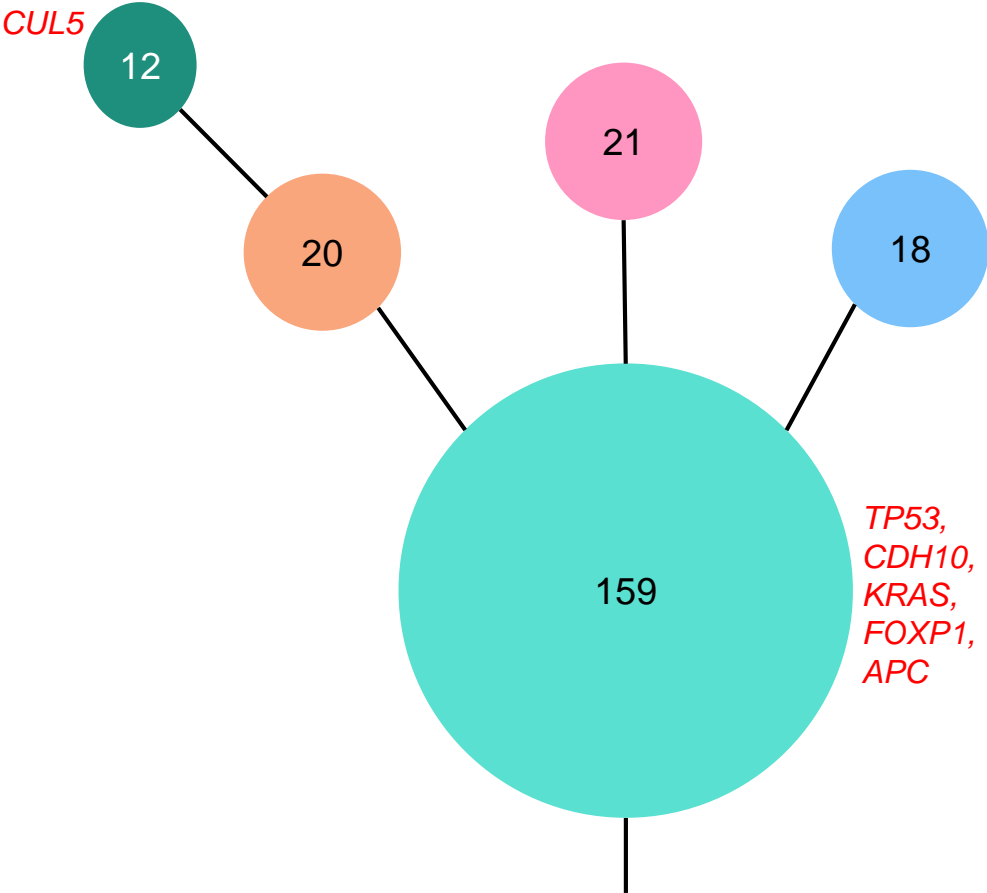
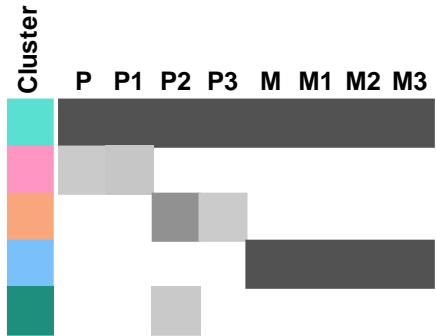
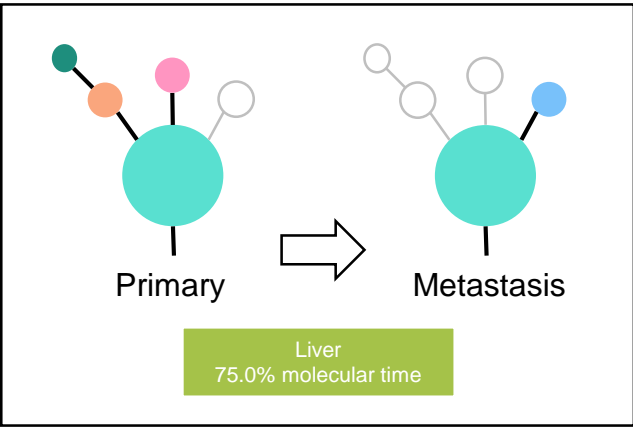


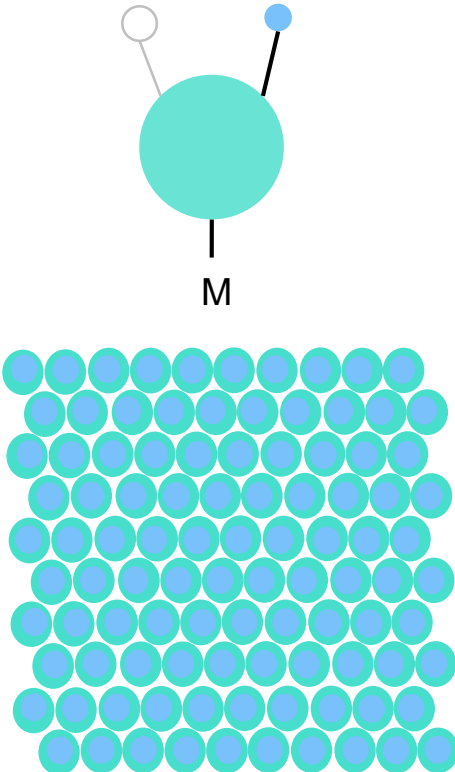
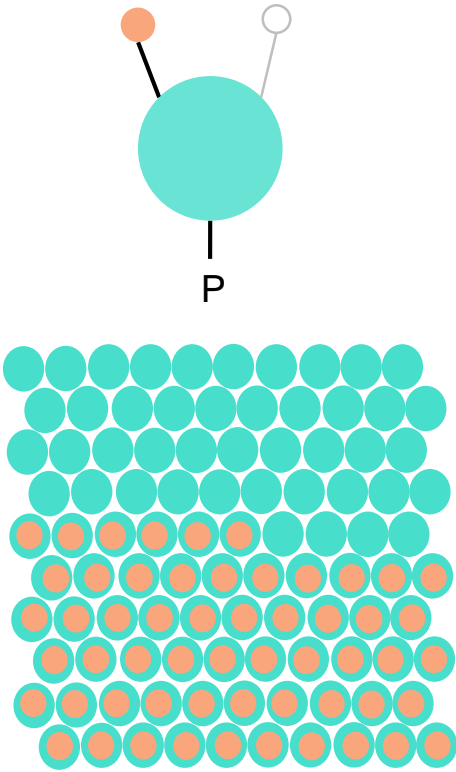
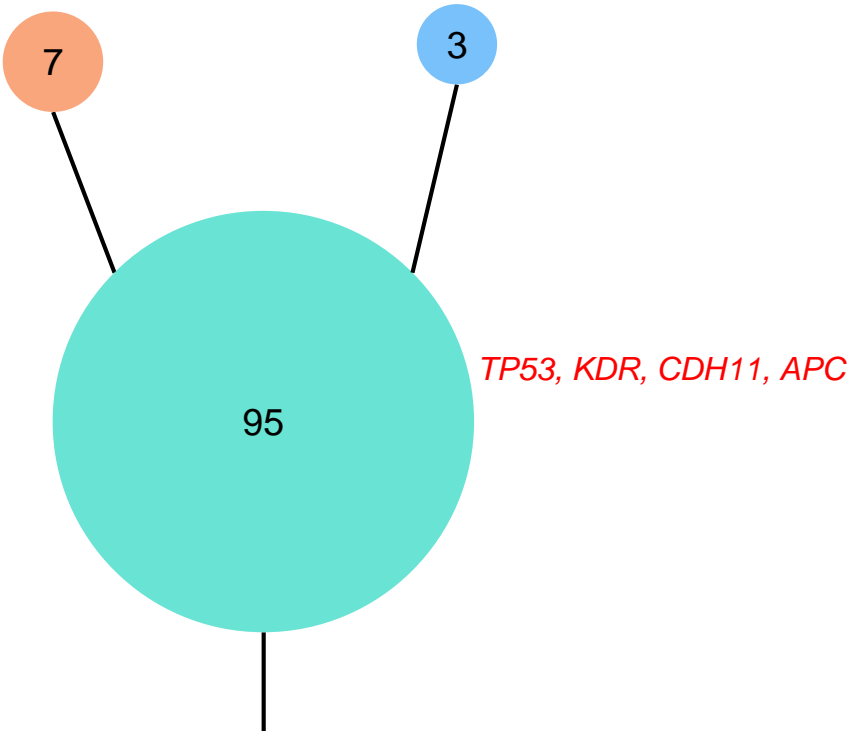
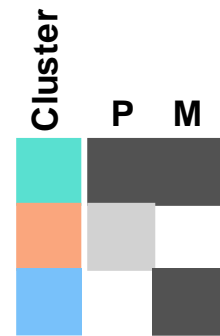
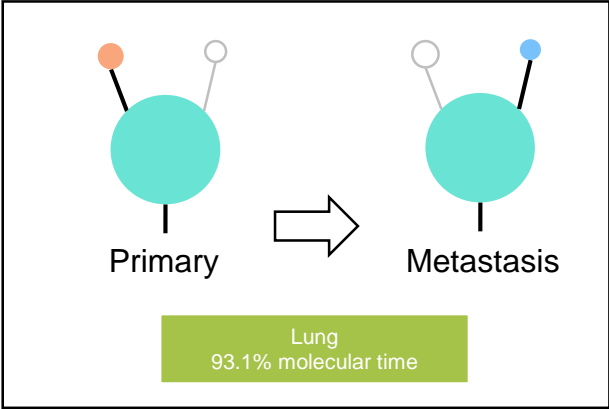


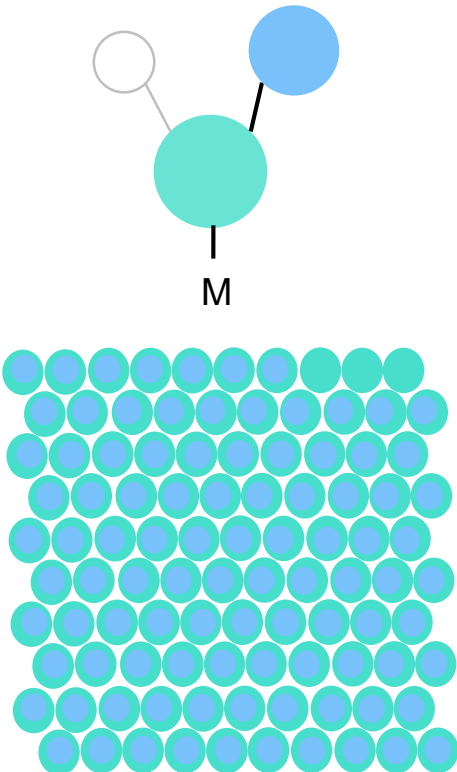
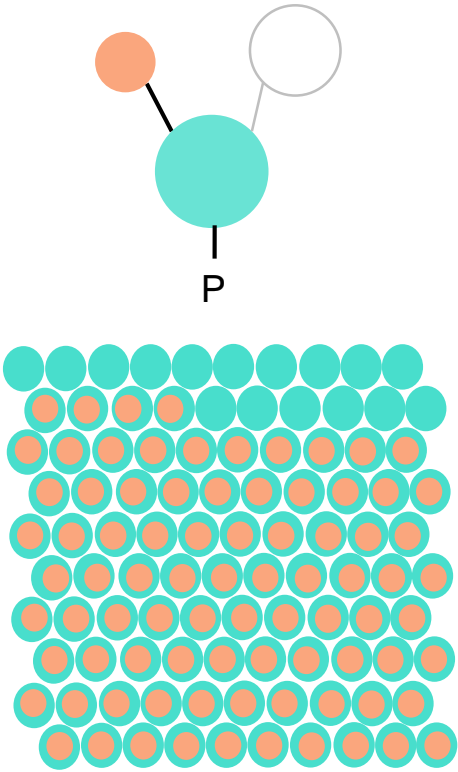
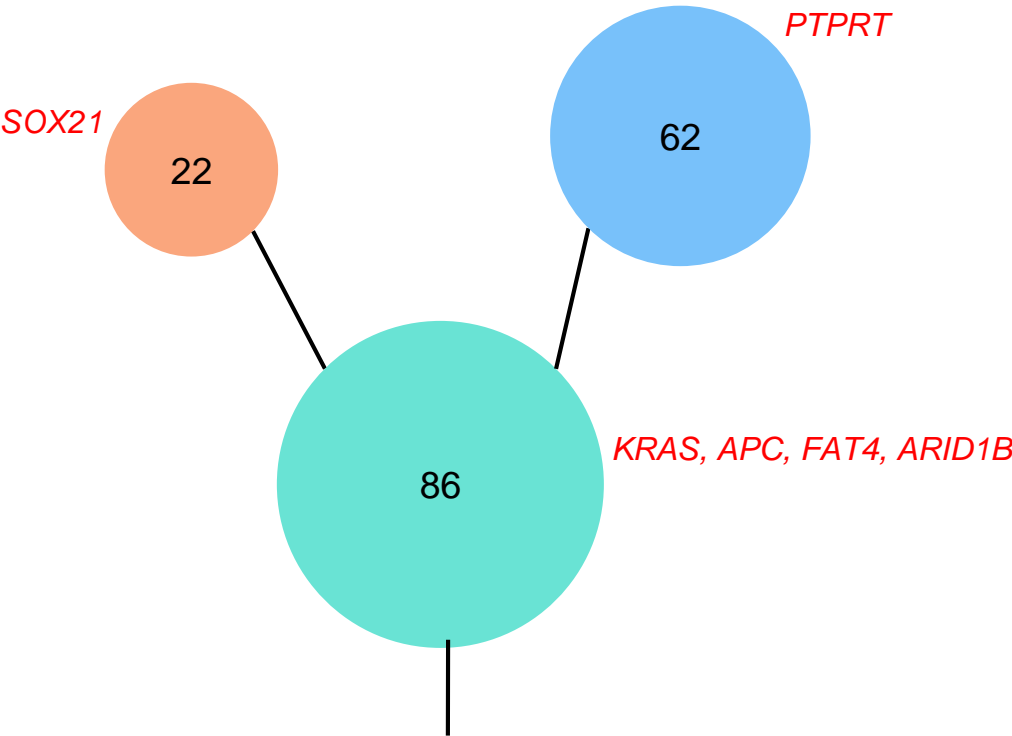
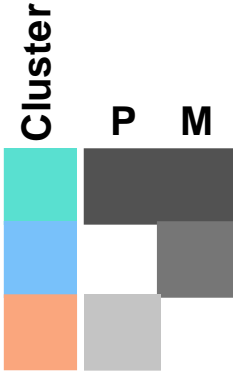
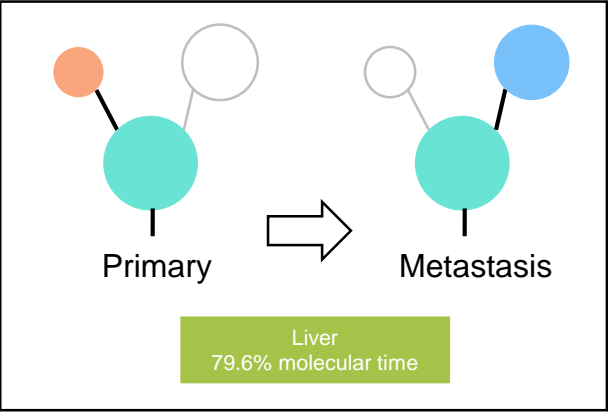




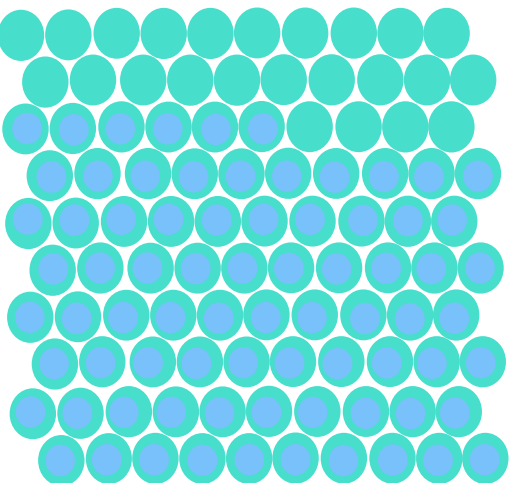
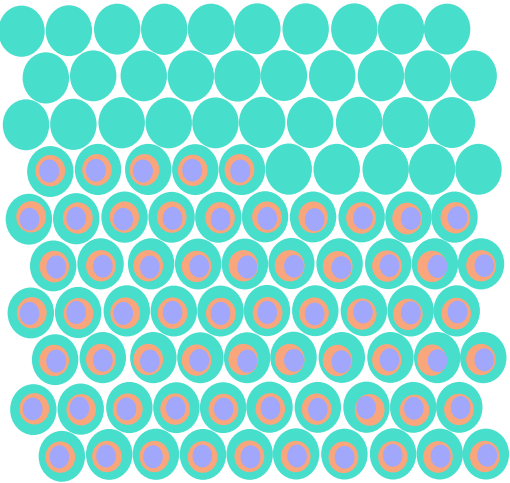
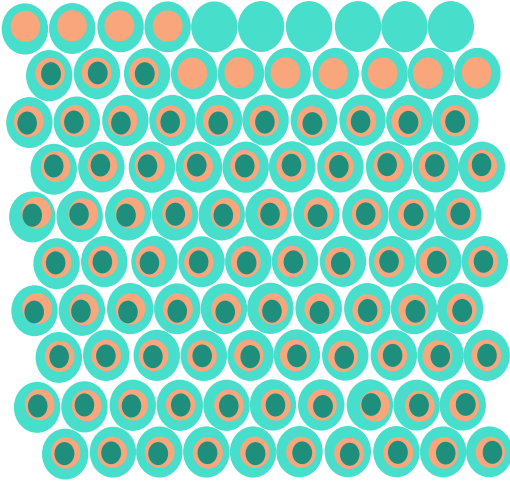
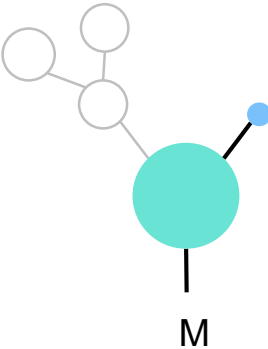
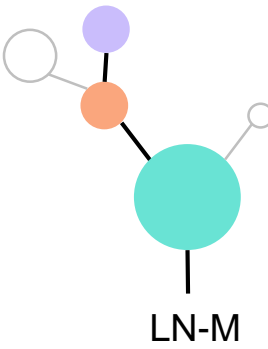
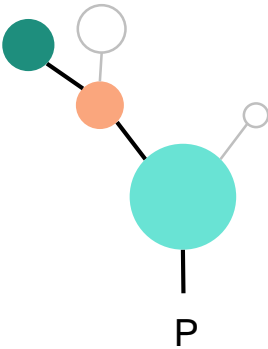
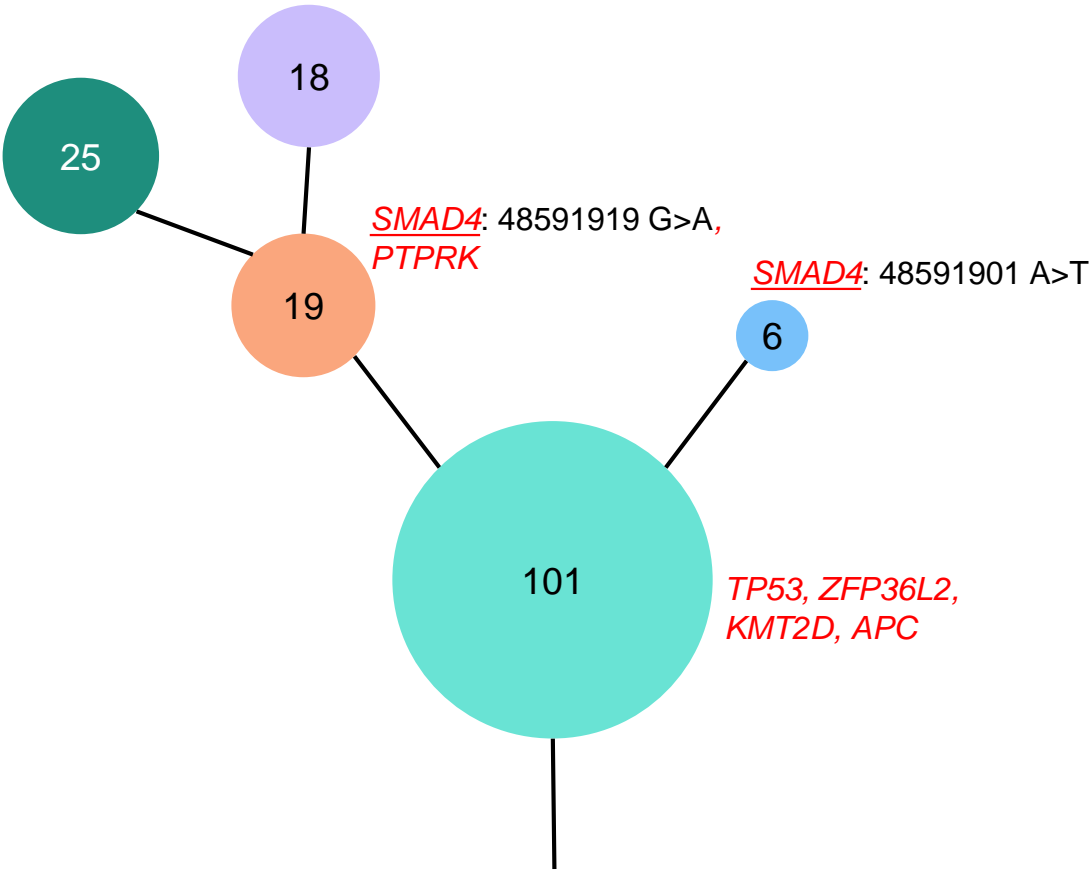
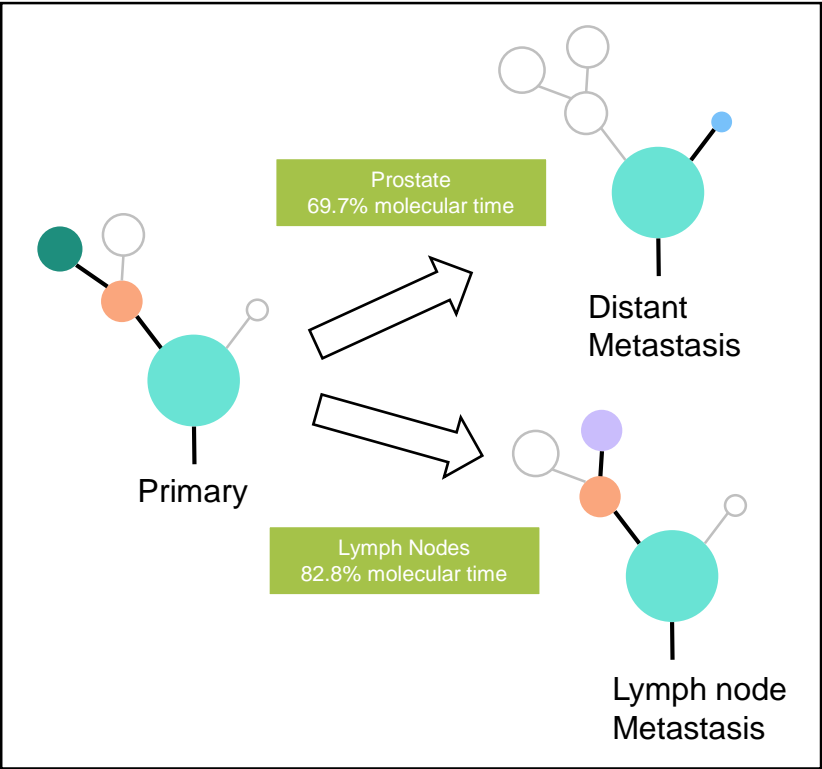


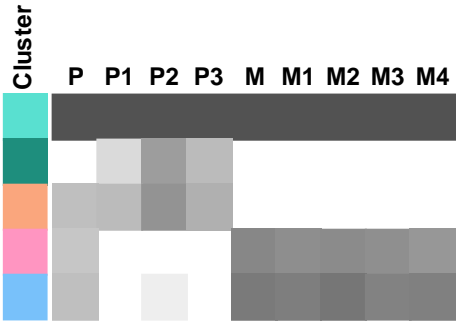
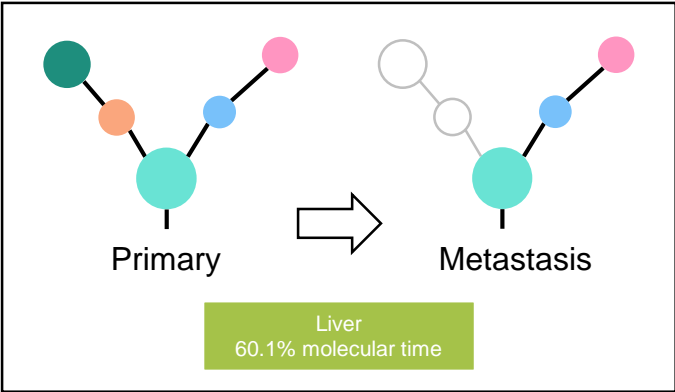






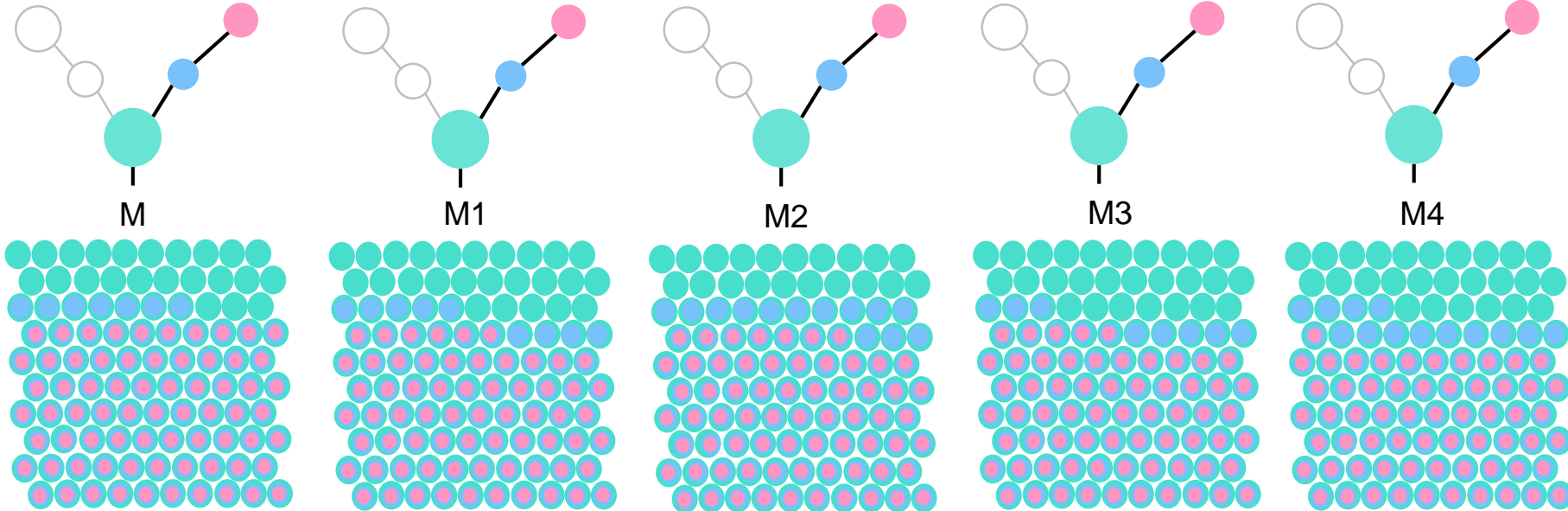
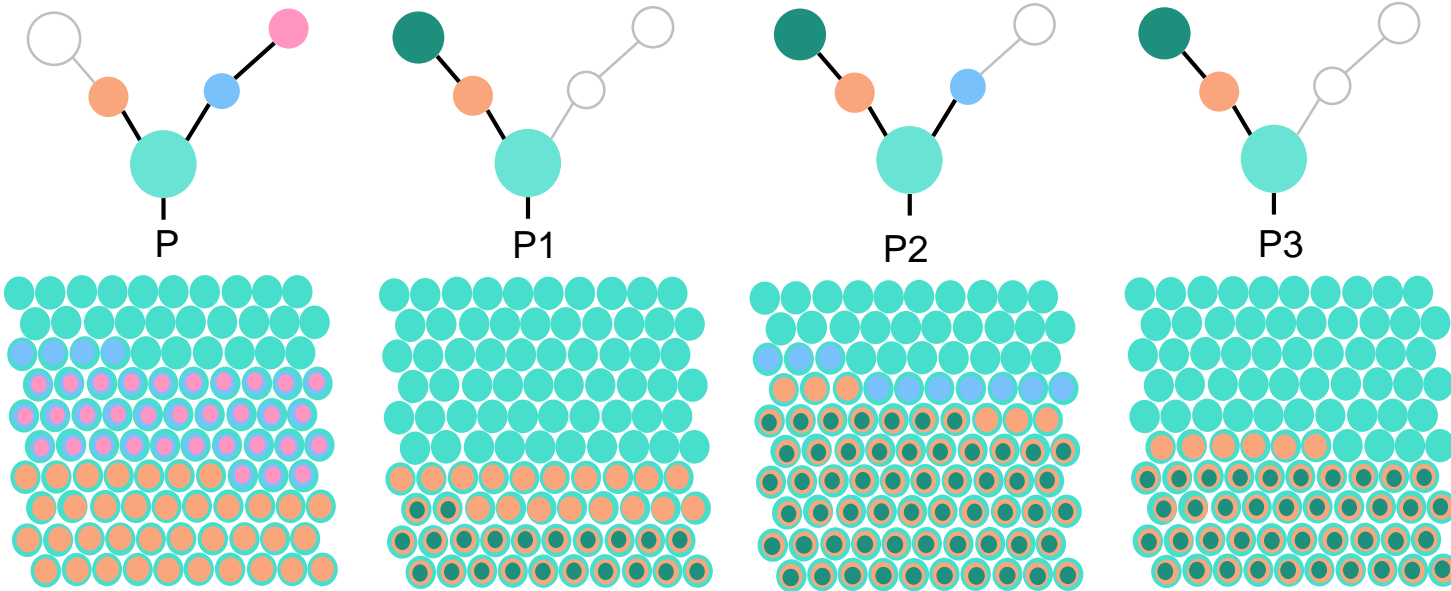
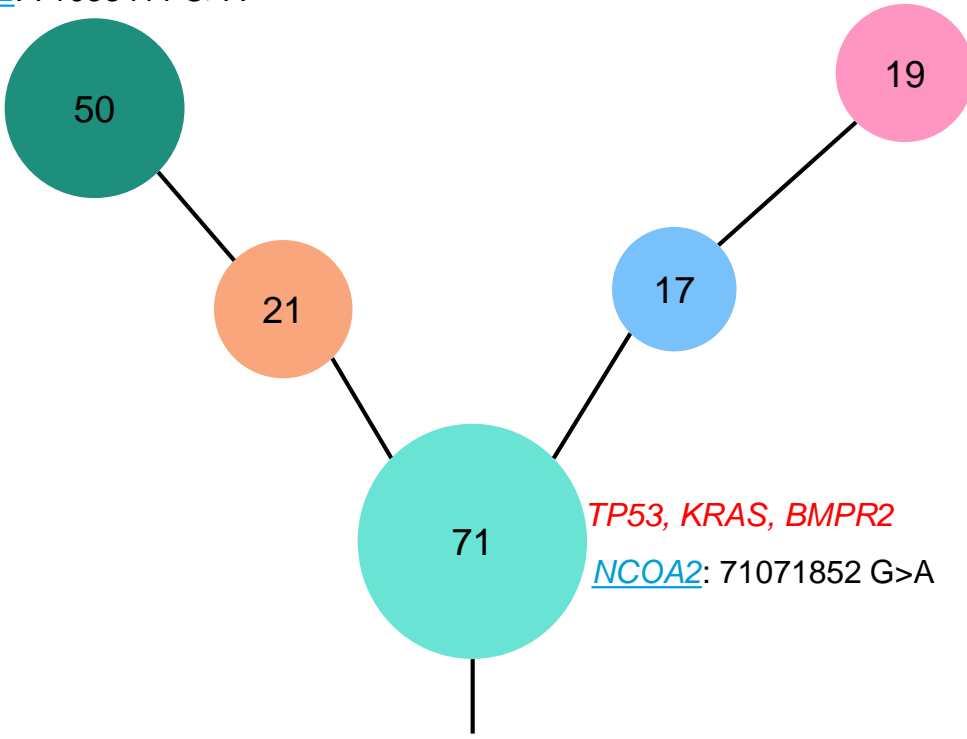


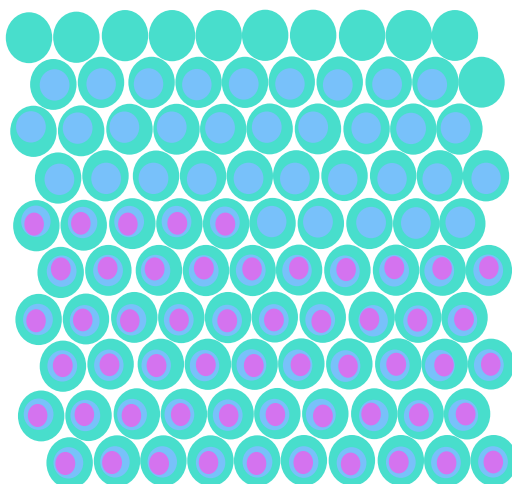
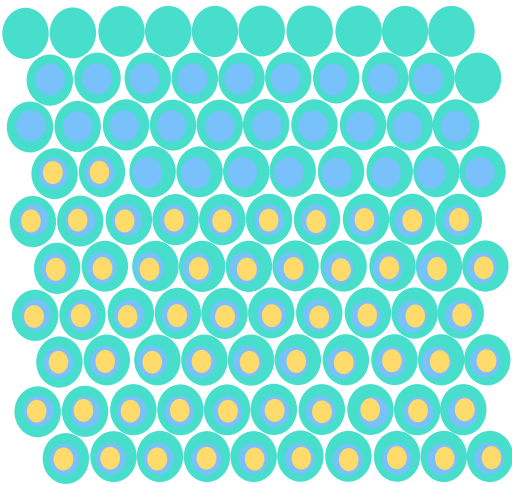
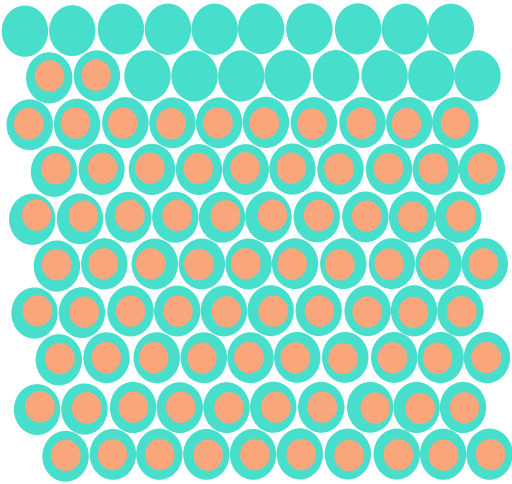
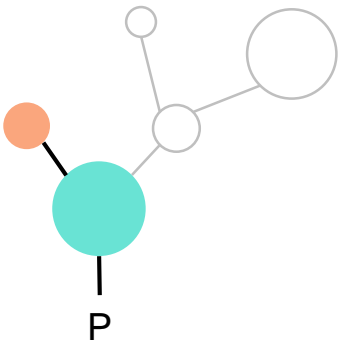
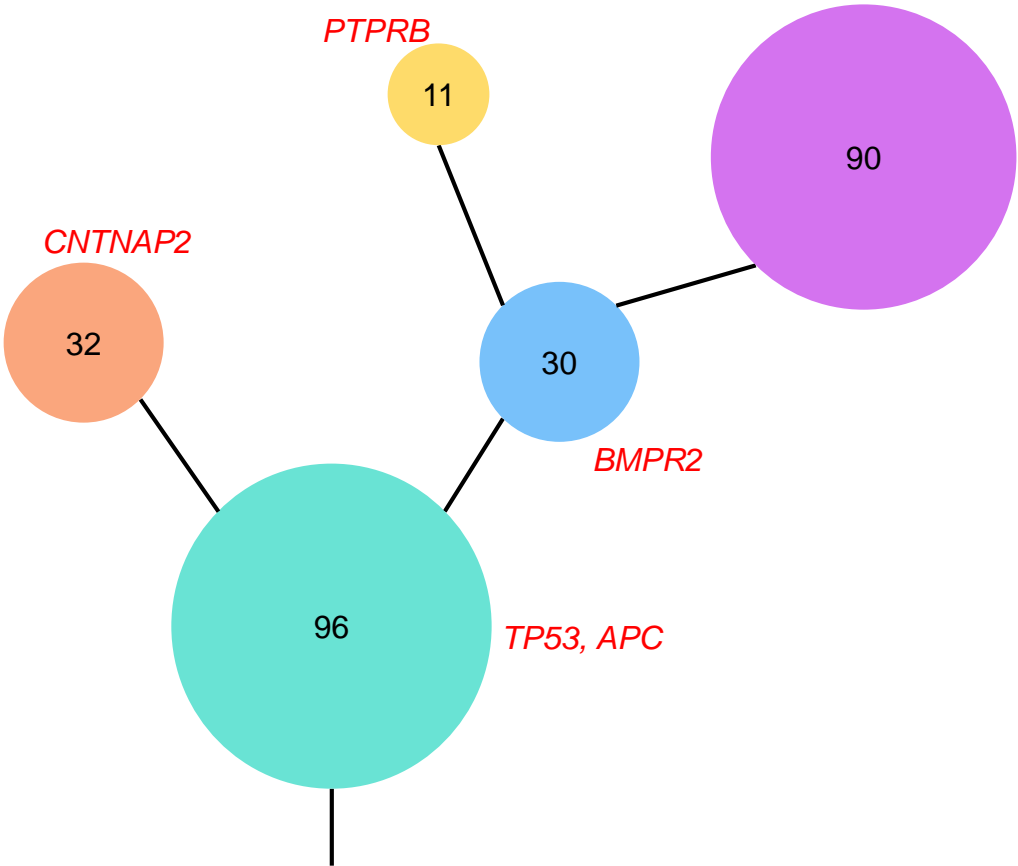
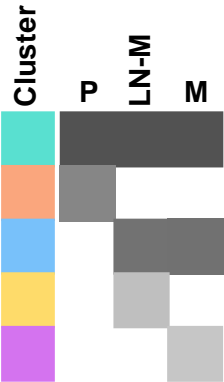
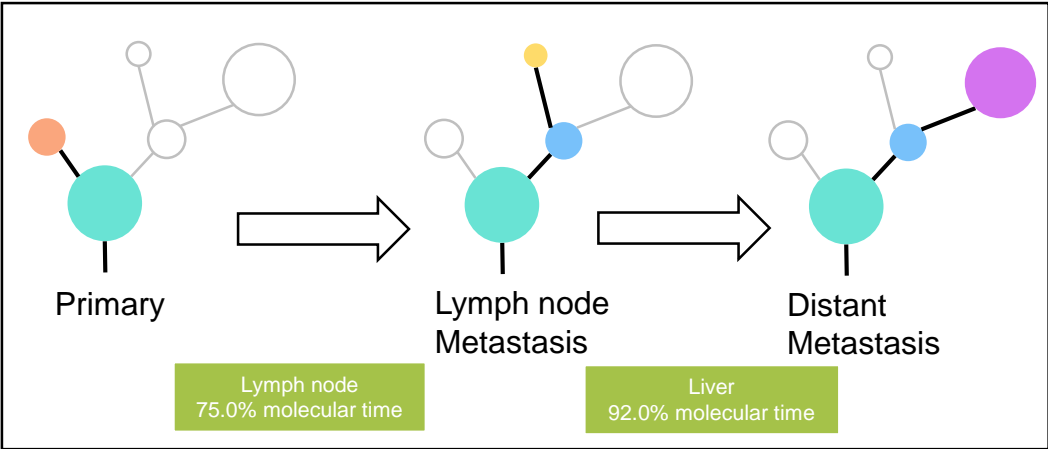




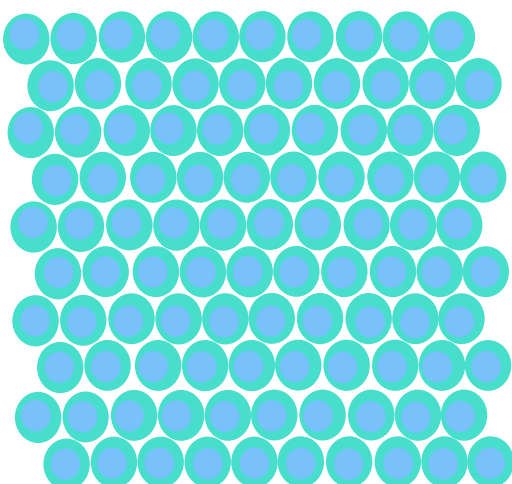
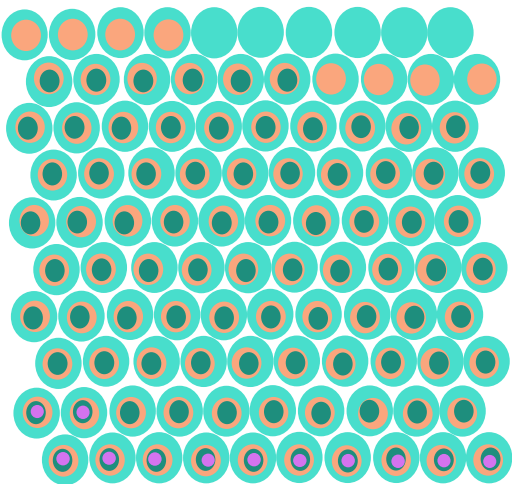
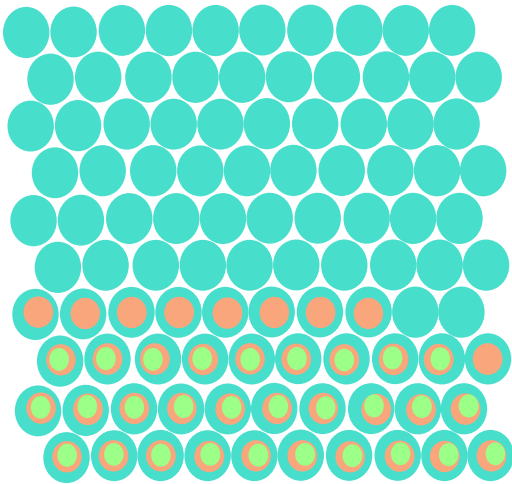
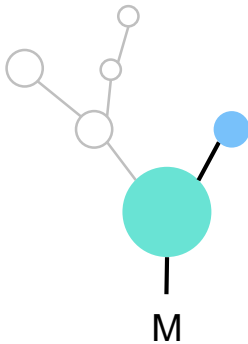
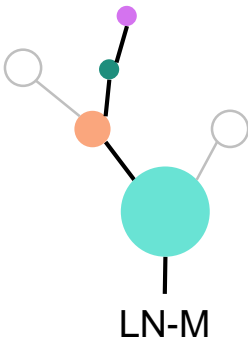
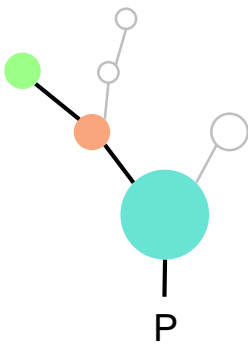
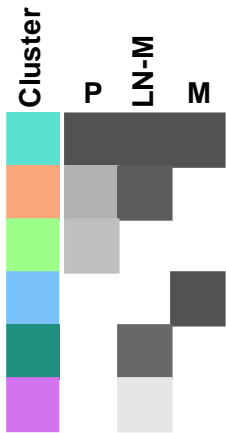
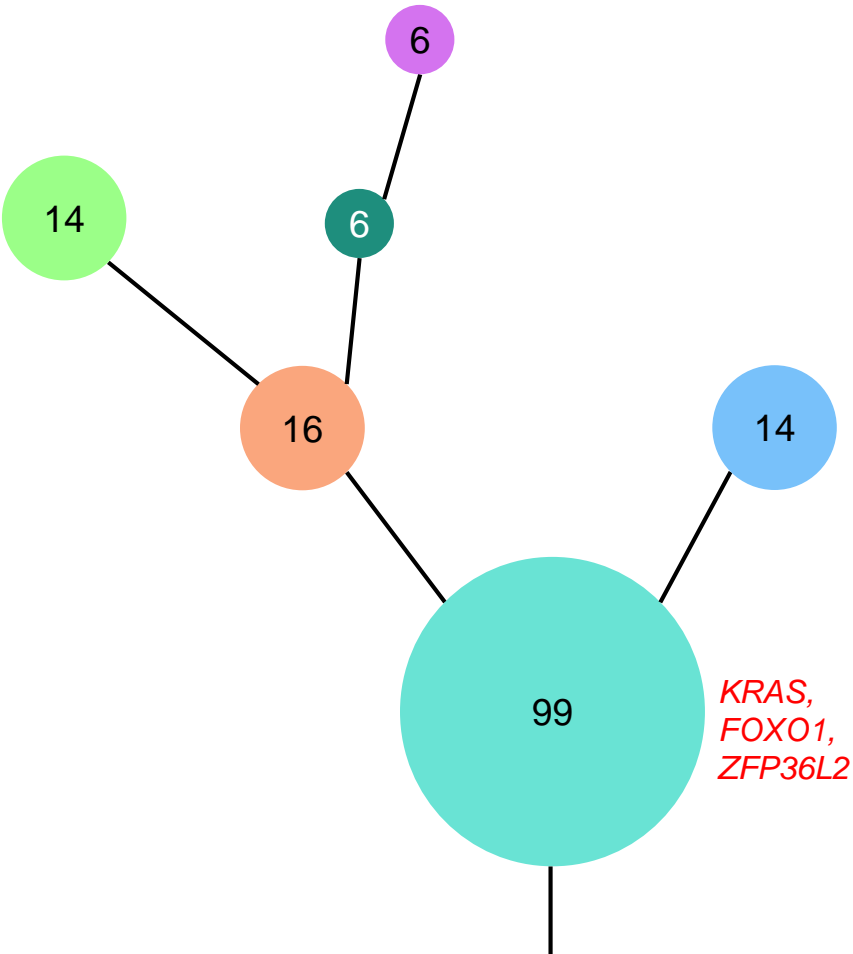
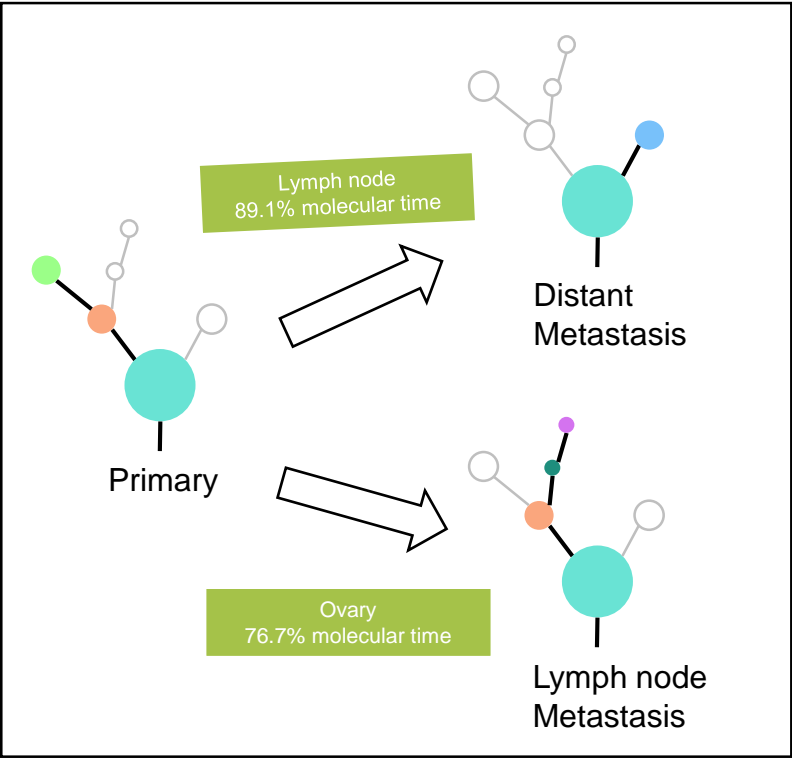
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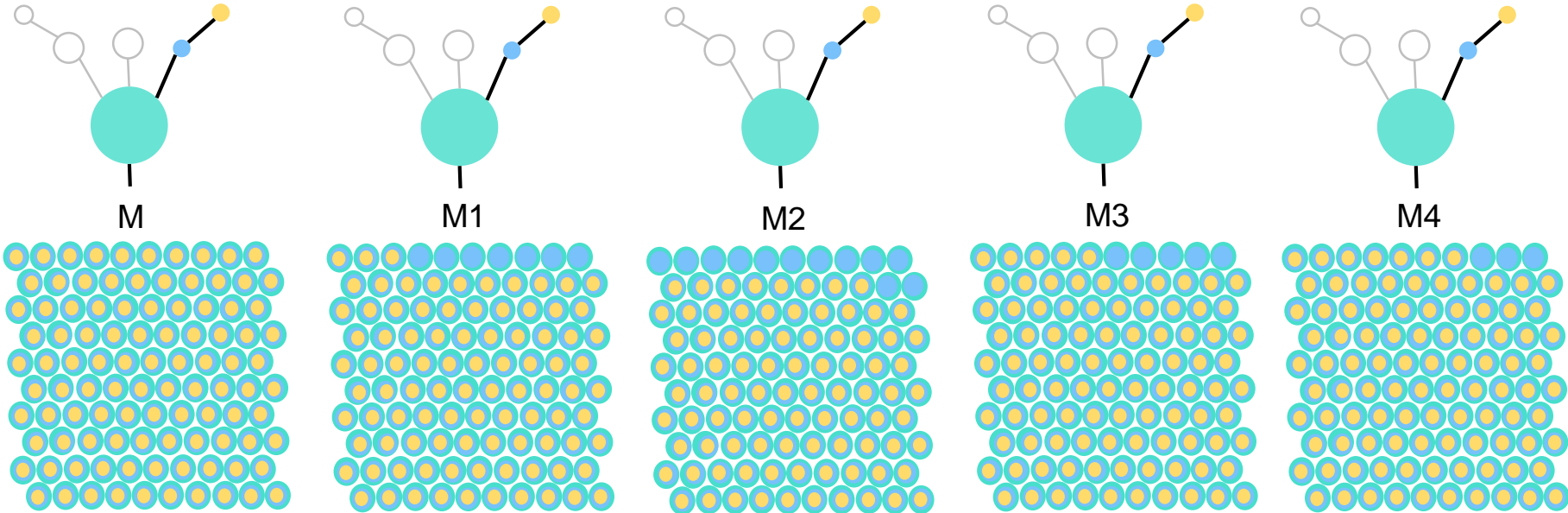
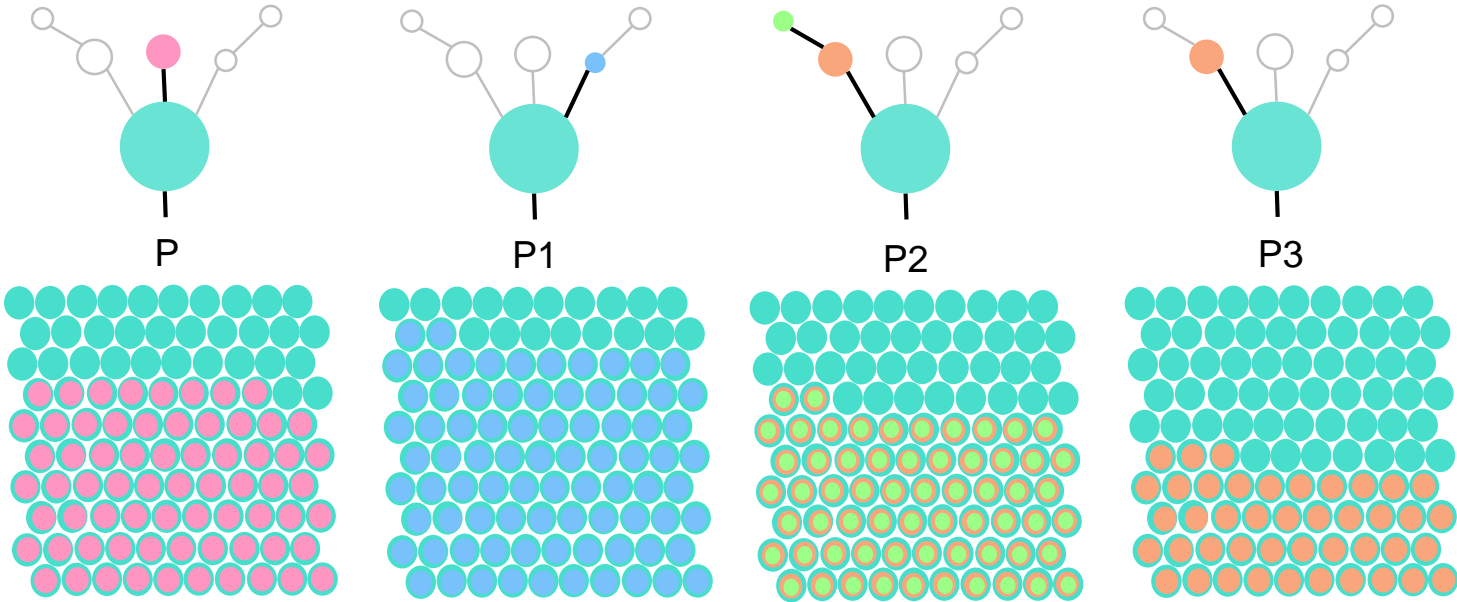
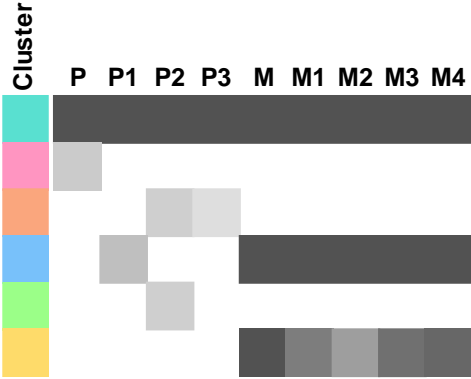
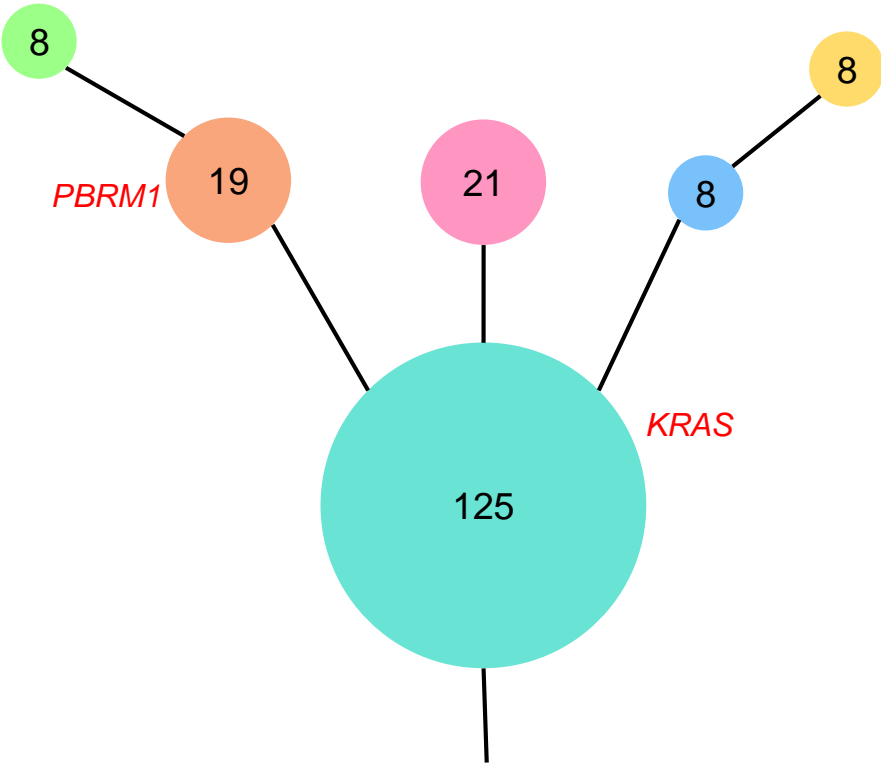
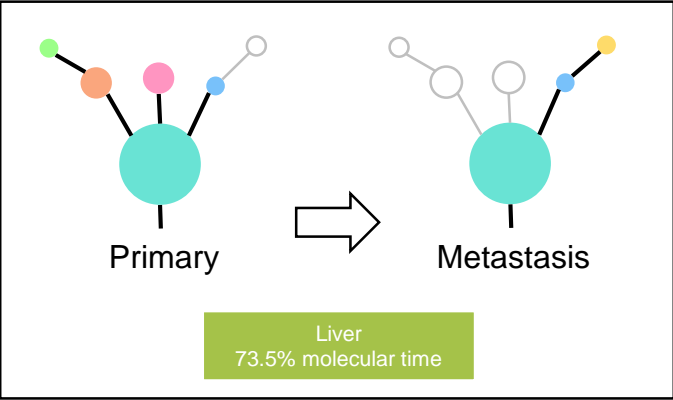
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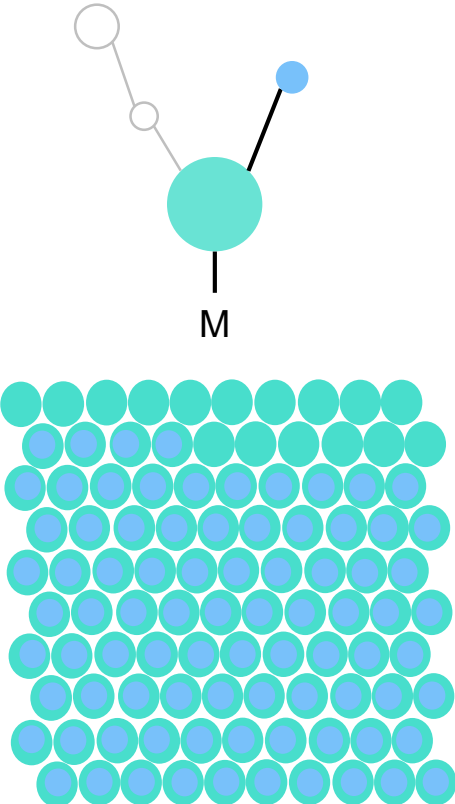
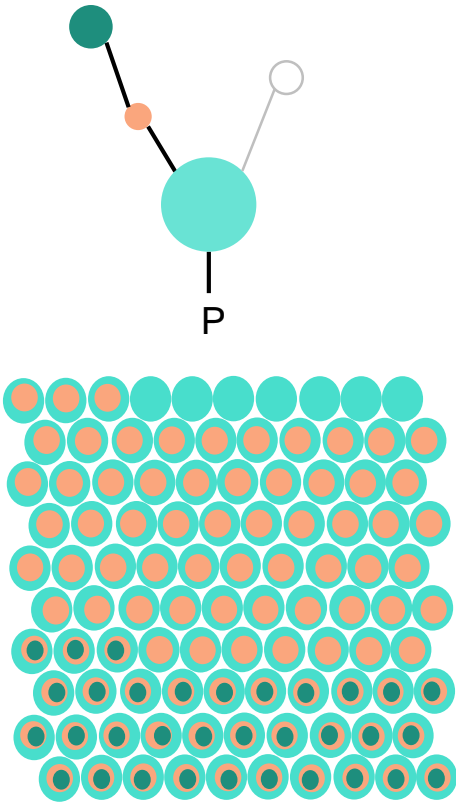
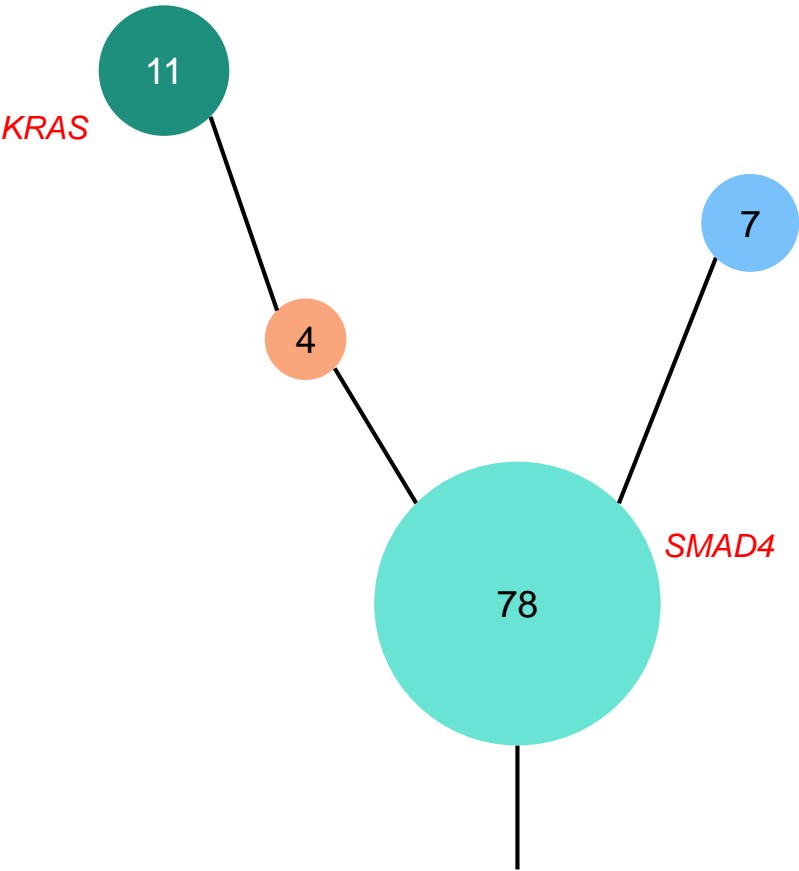
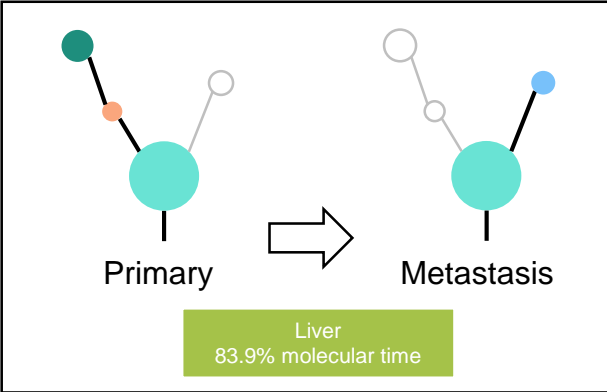




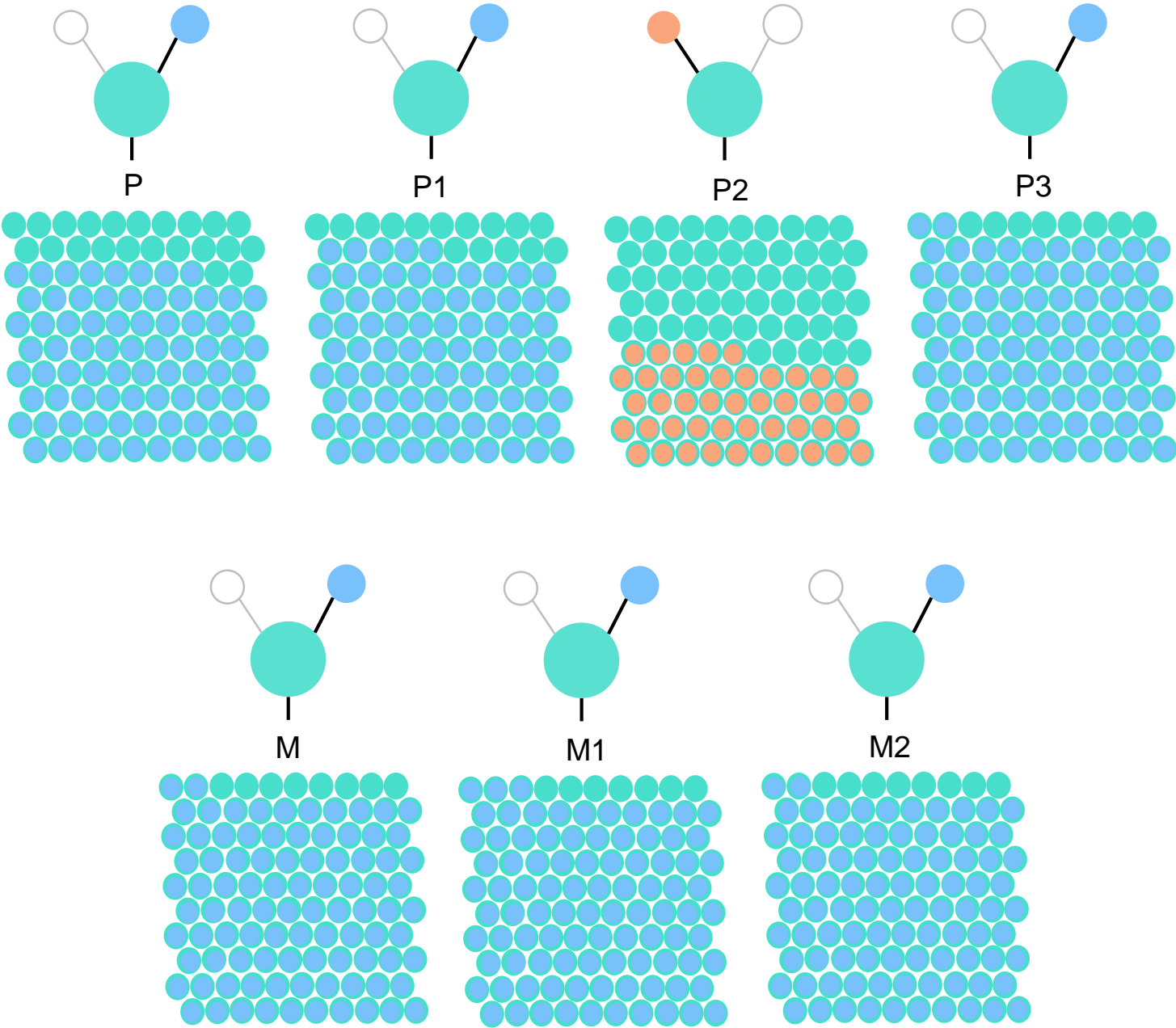
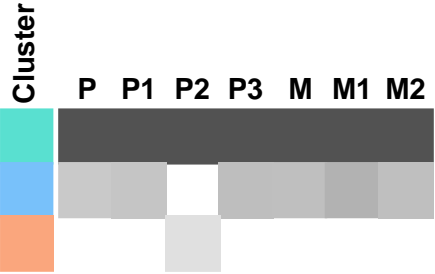
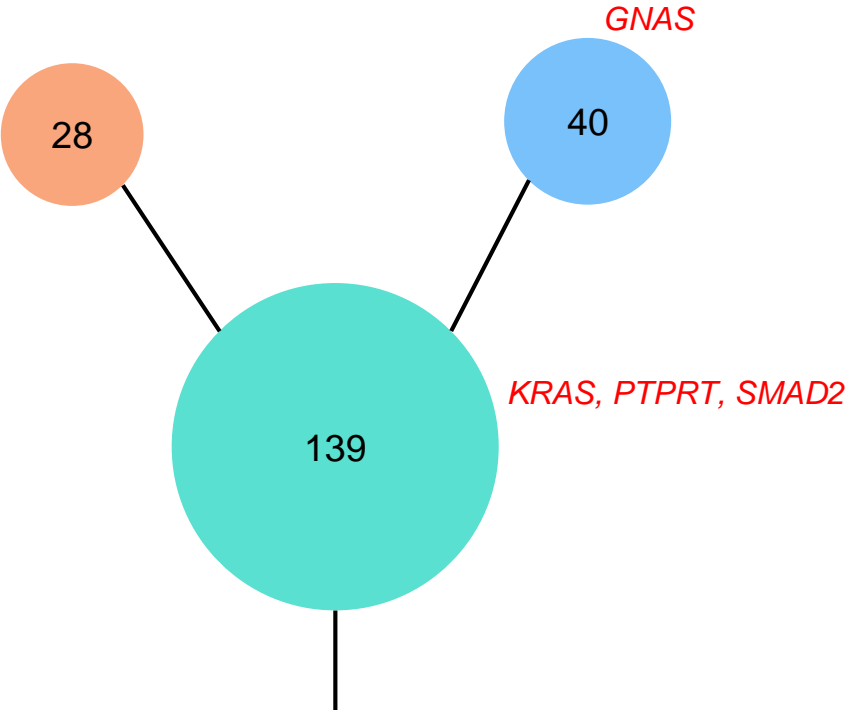
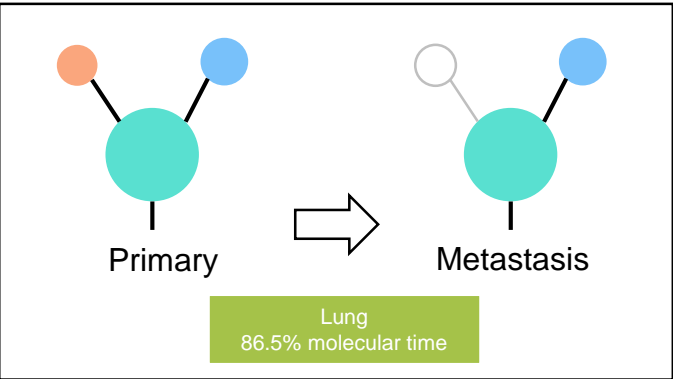


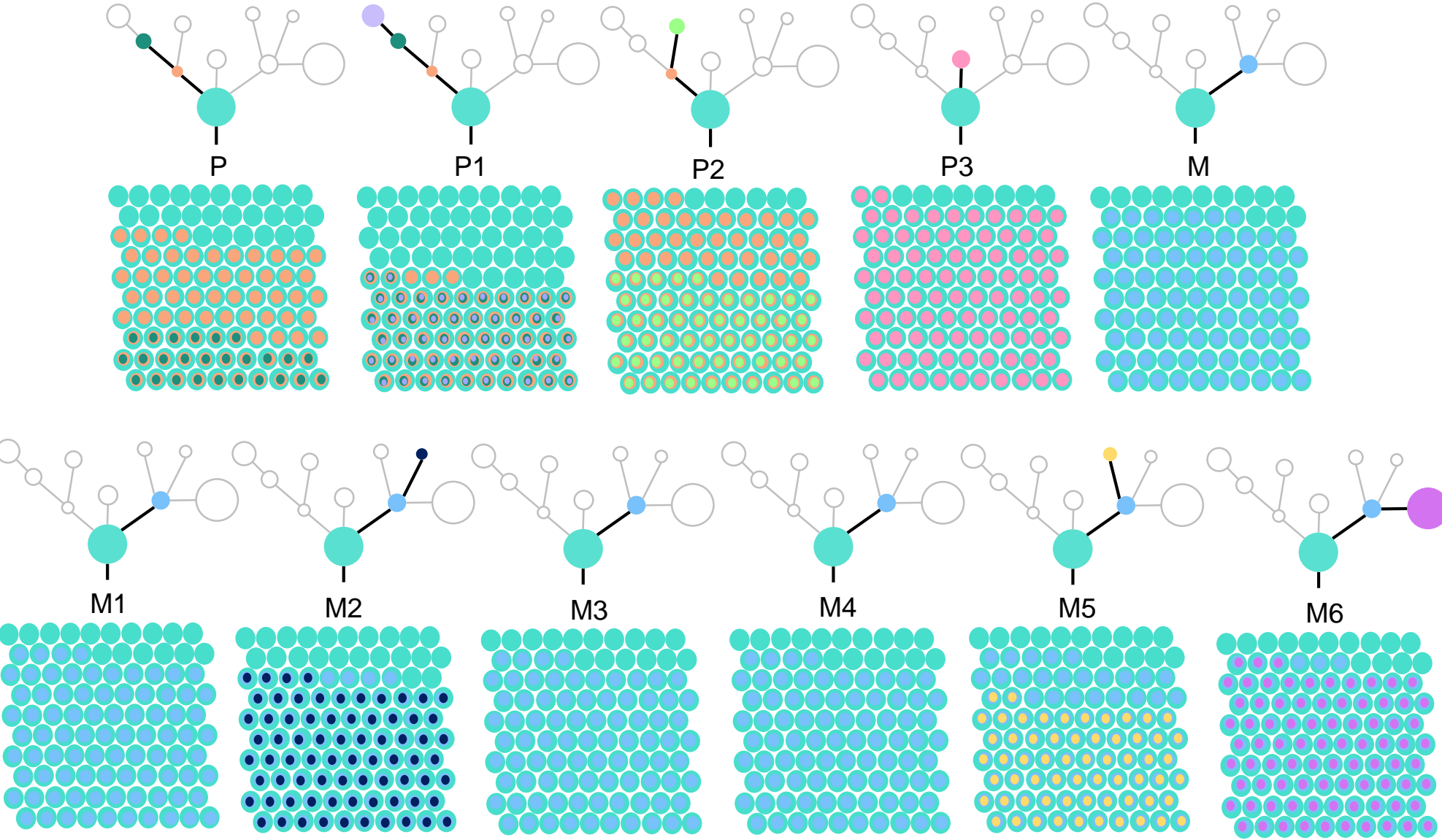
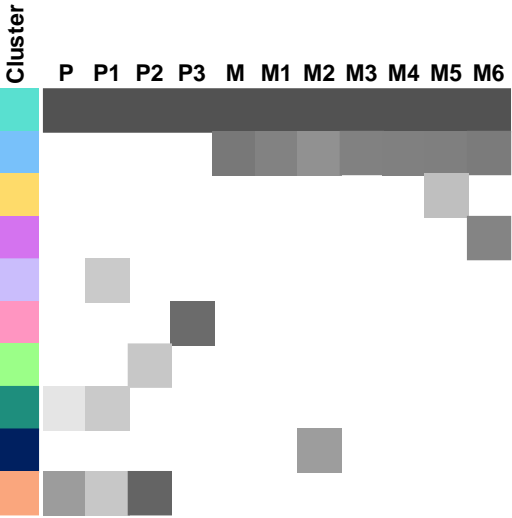
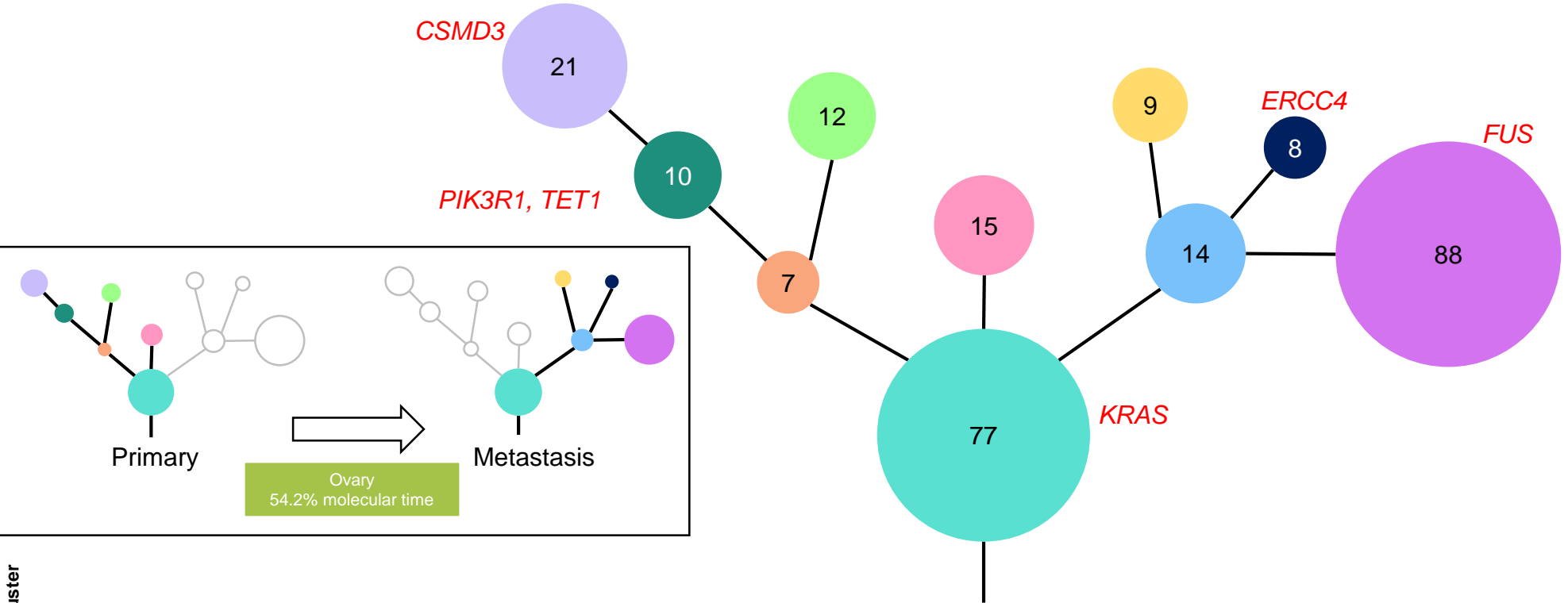


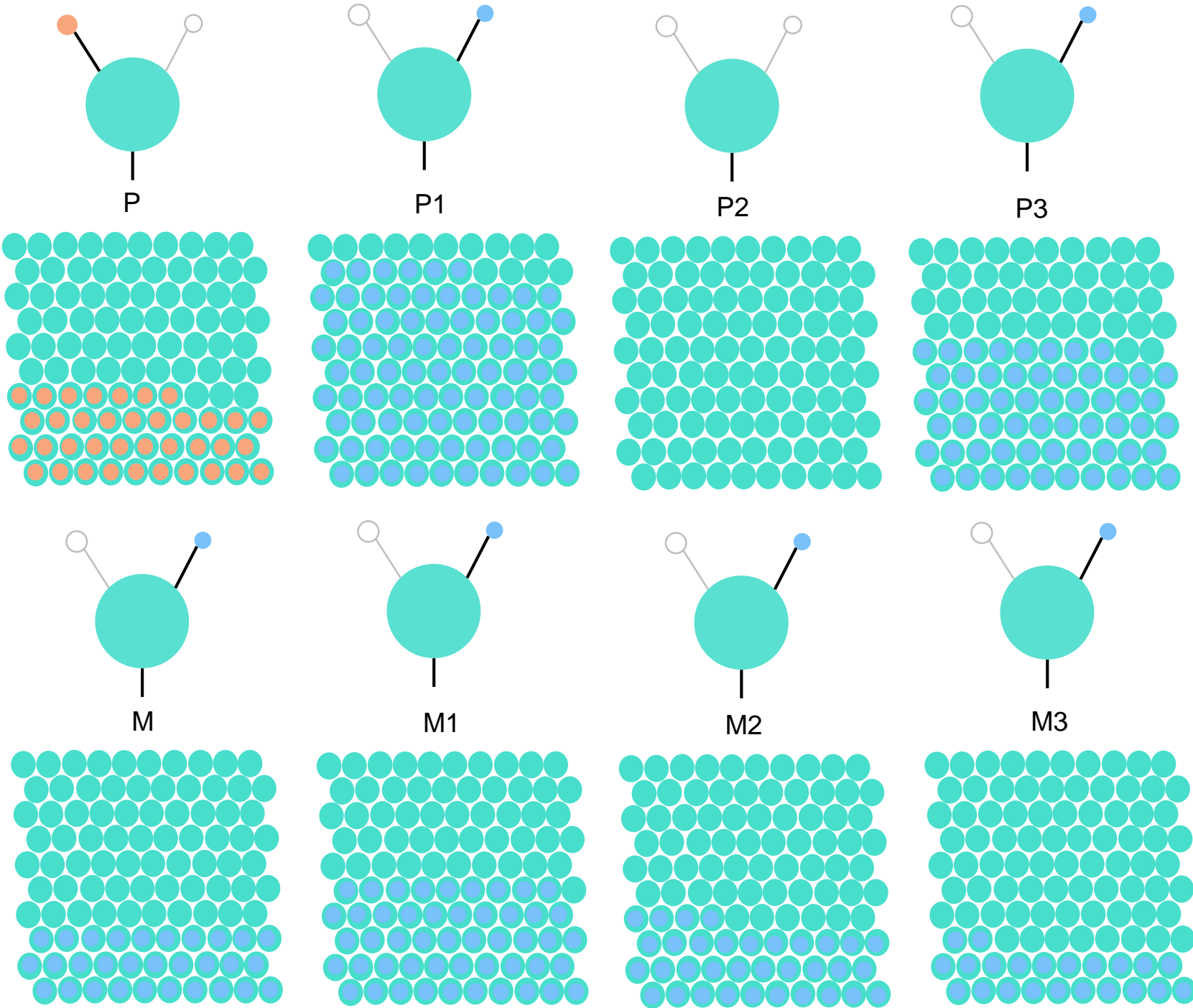
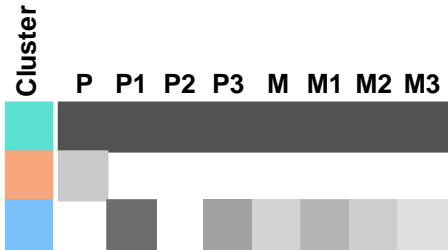
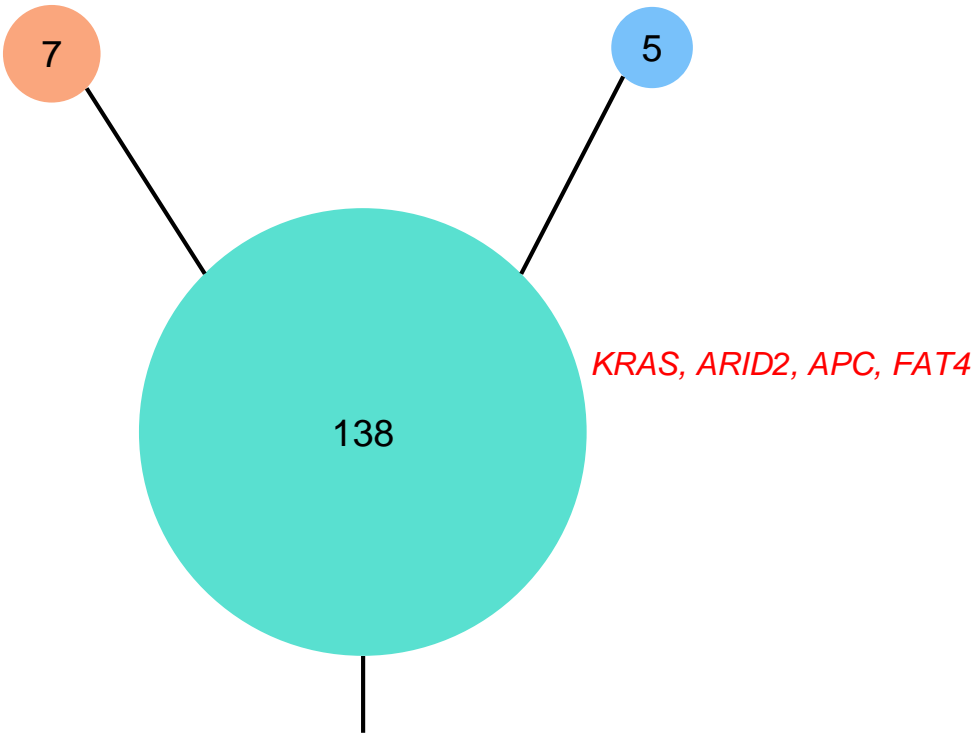
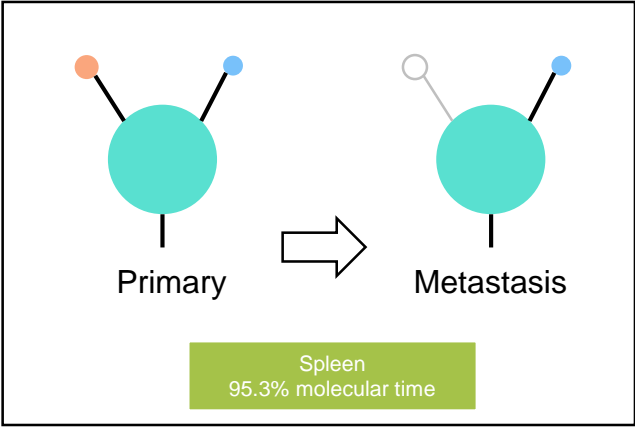


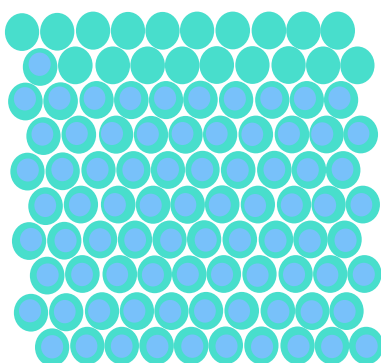
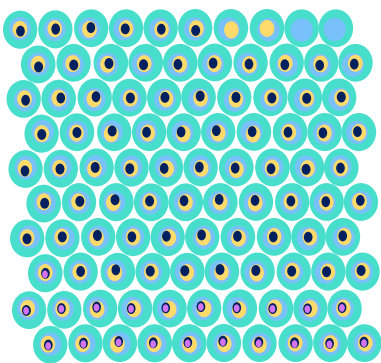
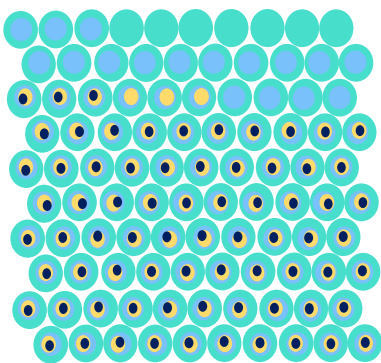
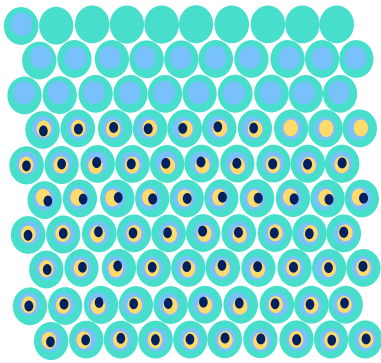
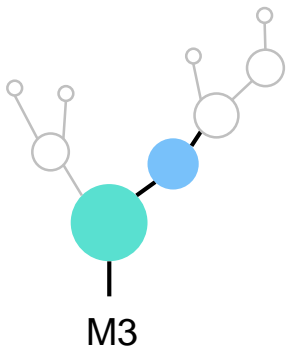
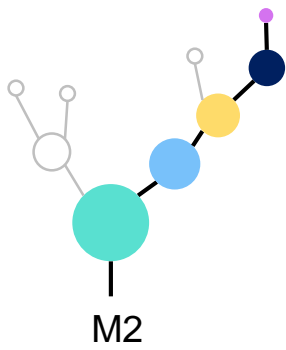
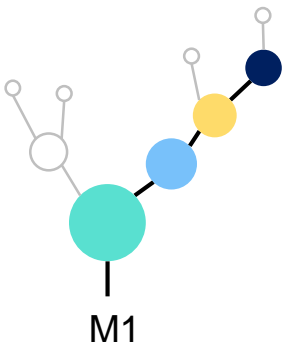
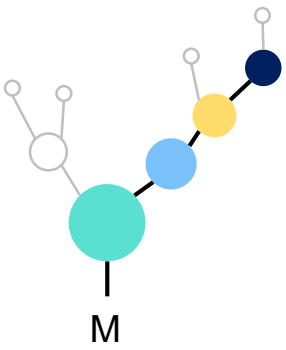
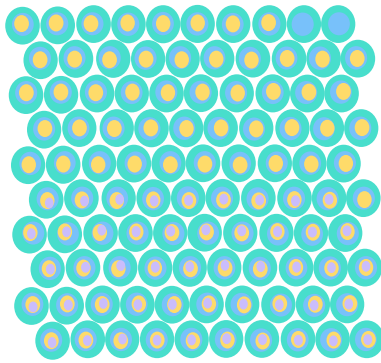
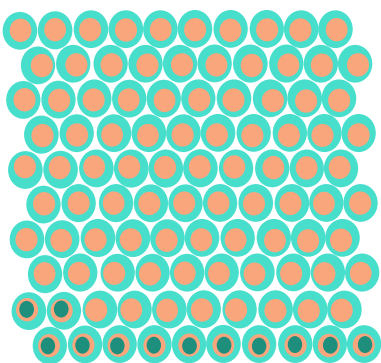
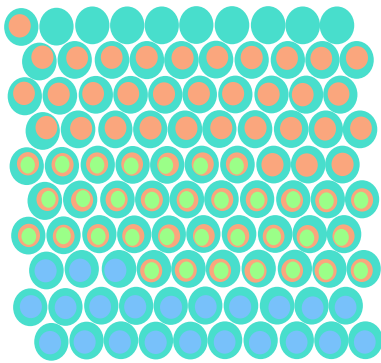
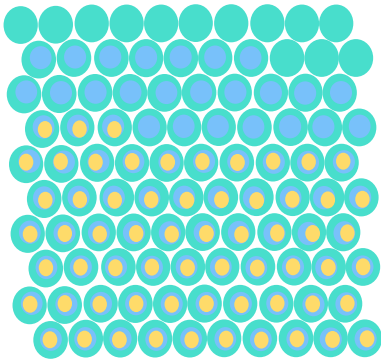
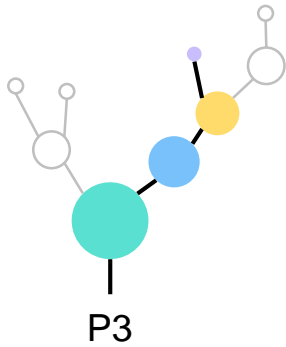
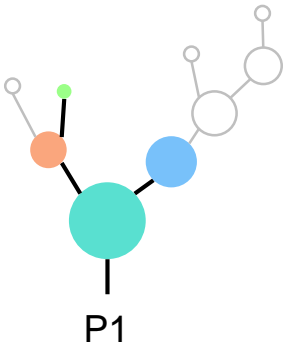
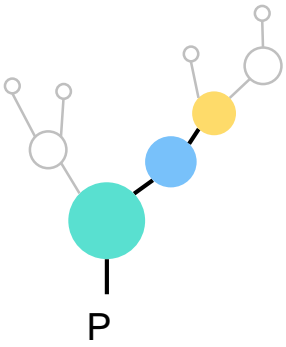
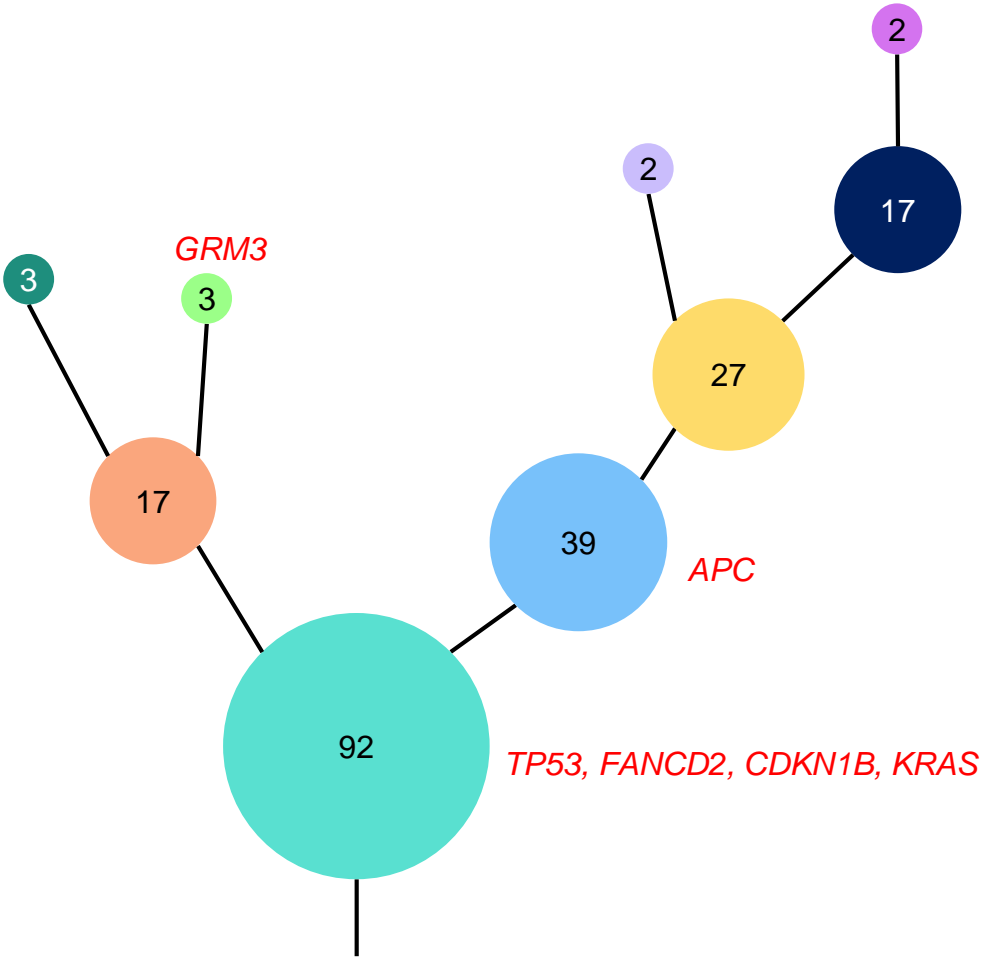
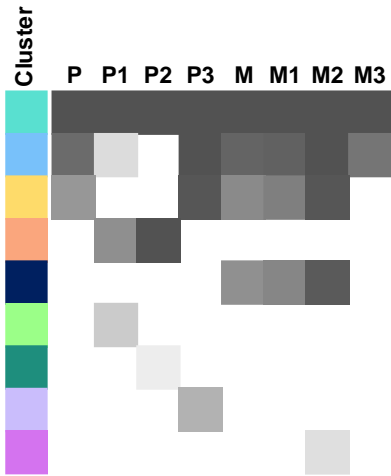
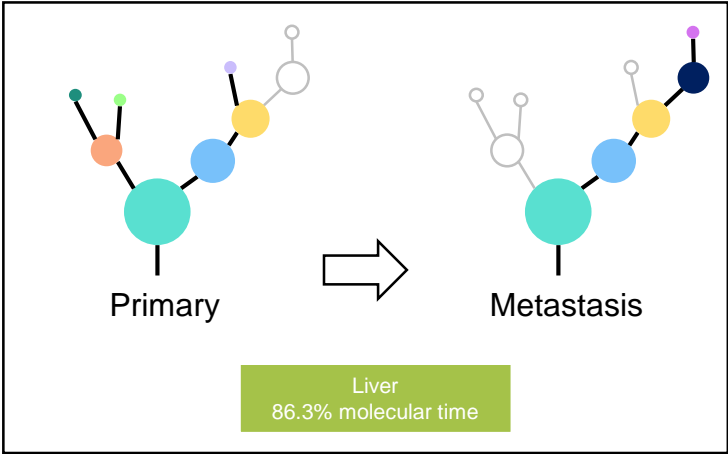




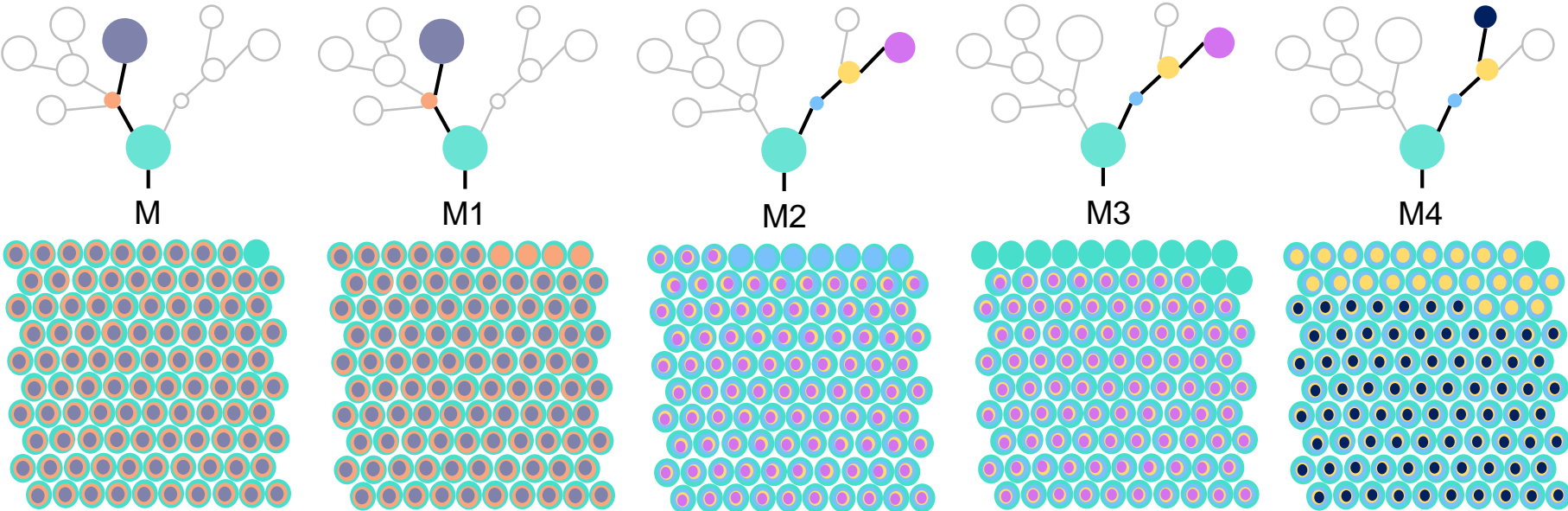
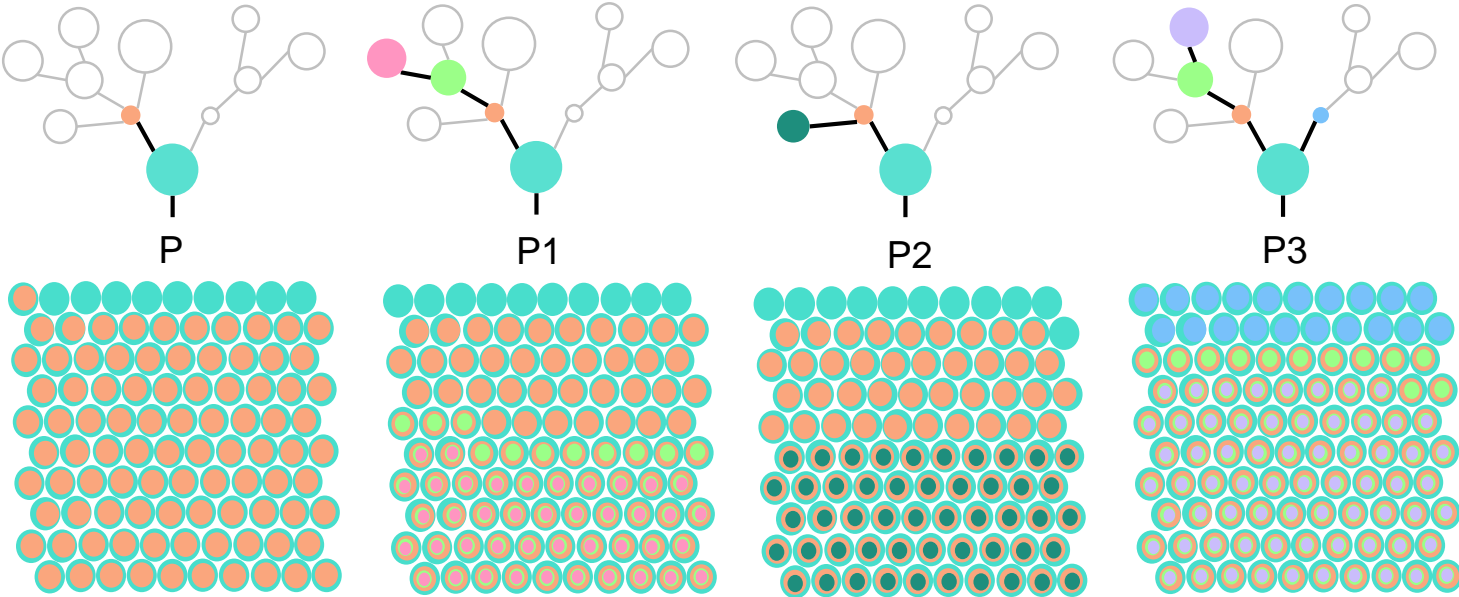
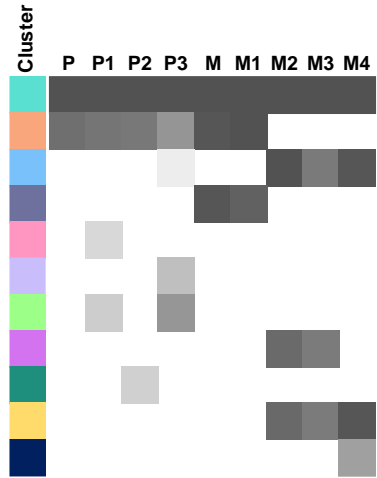
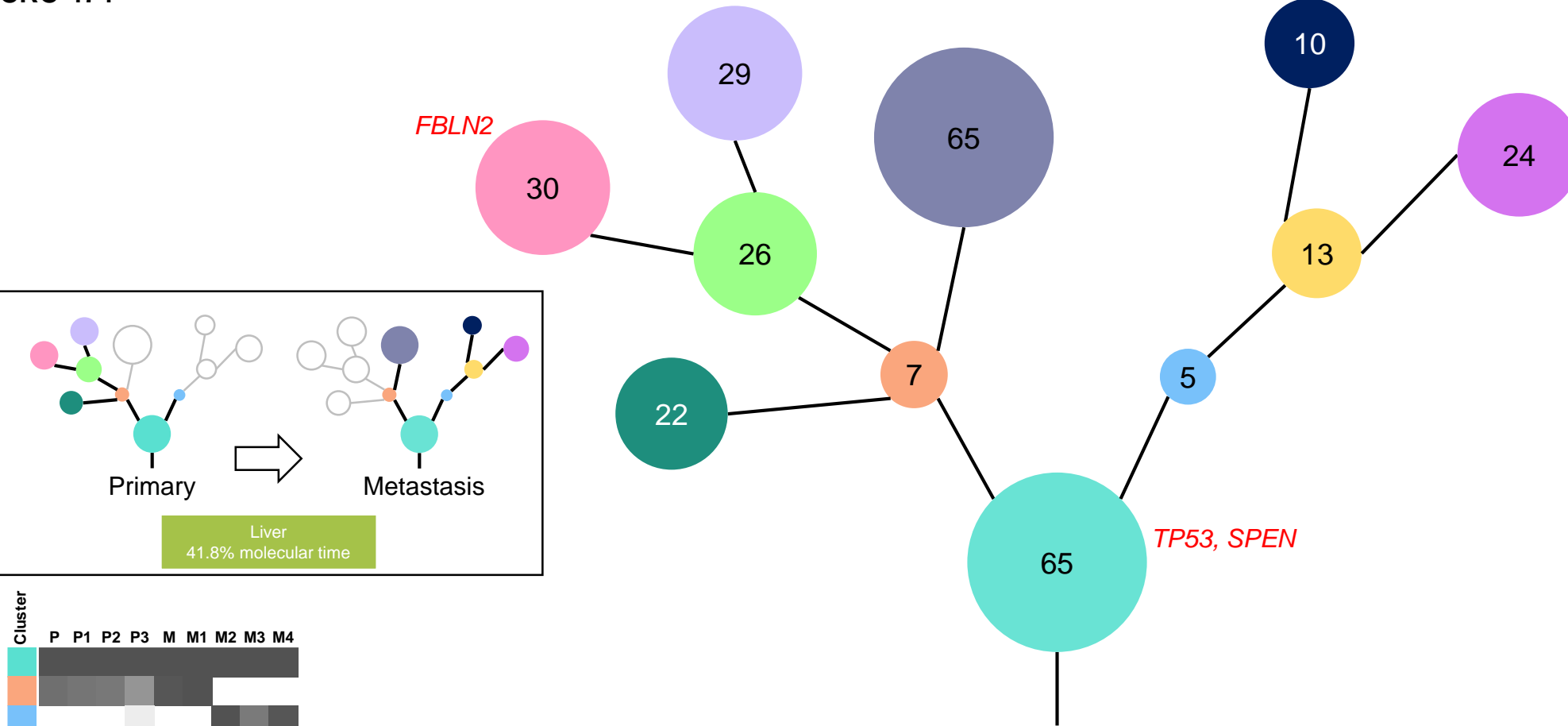


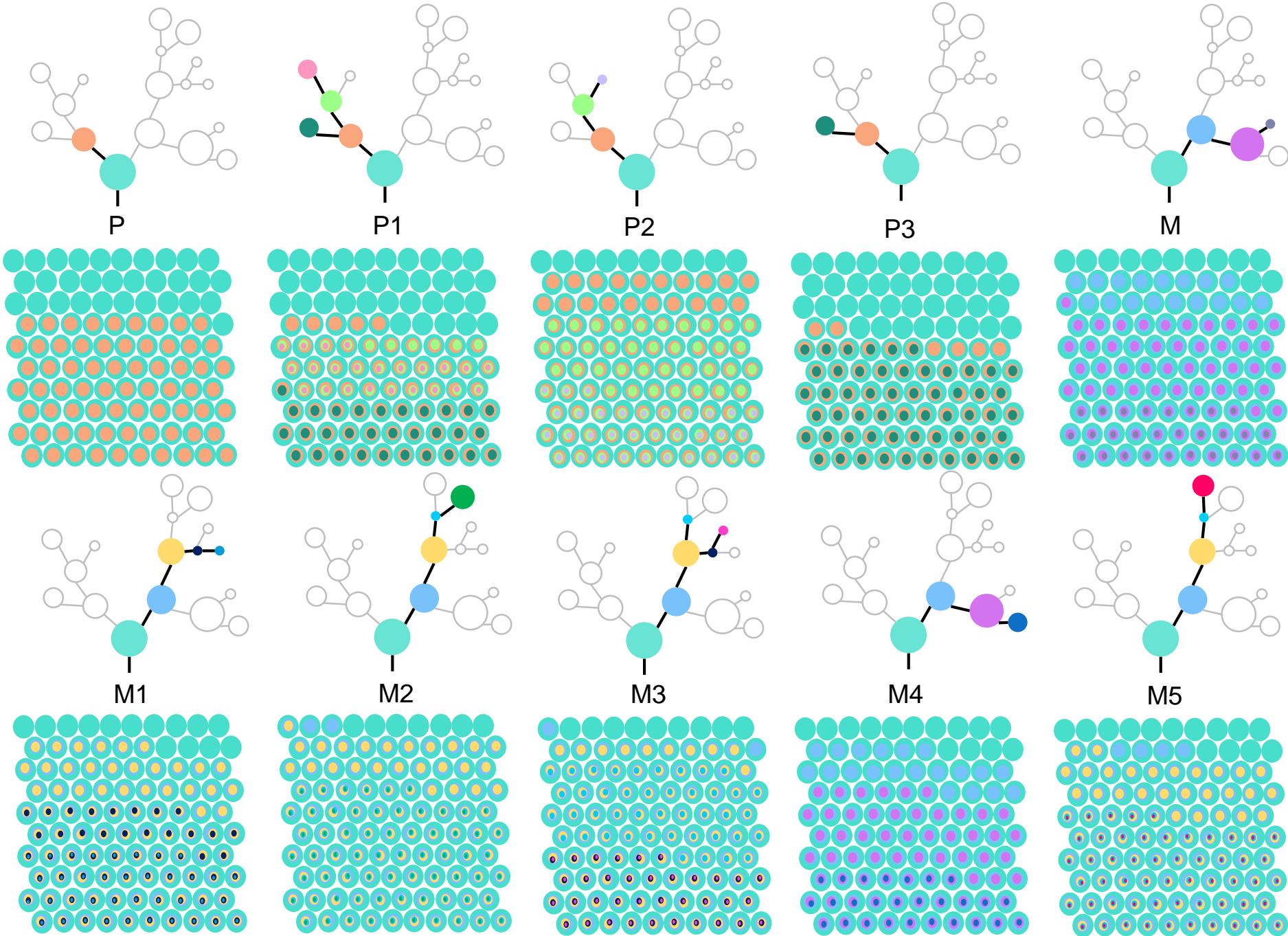
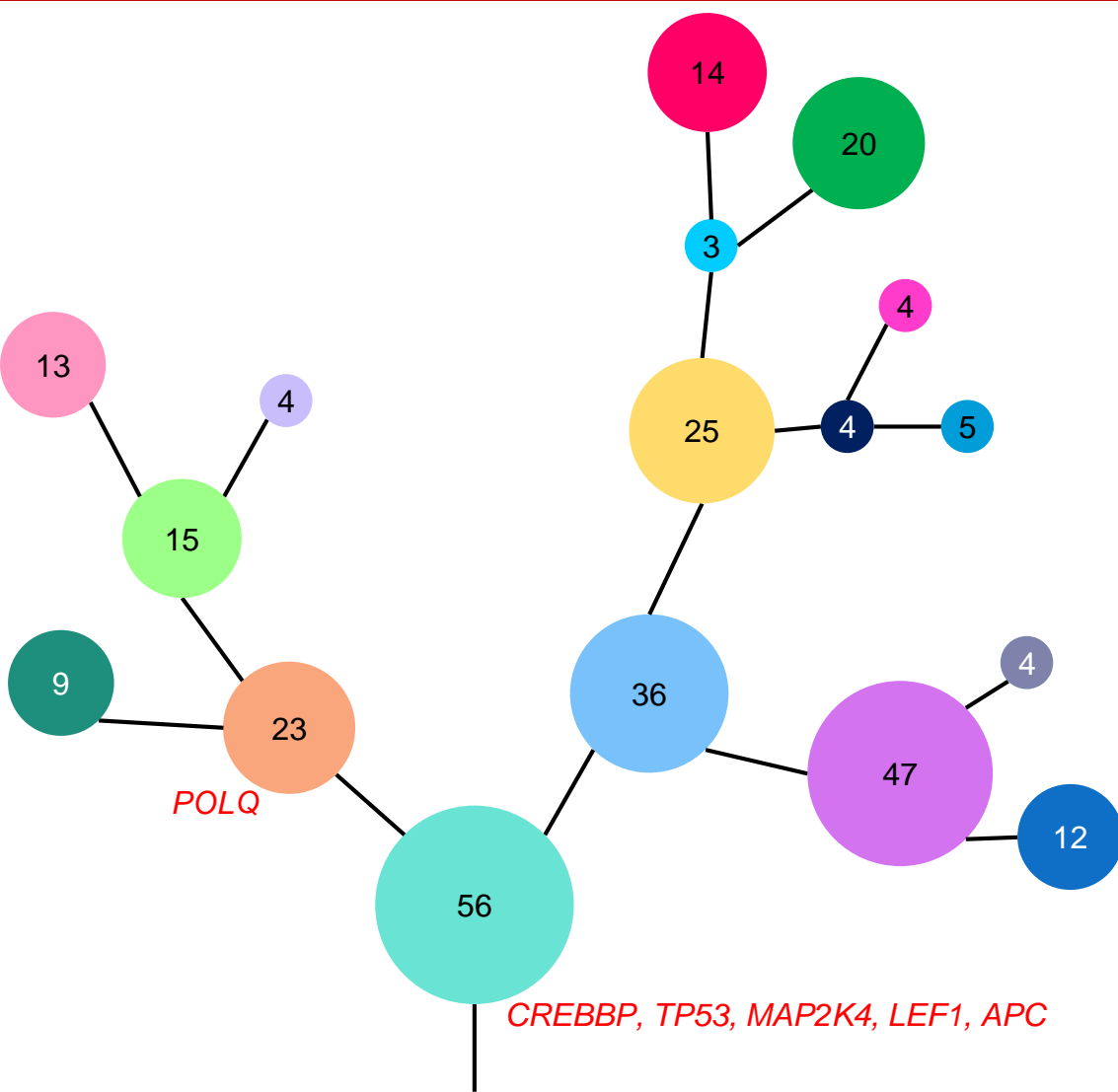
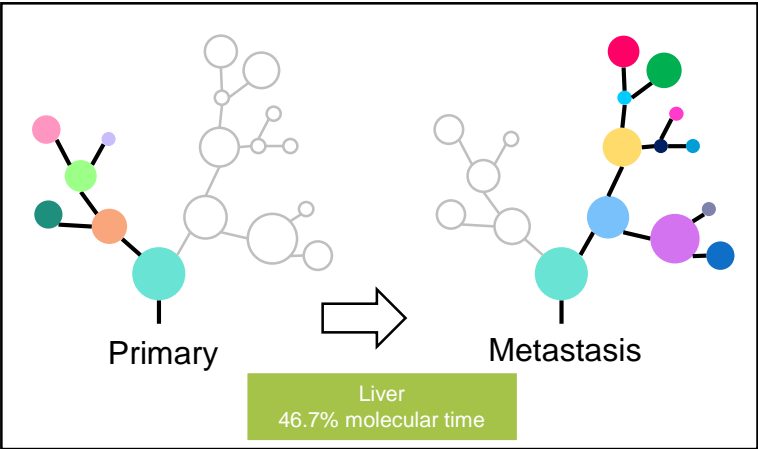




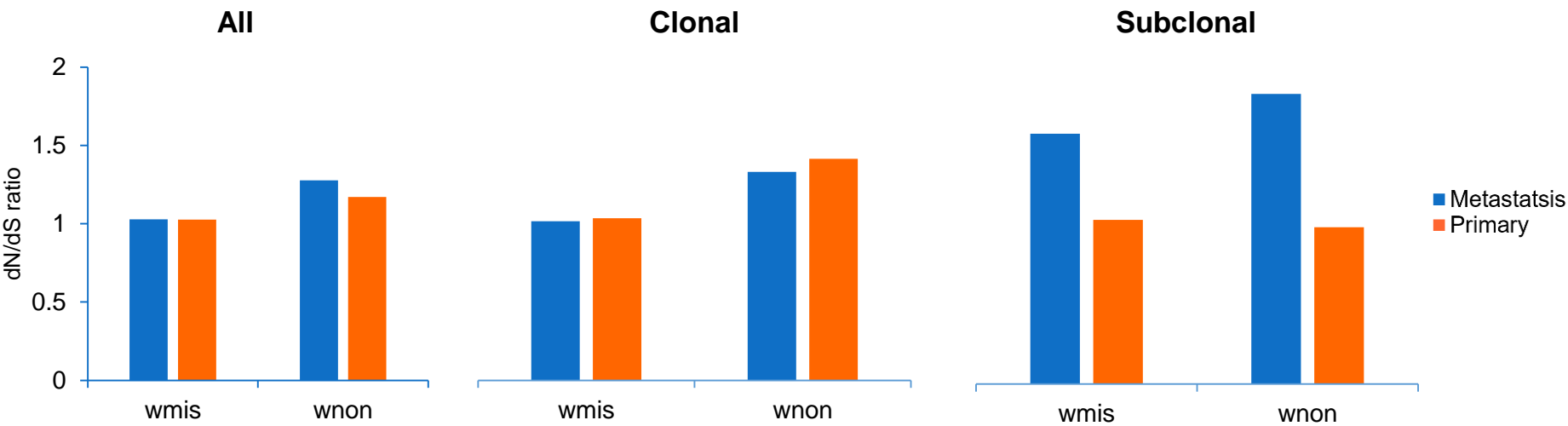




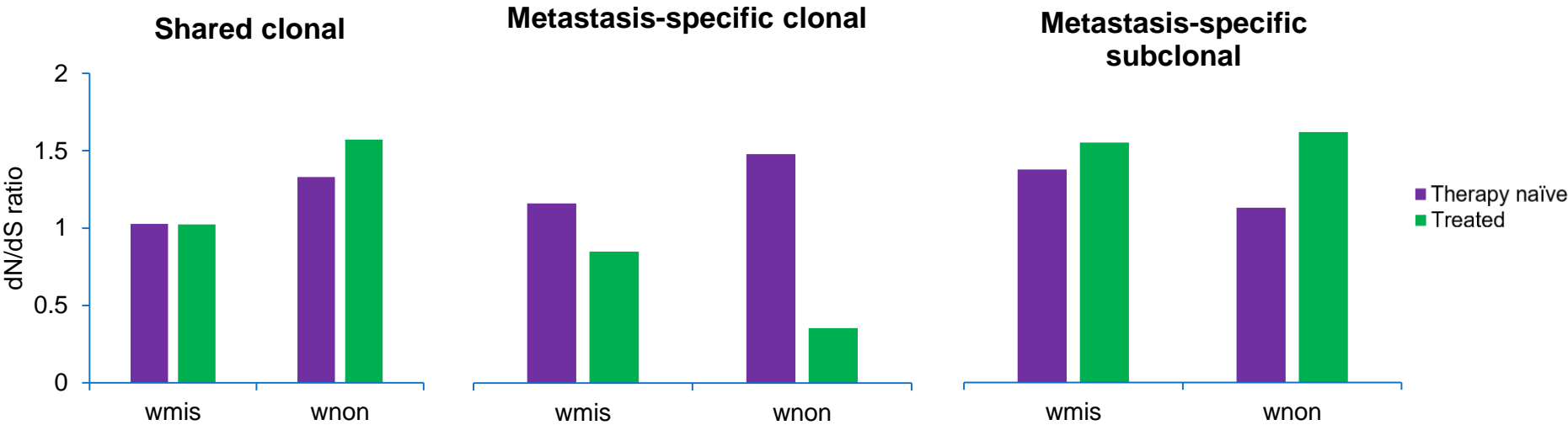




(a)



(b)



**Figure S5:** Selection in primary CRC and metastatic tumour lesions. Selection using ratios of substitution rate at nonsynonymous sites to those at synonymous sites (dN/dS), in (a) all, clonal and subclonal nonsense and missense mutations in primary CRC tumours and metastatic lesions; and in (b) shared clonal, metastasis-specific clonal and subclonal nonsense and missense mutations in therapy-naïve and treated tumours.