Supplementary Materials

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Supplementary Figure 1. Mutational Signatures. The trinucleotide contexts of somatic mutations in TP53-mutated samples were evaluated using the COSMIC Mutational Signatures v3.3 database and the deconstructSigs R package. The resulting mutational signatures reveal generally consistent signatures dominated by 5mC deamination, a finding consistent with most other AMLs. Additional studies will be needed to mechanistically characterize the samples with substantial contributions from other mutational processes.

Supplementary Figure 2. Circos Plots. Circos Plots output by Purple. Outermost track shows b-allele frequencies of somatic mutations. The next track inward is purity-adjusted copy number, with red indicating copy losses, and green indicating copy gains. The next track inward shows purity-adjusted minor allele copy number, with orange indicating loss of heterozygosity. Finally, the innermost track shows novel adjacencies defined by structural variants.

Supplementary Figure 3. Telomere Content. **A.** Comparison of per-sample telomere content measurements by Telseq (in units of Kb of telomere length) vs TelomereHunter (in units of TRPM; telomeric reads per GC-matched million reads). **B.** Telomere content (in TRPM) vs age in normal samples, color indicates *TP53*- (red) or CBF-mutant (blue) samples. **C.** Telomere content (in TRPM) vs age in tumor samples, color indicates *TP53*- (red) or CBF-mutant (blue) samples.

Supplementary Figure 4. Expression of telomeric genes. Expression (CPM) of *TERT*, *ATRX*, and *DAXX* in CBF (blue), normal karyotype (red), and *TP53*-mutant (yellow) AML/MDS.

Supplementary Figure 5. Benchmarking of SV calls. GRISS/Purple calls were compared to Manta and SVABA calls using different filtering strategies. **A.** Sensitivity to detect true positive CBF rearrangements. (y-axis is the fraction out of 18 CBF samples). **B**. Overlap of GRIDSS/Purple calls by orthogonal SV calls. Bar height is the total number of GRIDSS/Purple calls; color indicates if call is overlapped on both ends (yellow), one end (red), or neither end (blue) by orthogonal variant calls from each set. **C**. Overlap of orthogonal SV calls by GRIDSS/Purple calls. Bar height is the total number of SV calls; color indicates if call is overlapped on both ends (yellow), one end (red), or neither end (blue) by a GRIDSS/Purple call.

Supplementary Tables

The supplementary tables are deposited in Zenodo repository doi: 10.5281/zenodo.7523559

Supplementary Table 1. WGS coverage depth metrics and estimated tumor purity

Supplementary Table 2. Clinical and molecular details. UPN: Unique patient number; BM: bone marrow; PB: peripheral blood; nc: not classified; NOS: not otherwise specified; M: male; F: female; C: Caucasian; AA: African American; WBC: White blood cell count; VAF: variant allele frequency; CNA: Copy number alteration; SNV: single nucleotide variants; CN-LOH: copy-neutral loss of heterozygosity; WGS: whole genome sequencing; TCGA: The Cancer Genome Atlas; ICC: International Consensus Classification; WHO: World Health Organization classification; FAB: French-American-British classification; MPX: Myeloperoxidase; NBE: Naphthyl Butyrate Esterase; n/a: not applicable; CBF: core-binding factor.

Supplementary Table 3. Somatic SNV and indel calls

Supplementary Table 4. Somatic SV calls

Supplementary Table 5. Chromothripsis events

Supplementary Table 6. Gene-based somatic copy-number variant calls

Supplementary Table 7. Somatic copy-number variant calls

Supplementary Table 8. CNV analysis of *TP53*-mutated cases in BeatAML cohort.

Supplementary Table 9. RNA Expression data. Differential gene expression calculated for *TP53*-mutated cases compared to combined NK and CBF cases.

Supplementary Table 10. Telomere length estimates

Supplementary Table 11. Telomere insertion calls

Supplementary Table 12. Manta SV calls

Supplementary Table 13. SVABA SV calls

Supplementary Methods

SNV calling

SNVs and small indels were detected using MuTect2[1], VarScan2[2], Strelka2[3], and GATK[4]. Variants with a population frequency in gnomAD of greater than 0.1% were removed[5], as were those in regions of low-quality mapping (< 10% of reads with MQ0), low coverage (< 20X), and those called by Varscan only. Variant annotation was performed with the Variant Effect Predictor[6], version 95. Manual review was performed to remove further artifacts and to recover low variant allele frequency (VAF) variants in known AML driver genes with at least three supporting reads of evidence. Additional artifacts were excluded by removing calls that occurred at a homopolymer tract and had at least two different indels called at that same location. The entire somatic pipeline is available as a CWL workflow at https://github.com/genome/analysis-workflows (commit URL: https://github.com/genome/analysis-workflows/tree/0952c3f53a5eceaa32a2b8c1e974da79e01b76de).

Structural variant and CNV calling

Structural variant and CNV calling were performed using the GRIDSS-Purple-Linx pipeline as described (https://github.com/hartwigmedical/gridss-purple-linx/blob/master/gridss-purple-linx.sh) using as input the aligned tumor and normal bam pairs, the filtered, high-confidence somatic SNV/indel calls and the following tool versions: GRIDSS_VERSION=2.9.4, GRIPSS_VERSION=2.1, AMBER_VERSION=3.9, COBALT_VERSION=1.13, PURPLE_VERSION=3.4.1, LINX_VERSION=1.19.

Following an initial run of the pipeline, purity estimates from Purple, followed by manual review (Supplementary Table 1), were used as input parameters to the GRIPSS filtering and downstream tools. SV were filtered for FILTER status=PASS and length>50bp. Linx was used for clustering complex variants. Fractional absolute copy number calls from Purple were rounded to the nearest integer value for classification as ‘gain’ or ‘loss’. Copy-neutral loss-of-heterozygosity was called using the MinorAlleleCopyNumber estimate provided by Purple. All mutations affecting *TP53* were manually reviewed.

SV Benchmarking

In order to benchmark SV calls from the GRIDSS/Purple/Linx pipeline, we ran two additional, established methods for somatic SV calling: Manta[7] and SVABA[8]. Variant calls from these additional SV callers are supplied in Supplementary Tables 12 and 13. Manta (v1.6.0) was run using default options for somatic SV calling for tumor/normal pairs. SVABA (v1.1.0) was also run using default options for somatic SV calling. Variants were filtered for PASS status, and small indels of length<50bp were removed. SV calls were converted to bedpe format and compared using bedtools (v2.32.0) pairtopair allowing 1kb slop and ignoring strand, using `bedtools pairtopair -slop 1000 -is -type both` and `bedtools pairtopair -slop 1000 -is -type either`, to detect double-end and single-end overlaps.

Using the canonical core-binding factor (CBF) fusions inv(16) and t(8;21) as positive controls, both Manta and SVABA exhibited low sensitivity, detecting only 8/18 (44%) and 12/18 (67%), respectively; this was in part due to 'contamination' of the normal samples by tumor cells. We then supplemented the original Manta and SVABA callsets ('Manta_Somatic_Pass', and 'SVABA_Somatic_Pass') with 3 additional, more inclusive, SV variant callsets 1) 'Manta_Somatic_Unfiltered' (all Manta somatic SV calls, regardless of FILTER status); 2) 'SVABA_Somatic_Rescue' (SVABA filter PASS somatic variants plus filter-PASS germline variants with 0 supporting reads in normal and >5 supporting reads in the tumor samples or >5X as many supporting reads in the tumor as in the normal); 3) 'Manta_plus_SVABA' (the union of 'Manta_Somatic_Unfiltered' and 'SVABA_Somatic_Rescue'). These more comprehensive variant lists provided greater sensitivity to detect the CBF fusions, though only GRIDSS/Purple and 'Manta_plus_SVABA' achieved 100% sensitivity (Supplementary Figure 5a).

Additionally, we assessed the extent of overlap between GRIDSS/Purple variant calls and the 5 orthogonal callsets. In the TP53 mutated samples, a median of 75.9% (range 19-100%) of GRIDSS/Purple calls overlapped on both ends a call in the most inclusive 'Manta_Plus_SVABA' callset. Similarly, a median of 88.7% (range 23-100%) of GRIDSS/Purple overlapped on at least one end a call in the most inclusive 'Manta_Plus_SVABA' callset. Slightly lower rates of overlap were observed for the less comprehensive callsets (Supplementary Figure 5b)

Conversely, we examined the set of calls from each of the 5 orthogonal callsets that were overlapped by GRIDSS/Purple calls. (Supplementary Figure 5c). In the TP53 mutated samples, a median of 35.7% (range 2-75%) of 'Manta_Somatic_Pass' variants were overlapped on both ends by a GRIDSS/Purple call. Similarly, in the TP53 mutated samples, a median of 38.8% (range 3-83%) of 'Manta_Somatic_Pass' variants were overlapped on at least one end by a GRIDSS/Purple call. Correspondingly lower rates of overlap were observed for the more inclusive variant sets (Supplementary Figure 5c).

Chromothripsis detection

Chromothripsis detection was performed using Shatterseek (https://github.com/parklab/ShatterSeek, commit 4b8b41011ecfe6d1496e906e5d9ec7d65467d476), using the filtered SV (DEL, DUP, INV, and BND types only) and copy number outputs from Purple as input, and default parameters for Shatterseek. Filtering for high-confidence chromothripsis regions was performed as recommended in the Shatterseek documentation, and was followed by manual review to exclude false-positive calls.

Comparison of recurrent cell-type specific recurrent CNV

Comparison to the PCAWG per-gene copy number calls were performed using copy number estimates downloaded from https://dcc.icgc.org/api/v1/download?fn=/PCAWG/consensus_cnv/gene_level_calls/all_samples.consensus_CN.by_gene.170214.txt.gz. From the set of ICGC public dataset, we selected the 623

samples identified as having a *TP53* driver mutation (https://dcc.icgc.org/api/v1/download?fn=/PCAWG/driver_mutations/TableS3_panorama_driver_mutations_ICGC_samples.public.tsv.gz) irrespective of allelic status or mutation type. Samples reported to have undergone whole genome duplication were excluded (based on https://dcc.icgc.org/api/v1/download?fn=/PCAWG/consensus_cnv/consensus.20170217.purity.ploidy.txt.gz), and samples for which fewer than 50% of autosomal genes were estimated copy neutral were also excluded. We combined the PCAWG tumor type classifications Lymph-BNHL and Lymph-CLL to form a single 'Lymphoid' malignancy tumor type, and then restricted our analysis to tumor types with at least 20 samples meeting the above criteria.

Estimation of telomere content

Telomere content was estimated using TelomereHunter (v1.1.0)[9] in tumor-normal mode, using default parameters, and Telseq (v0.0.1)[10] separately for tumor and paired normal samples. Estimates of telomere content from these two independent approaches were highly correlated (R^2=0.88, Supplementary Figure 3), so we report only the results of TelomereHunter. Analyses of TVR (telomere variant repeats) in singleton context (i.e., flanked by at least 3 t-type telomeric hexamers to either side) were based on the per-sample tumor/normal ratio of normalized singleton read counts, as provided by TelomereHunter.

Identification of intrachromosomal telomeric insertions

Identification of intrachromosomal insertions of telomeric repeats was performed following the approach previously described[11]. Using the telomeric reads identified by TelomereHunter (i.e., with at least six t-type, c-type, g-type or j-type hexameric repeats), we identified reads such that only one member of the pair was classified as telomeric. We then identified candidate insertion regions as 1Kb windows containing 3 or more of these 'orphaned' telomeric reads in the tumor and none in the paired normal sample, excluding assembly gaps and the terminal cytoband of each chromosome. Within these candidate regions, we identified soft-clipped reads with mapping quality>30, excluding duplicates, secondary, and supplementary reads, where at least one t-type, c-type, g-type or j-type hexamer was present in the soft-clipped region. We identified all positions at the site of clipping in 4 or more reads from the tumor, followed by filtering of sites within segmental duplications or simple repeats, sites with the presence of soft-clipped telomeric repeats in the paired normal, and sites identified in more than 2 samples. Finally, all candidate insertions were manually reviewed to exclude false positives.

Copy Number Analysis of BeatAML cohort

Copy number analysis in the BeatAML cohort[12] was performed using all primary AML cases and all available normal controls. In instances where more than one sample per primary AML case was provided, we chose one sample at random, which preference for bone-marrow samples when available. Copy number analysis was performed using cnvkit (v0.9.8)[13] and with masking of assembly gaps and centromeric regions, using the full set of normal samples as a panel of normal, and according to the cnvkit authors' recommended workflow. In order to account for observed systematic noise due to, e.g., differences in GC-content between adjacent genomic bins, we re-

centered the log2 copy number ratio in each bin by subtracting the median log2r ratio across all tumor samples, and then performed a second round of copy number segmentation.

Subclonal inference

Our group has shown in the past that while 60x WGS is sufficient to detect most genomic variants, sampling error makes the data "noisy"[14]. Without higher-depth capture sequencing or additional timepoints, it is difficult to accurately infer subclonal populations[14]. By setting a purity-corrected VAF threshold equivalent to presence in 50% of tumor cells, we were able to identify whether subclonal populations exist, even if we cannot cleanly distinguish them. We observed that samples contain a median of 30.6% of their variants below that level (range 5.1 - 91.6%), and every sample contains a substantial number of variants below that range, suggesting that every tumor contained one or more subclones.

RNA sequencing

Cryopreserved cells were available for bulk RNA sequencing from 10 cases of multi-hit *TP53* AML/MDS, 11 cases of CBF AML, plus an additional 52 AML cases with normal karyotype and 4 AML cases with multi-hit *TP53* mutation (but lacking paired normal tissue for inclusion in other analysis). RNA was extracted (Quick-RNA kit, Zymo Research) for preparation of total RNA sequencing libraries (TruSeq Stranded Total RNA kit with Unique Dual Indices, Illumina). Paired-end sequencing was performed at McDonnell Genome Institute on NovaSeq S4 flow cells (Illumina) using 2 x 150 bp read lengths to achieve 15 Gb of coverage per sample. Transcript abundance was quantified with kallisto[15] using Ensembl[16] version 95 and scaled to library size and average transcript length. Normalized read counts were used for differential gene expression by edgeR[17].

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Case descriptions

#100232. 81 year old male diagnosed with AML following presentation with progressive fatigue and weight loss over a one month period. Blood counts at presentation were WBC 1,500 cells/mm3, hemoglobin 10.2 g/dl, and platelets 39,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 60% cellularity, with 46% myeloblasts consistent with AML M2. Cytogenetics showed a complex karyotype: 46~49, XY, del(3)(p14), del(5)(p11.2q33), del(17)(q21q21), add(21)(p11.2), +22,+mar[cp20]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, and NPM1 negative. Initial therapy consisted of 10 days of lenalidomide on a clinical trial, shortly following which he was admitted to the hospital with fever and worsening dyspnea attributed to pneumonia with which he experienced rapid deterioration. He expired six weeks following diagnosis, prior to a repeat bone marrow biopsy to assess for response.

#128392. 65 year old male with no significant past medical history presented with diverticulitis and pancytopenia and was diagnosed with AML. Blood counts were WBC 900 cells/mm3, hemoglobin 10.4 g/dl, and platelets 94,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 60% cellularity, with 83% blasts consistent with AML M0. Cytogenetics showed a complex karyotype: 46~50,XY,1,1del(2)(?p24),del(5)(q22q33),der(7)t(1;7)(q21;p13),add(7)(p11.1),+8, +add(11)(p15),+add(11)(p15),+der(11)t(11;11)(?p11.2;?q13),del(12)(p12),del(13)(q22),der(13)t(?1;13)(?p13;?p11.1),-15,add(17)(p11.1), 20,20,+22,+marx2,+mar1,+mar3,+mar6[cp20]. Molecular diagnostic studes included: FLT3 ITD positive, FLT3 D835 negative, and NPM1 negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated persistent disease with 85% blasts and he was reinduced with 5 + 2. A repeat marrow at count recovery demonstrated morphological remission but complex cytogenetics were seen in 2/20 metaphases: 49,Y,-X,+2,+3,-7,-7,+8,i(11)(q10),+12,del(17)(p11.2),-18,-20,+4-5mar[cp2]/46,XY[18]. He subsequently underwent matched sibiling donor allogeneic stem cell transplant following anti-thymoglobulin, cytarabine and clofarabine conditioning. His transplant course was complicated by perforated diverticulitis and other infectious complications requiring laparotomy and colostomy. Two months post-transplant, peripheral blood chimerism studies showed 76% donor/24% recipient myeloid, and 90% donor/10% recipient STR chimerism, with FLT3 ITD studies negative. At 6 months post-transplant, a bone marrow biopsy demonstrated overt dysplasia with recurrent detection of FLT3 ITD. A second transplant was performed from same donor at 7 months post first transplant and he again achieved disease remission, but died of diverticulitis complications 17 months from initial diagnosis.

#142083. 50 year old female with past medical history significant for hypertension and pre-eclampsia presented with pancytopenia on routine screening labs and was diagnosed with AML. Blood counts were WBC 2100

cells/mm3, hemoglobin 10.1 g/dl, and platelets 51,000 cells/m3, with 8% circulating blasts. A bone marrow biopsy demonstrated 50-60% cellularity, with 27% blasts consistent with AML M2. Cytogenetics showed a complex monosomal karyotype: 43~45,X,-X,del(5)(?q13q35),-7,-11,-13,-16,-17,-19,-19,-21,+1~7mar[cp5]/46,XX[1]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, and NPM1 negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. She developed Moraxella catarrhalis sepsis and expired 16 days post initiation of chemotherapy, prior to a repeat bone marrow assessment for response.

#147444. 55 year old female with past medical history significant for small cell/non-small lung cancer treated initially with resection and adjuvant cisplatinum and irinotecan, followed by etoposide and carboplatin and local and whole brain radiotherapy at relapse. She subsequently presented two years later with progressive anemia and thrombocytopenia, and was diagnosed with treatment-related MDS. Blood counts were WBC 5900 cells/mm3, hemoglobin 9.7 g/dl, and platelets 105,000 cells/m3, with 23% circulating monocytes and no circulating blasts. A bone marrow biopsy demonstrated 60% cellularity, with >15% ringed sideroblasts consistent with MDS with ringed sideroblasts. Cytogenetics showed a complex monosomal karyotype: 44,XX,-5,-7,-20,+mar[15]/46,XX[5]. Molecular diagnostic studies included: Flt3 ITD negative and JAK2 negative. She was initially treated supportively with transfusions, and subsequently underwent matched sibling donor allogeneic stem cell transplantation following busulfan and cyclophosphamide conditioning. Repeat bone marrow biopsies obtained at approximately 1 and 3 months post transplant, respectively, demonstrated complete remission with full donor engraftment. Her post-transplant course was complicated by skin and GI GVHD, with subsequent C. difficile colitis, vancomycin-resistant Enterococcus faecium bactermia, and Aspergillus pneumonia, from which she expired 7 months post transplant.

147796. 78 year old male with past medical history significant only for gout, incidentally noted to have an absolute monocytosis following presntation with pseudogout and diagnosed with AML. Blood counts were WBC 9300 cells/mm3, hemoglobin 10.6 g/dl, and platelets 242,000 cells/m3, with 68% circulating monocytes and no blasts. A bone marrow biopsy demonstrated 80% cellularity, with 32% monoblasts consistent with AML M4. Cytogenetics showed a complex monosomal karyotype: 44-45,X,-Y,-5,add(16)(q22),-17,-18,+iso(21)x2,+mars[cp5]/82-84,XX,-Y,-3,-4,-11,-12,-19,--21,+21[cp15]. Initial therapy consisted of a cycle of azacytidine. He expired at an extended care facility prior to a repeat bone marrow assessment for response.

#188798. 65 year old female with past medical history significant for osteoarthritis and irritable bowel syndrome presented with a 3 month history of progressive weakness, 30 pound weight loss, and easy brusing, and was diagnosed with AML. Blood counts were WBC 4500 cells/mm3, hemoglobin 4.4

g/dl, and platelets 41,000 cells/m3, with 29% circulating blasts. A bone marrow biopsy demonstrated 93% cellularity, with 23% blasts and marked fibrosis consistent with AML with multilineage dysplasia. Cytogenetics showed a complex karyotype: 47,XX,der(1)t(1;7)(q32;p13),del(5)(q22q35),-7,+8,del(12)(p11.2),der(13)del(13)(q14q14)inv(13)(p13q13),add(18)(p11.2),+19[4]. Molecular diagnostic studies included: bi-allelic TP53 positive, Flt3 ITD negative, Flt3 D835 negative, and NPM1 negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated persistent disease and she underwent reinduction wirh 5 + 2. A repeat bone marrow biopsy at count recovery demonstrated morphological remission but flow cytometry-based minimal residual disease (MRD) was detected at 4.1%. She subsequently underwent one cycle of high dose cytarabine consolidation, prior to matched unrelated donor stem cell transplantation following myeloablative conditioning with fludarabine busulfan and thymoglobulin. Her post-transplant course was notable for skin GVHD treated with steroids and ruxolitinib, and multiple vertebral compression fractures. Bone marrow biopsies at one and three months post-transplant, respectively, demonstrated MRD negative complete remission with full donor engraftment, however at six months post-transplant her marrow MRD was 0.4% and circulating blasts were subsequently observed. She was treated with decitabine and venetoclax with subsequent donor lymphocyte infusion. A repeat bone marrow biopsy demonstrated 14% blasts. She expired in hospice at 15 months post diagnosis, 11 months post transplant.

#190938. 60 year old male with past medical history significant for chronic renal insufficiency, diabetes, hypertension, mild congestive heart failure, and low grade MDS, presented with worsening cytopenias and was diagnosed with AML. Blood counts were WBC 1300 cells/mm3, hemoglobin 8.5 g/dl, and platelets 35,000 cells/m3, with 2% circulating blasts. A bone marrow biopsy demonstrated 60-70% cellularity, with 39% blasts consistent with AML M0. Cytogenetics showed a complex monosomal karyotype: 46,XY,-5[17],del(7)(q32q36)[6],del(7)(q22q36)[6],-11[17],-12[17],-16[6],-17[17],-20[6],add(20)(p12)[6],+2~5mar[cp17]/46,XY[3].Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, JAK2 negative, and NPM1 negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated 10-20% cellularity with 18% blasts. Reinduction chemotherapy consisted of mitoxantrone, high dose cytarabine, and etoposide (MitoEC), and a bone marrow biopsy repeated at count recovery demonstrated complete remission. He subsequently underwent matched unrelated donor stem cell transplantation following myeloablative conditioning with busulfan and cyclophosphamide. Bone marrow biopsies at approximately three, six, and twelve months post transplant demonstrated complete remission with full donor engraftment. Disease relapse was observed at 34 months post-transplant and treated with an investigational anti-CD33

antibody, but he expired from respiratory failure prior to response assessment 38 months post diagnosis, 35 months post transplant.

#199019. 60 year old female with past medical history significant for hypertension and depression presented with thrombocytopenia and was diagnosed with MDS. Blood counts were WBC 4500 cells/mm3, hemoglobin 10.1 g/dl, and platelets 50,000 cells/m3, without circulating blasts. A bone marrow clot specimen demonstrated 90% cellularity, with multilineage dysplasia and 1% blasts consistent with “MDS best classified as refractory cytopenias with multilineage dysplasia.” Cytogenetics showed a complex monosomal karyotype: 45-49,XX,+1,add(3)(p11),del(5)(q13q33),del(10)(q24q26),add(18)(q21),+19,-20,+21,+1-2mar[cp20]. Initial therapy consisted of lenolidomide without significant response. She became increasingly transfusion dependent and underwent matched unrelated donor allogeneic stem cell transplant following myeloablative busulfan and cyclophosphamide conditioning. Her post-transplant course was complicated by acute and chronic GVHD and HSV stomatitis. Bone marrow biopsies at approximately 3, si and twelve months post transplant demonstrated complete remission with full donor engraftment. Relapse and progression to AML with gastric and acetabulum myeloid sarcomas was observed at 26 months post-transplant and treated with 7 + 3 induction with cytarabine and idarubicin, and subsequent donor lymphocyte infusion. Recurrent biopsy-proven subcutaneous myeloid sarcomas were observed at 40 months post-transplant, for which she received no further therapy and expired at 49 months post MDS diagnosis, 41 months post-transplant.

#199994. 76 year old male with past medical history significant for colorectal cancer treated with neoadjuvant chemoradiation (details unavailable) followed by resection, as well as gout, hypertension, and hyperlipidemia, who presented for evaluation of abdominal pain and incidentally noted anemia with circulating blasts, and was diagnosed with AML. Blood counts were WBC 7,100 cells/mm3, hemoglobin 11.4 g/dl, and platelets 169,000 cells/m3, with 15% circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, with 70% blasts consistent with AML M1. Cytogenetics showed a complex monosomal karyotype: 41~42,X,-Y,add(2)(q21),add(4)(q32),add(5)(q35),-7,-13,-17,-21,-22,+1~2mar[cp7]/46,XY[1]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, CEBPA negative, IDH1 negative, IDH2 negative, DNMT3A negative, and NPM1 negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10 for cycles 1-4, and subsequently days 1-5 for cycles 5-10. A bone marrow biopsy after cycle 1 demonstrated 3% blasts. Repeat marrows after cycles 2 and 4 demonstrated complete remission. A marrow after 6 cycles showed 10% blasts, however a repeat marrow cycle 7 again showed remission. After cycle 10 circulating blasts were noted and a bone marrow bipsy demonstrated relapse. He was enrolled in a clinical trial of autologous cytokine activated memory-like natural killer (CIML NK) cells, but developed Candida guilliermonii sepsis, and expired on hospice prior to formal response assessment, 15 months post diagnosis.

#269542. 76 year old male with past medical history significant for hernia repair and prostatectomy presented with abdominal pain and retroperitineal abcess, incidentally noted to have leukocytosis with circulating blasts and was diagnosed with AML. Blood counts were WBC 17,800 cells/mm3, hemoglobin 8.8 g/dl, and platelets 98,000 cells/m3, with 90% circulating blasts. A bone marrow biopsy demonstrated 90% cellularity, with 74% blasts consistent with AML M0. Cytogenetics showed a complex hyperdiploid karyotype: 53-56,XY,+1,de(2)(q33q34),+8,+10,+11x2,+13x1-2,+14,del(17)(p11.2),+19,add(21)(q22),+22[cp20]/46,XY[1]. Molecular diagnostic studies were not performed. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. Despite percutaneous drainage of his retroperitoneal abcess and broad spectrum antibiotics, he experienced progressive clinical decline and expired due to Candida albicans sepsis prior to formal assessment of response to therapy, 2 weeks post diagnosis.

#285619. 72 year old female with past medical history significant for hypertension, osteoarthritis, gastroesophageal reflux, and trigeminal neuralgia presented with back and right upper quadrant abdominal pain and incidentally found to have pancytopenia, workup of which led to a diagnosis of AML. Blood counts were WBC 2000 cells/mm3, hemoglobin 8.5 g/dl, and platelets 99,000 cells/m3, with 2% circulating blasts. A bone marrow biopsy demonstrated 70-80% cellularity, with 57% blasts consistent with AML with multilineage dysplasia. Cytogenetics showed a complex monosomal karyotype: 42~45,XX,add(1)(p36.1),-5,del(5)(?q11.2q33),?add(11)(p?11.2),-13,-17,add(17)(p11.2),-18,-20,-21,+1~4mar[cp15]/46,XX[5]. Molecular diagnostic studies included: Flt3 ITD negative and Flt3 D835 negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy after one cycle demonstrated 10-20% celluarity with 7% blasts, and persistence of the previously observed karyotypic abnormalities in 17/20 metaphases. A bone marrow biopsy after 2 cycles demonstrated 10% cellularity with 4% blasts, and 1/20 metaphases positive for deletion 5q. Bone marrow biopsies after 4 and 6 cycles, respectively, demonstrated morphologic and cytogenetic complete remission, on the basis of which decitabine was reduced to 5 days after cycle 4. A bone marrow biopsy after 8 cycles demonstrated relapse with 13% blasts, and remergence of the previously observed karyotypic abnormalities in 1/20 metaphases. Based on a gradual, progressive clinical decline, she subsequently received supportive care only and expired approximately 12 months post diagnosis.

#301960. 70 year old male with past medical history significant for hypertension, hyperlipidemia, amaurosis fugax, alcoholism, and multiple dental abcesses presented with progressive fatigue, cough, and pancytopenia and was diagnosed with AML. Blood counts were WBC 900 cells/mm3, hemoglobin 9.4 g/dl, and platelets 63,000 cells/m3, with 2% circulating blasts. A bone marrow biopsy demonstrated 40-50% cellularity, with 37% blasts consistent with AML with MDS-

related changes. Cytogenetics showed a complex monosomal karyotype: 46,XY,del(5)(q13q31)[8]/42~43,idem,-4,der(7;17)t(?;17)(?;q25)t(?;7)(?;p21),add(13)(p11.2),-17,-18,-22,+mar[cp11]/46,XY[1]. Molecular diagnostic were not performed. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy following cycle 1 demonstrated persistent disease with 26% blasts. A bone marrow biopsy following cycle 2 demonstrated reduction to 6% blasts. A repeat marrow biopsy after cycle 3 demonstrated no excess blasts, without evidence of previously observed karyotypic abnormalities, based on which decitabine dosing was reduced to days 1-5. He went on to receive 7 additional cycles, prior to relapse with 38% marrow blasts and re-emergence of previously observed karyotypic abnormalities. He expired from pneumonia and respiratory failure one month later, 11 months post-diagnosis.

#326772. 47 year old female without significant past medical history presented with fever, arthralgias and atypical pneumonitis and was diagnosed with AML. Blood counts were WBC 14,900 cells/mm3, hemoglobin 9.3 g/dl, and platelets 69,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 70% cellularity, with 37% blasts consistent with AML M2. Cytogenetics showed a complex monosomal karyotype: 39~47,XX,del(5)(q13q33),-7,der(8)t(8;?8;8)(p23;?p11.2p23;q11.2),der(14)t(1;14)(p12;p11.2),der(16)t(7;16)(p15;q22),+2mar[cp19]. Molecular diagnostic studies were not performed. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated persistent disease with 90% cellularity and 85% blasts, and she was reinduced with mitoxantrone, etoposide, and high dose cytarabine (MitoEC). A repeat bone marrow biopsy at count recovery demonstrated persistent disease with 70% celluarity and 16% blasts. She subsequently received a salvage regimen of azacytidine, following which a repeat bone marrow biopsy showed 10% blasts. She subsequently underwent a T cell depleted haploidentical stem transplant following reduced intensity fludarabine, cyclophosphamide, and total body irradiation conditioning, and subsequent infusion of haploidentical NK cells and IL-2. Repeat bone marrow biopsies post transplant showed persistent disease. She was subsequently maintained sequentially on azacytidine and low dose cytarabine without achieving remission, and expired 8 months post transplant, 12 months post diagnosis.

#387082. 65 year old male with past medical history significant for coronary artery disease (S/P stents), COPD, and nephrectomy, presented with shortness of breath and chest discomfort and was diagnosed with AML. Blood counts were WBC 2300 cells/mm3, hemoglobin 7.6 g/dl, and platelets 49,000 cells/m3, with 10% circulating blasts. A bone marrow biopsy demonstrated 80-90% cellularity, with 13% blasts (29% by flow cytometry) and marked background multilineage dysplasia consistent with AML M6. Cytogenetics showed a complex monosomal karyotype: 44~47,XY,del(5)(q13q33), -7,add(12)(p11.1),t(12;13)(p11.2;q12),+1~3der(13)t(12;13),del(16)(q22),add(17)(p

13),-19[cp20]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, IDH1 negative, and IDH2 negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy after one cycle demonstrated stable disease with 25% blasts. A subsequent bone marrow biopsy after 3 cycles demonstrated complete morphologic and cytogenetic remission. He subsequently underwent a matched sibling donor allogeneic stem cell transplant following reduced intensity conditioning with fludarabine and busulfan. His post transplant course was complicated by acute GVHD involving skin, treated with topical and systemic steroids. A repeat marrow at 8 months post transplant demonstrated relapse, again treated with 10 day decitabine followed by two donor lymphocyte infusions. Repeat bone marrow biopsies at 9 and 12 months post transplant, respectively, demonstrated complete morphologic and cytogenetic remission with full donor engraftment. He subsequently developed acute GVHD involving skin, GI tract, and liver, and expired from mutliorgan failure in the context of enterococcal and MRSA sepsis while in complete remission, 17 months post diagnosis and 13 months post transplant.

#432398. 67 year old male with past medical history significant for diabetes melitus presented with pancytopenia, noted in the workup of a slow healing leg wound, and was diagnosed with AML. Blood counts were WBC 2100 cells/mm3, hemoglobin 7.3 g/dl, and platelets 30,000 cells/m3, with 5% circulating blasts. A bone marrow biopsy demonstrated 60% cellularity, with 50% blasts consistent with AML M2. Cytogenetics showed a complex karyotype: 46,XY,del(5)(q11.2q31),-7,+8,+11,add(11)(q23),der(16;17)(q10;q10)[18]/51,idem,+1,+5,+8,+10,+21[2]. Molecular diagnostic studies were not performed. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A repeat bone marrow biopsy one month later in the face of persistent pancytopenia demonstrated persistent disease. Salvage therapy consisted of gemtuzumab ozogamicin, following which a subsequent bone marrow biopsy demonstrated complete morphologic remission. A subsequent bone marrow biopsy at 10 months post diagnosis demonstrated relapse, again treated with gemtuzumab ozogamicin without response, and he expired 12 months post diagnosis.

#434640. 71 year old male with past medical history significant for psoriasis and gastroesophageal reflux presented with fatigue and dyspnea and was diagnosed with AML. Blood counts were WBC 2000 cells/mm3, hemoglobin 6.4 g/dl, and platelets 60,000 cells/m3, with circulating blasts. A bone marrow biopsy demonstrated 50% cellularity, with 97% blasts consistent with AML M0. Cytogenetics showed a complex monosomal karyotype: 43,XY,-3,del(5)(q12q33),-7,der(10)t(10;11)(q26;q13),-12,-18,+2mar[20]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative,and NPM1

negative. Initial therapy consisted of decitabine administered days 1-5, despite which there there was progressive leukocytosis comprised primarily of blasts over the next 3 weeks, and he subsequently underwent 7 + 3 induction with cytarabine and idarubicin. His course was complicated by multifocal pneumonia and respiratory failure requiring prolonged intubation. He subsequently recovered and was extubated upon count recovery but did not undergo a repeat bone marrow biopsy prior to moving out of state to live with family. Details of further therapy are unavailable. He expired 7 months post diagnosis.

#439820. 69 year old male with past medical history significant for Crohn's disease presented with fatigue and was diagnosed with MDS. Blood counts were WBC 3000 cells/mm3, hemoglobin 7.6 g/dl, and platelets 194,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 70-80% cellularity, with 2% blasts and unenumerated "frequent ringed sideroblasts" consistent with MDS with multilineage dysplasia and refractory cytopenias. Cytogenetics showed a complex monosomal karyotype: 46,XY,del(7)(q22),del(20)(?q13.1)[12]/46,idem,?add(17)(p13)[4]/46,idem,add(17)(q25)[4]. Molecular diagnostic studies were not performed. Initial therapy consisted of azacytidine administered for 16 cycles, following which he developed progressive anemia and a subsequent bone marrow biopsy demonstrated 7% blasts consistent with progression to MDS-RAEB1. He was subsequently treated with high dose lenalidomide on a clinical trial without significant response, prior to undergoing a matched unrelated donor transplant following reduced intensity conditioning with fludarabine, cyclophosphamide, and 200 cGy total body irradiation. A bone marrow biopsy at 1 month post transplant in the face of persistent pancytopenia demonstrated multilineage dyspoiesis with 3% blasts. Chimerism studies demonstrated 11% donor cells. He expired from a sudden cardiac arrest 24 months post diagnosis, 6 weeks post transplant.

#455981. 52 year old female with past medical history significant for gastroesophageal reflux and cholycystectomy presented with fever, cough, and fatigue and was diagnosed with MDS. Blood counts were WBC 2400 cells/mm3, hemoglobin 8.6 g/dl, and platelets 45,000 cells/m3, with unenumerated "rare" circulating blasts. A bone marrow biopsy demonstrated 60% cellularity, with 11% blasts consistent with MDS/RAEB2. Cytogenetics showed a complex monosomal karyotype: 43~46,XX,-3,add(3)(p12),del(5)(q15q33),-6,add(9)(q12),-17,-18,-19,-20,-22,add(22)(p11.2),+1~5mar[cp14]/46,XX[6]. Molecular diagnostic studies were not performed. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. Bone marrow biopsies repeated after cycles 2 and 3, respectively demonstrated complete morphologic and cytogenetic remission, prior to undergoing matched unrelated door transplant following reduced intensity conditioning with fludarabine and busulfan conditioning. A bone marrow biopsy one month post transplant demonstrated morphologic complete remission with 4% recipient cells "suspicious for mixed chimerism." A repeat marrow 3 months post transplant showed relapse with 16% blasts. She was subsequently treated

with 7 + 3 induction with cytarabine and idarubicin, but expired 10 days later with typhlitis and E coli sepsis, 9 months post diagnosis, 4 months post transplant.

#480109. 49 year old female with past medical history significant for COPD, hemorrhagic stroke, chronic pain, and chronic anxiety, presented with progressive fatigue, fever, and night sweats over a 6 month period and was diagnosed with MDS. Blood counts were WBC 6800 cells/mm3, hemoglobin 8.3 g/dl, and platelets 101,000 cells/m3, with 7% circulating blasts. A bone marrow biopsy demonstrated >90% cellularity, with 5% blasts consistent with MDS/RAEB1. Cytogenetics showed a complex monosomal karyotype: 45~48,XX,t(1;14)(q12;q32),-2,add(5)(q11.2),dic(6;7)(q25;p15),add(12)(p11.2),-13,add(17)(q11.2),-22,+r,+2~6mar[cp15]/46,XX[7]. Molecular diagnostic studies included: JAK2 positive (<1.0% VAF). Initial therapy consisted of 3 cycles of azacytidine, with normalization of blood counts. A subsequent bone marrow biopsy demonstrated multilineage dysplasia without excess blasts and normal cytogenetics, prior to undergoing a matched sibling donor allogeneic stem cell transplant following myeloablative conditioning with busulfan and cyclophosphamide. A repeat bone marrow biopsy one month post transplant demonstrated no excess blasts and 88% donor chimerism. She subsequently presented with a left middle cerebral artery stroke, and expired 7 months post diagnosis, 2 months post transplant.

#489196. 42 year old female with past medical history significant for breast cancer treated with modified radical mastectomy with adjuvant cyclophosphamide, doxorubicin, paclitaxel, and radiation, found to have Li-Fraumeni syndrome on genetic testing, presented with incidentally noted pancytopenia on followup and was diagnosed with MDS. Blood counts were WBC 1600 cells/mm3, hemoglobin 9.5 g/dl, and platelets 73,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated variable cellularity (5-60%), with 14% blasts consistent with MDS/RAEB2. Cytogenetics showed a complex monosomal karyotype: 45,XX,t(13;17)(q25;p11.2),-20[1]/44-45,XX,del(1)(p36.1),add(2)(q33),t(3;17)(q25;p11.2),add(4)(q21),-7,add(11)(p11.2),-20,+mar[cp17]/46,XX[2]. She underwent matched sibling donor allogeneic stem cell transplant following myeloablative conditioning with busulfan and cyclophosphamide. Repeat bone marrow biopsies at 1, 3, and 6 months post transplant demonstrated complete remission with full donor engraftment, but at 12 months demonstrated multilineage dypoiesis without excess blasts and 32% recipient chimerism, for which she received a 5 day course of decitabine. A vertebral body biopsy 1 month later demonstrated a myeloid sarcoma for which she underwent salvage chemotherapy with cladribine and cytarabine (CLAG) and subsequent donor lymphocyte infusion. A repeat biopsy 2 months later confirmed marrow relapse with 10-15% blasts. She subsequently was treated with mitoxantrone, cytarabine, and etoposide (MitoEC) without response, followed by an additional cycle of decitabine, but expired prior to formal response assessment, 22 months post diagnosis, 20 months post transplant.

#493129. 58 year old female with past medical history significant for atrial fibrillation and previously unexplained intermittent neutropenia presented with pancytopenia and was diagnosed with MDS. Blood counts were WBC 2800 cells/mm3, hemoglobin 8.3 g/dl, and platelets 35,000 cells/m3, with unenumerated “occasional” circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, with 14% blasts consistent with MDS/RAEB2. Cytogenetics showed a complex monosomal karyotype: 44~46,X,-X,der(1)del(1)(p?13p?22)del(1)(q12q25),-5,-7,add(11)(q14),del(12)(p12),-16,-18,+2~5mar[cp17]/90~91,idemx2[2]/46,XX[1]. Molecular diagnostic studies were not performed. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10, complicated by presumed fungal pneumonia and pulmonary embolism. Repeat bone marrow biopsies after cycles 1, 2, and 3 demonstrated no excess blasts and normal cytogenetics. She subsequently underwent a matched sibling donor stem transplant following myeloablative conditioning with busulfan and cyclophosphamide. Repeat bone marrow biopsies at 1 and 3 months post transplant, respectively, demonstrated complete remission with full donor engraftment, but at 5 months post transplant circulating blasts reappeared in peripheral blood and a repeat marrow confirmed relapse. She was weaned off immunosuppression and retreated with 2 courses of 10 day decitabine, but developed significant GI graft vs host disease requiring resumption of systemic immunosuppression, and subsequently developed biopsy proven hepatic mucormycosis. A repeat bone marrow biopsy demonstrated complete remission with normal cytogenetics and full donor engraftment. She subsequently received a CD34 selected stem cell boost for worsening cytopenias 12 months post transplant, and remained on prolonged systemic antifungal therapy. At 29 months post transplant she was noted to have a new abdominal mass that was biopsied and demonstrated to represent a mesenteric myeloid sarcoma. A bone marrow biopsy at that time demonstrated complete remission with full donor engraftment. She was retreated with a single 5 day course of decitabine and 6 courses of ipilumumab. Following a repeat CT that demonstrated persistence of the mesenteric mass with compression of the superior mesenteric artery, she underwent salvage chemotherapy with fludarabine, cytarabine, and idarubicin (FLAG-Ida) and another donor lymphocyte infusion. Repeat PET scans showed a transient partial response with rapid subsequent progression. A repeat bone marrow biopsy again showed no evidence of marrow involvement and she was subsequently treated with azacytidine and venetoclax without response, prior to undergoing palliative local radiation with transient response. She then received a course of palliative low dose cytarabine with venetoclax at the time of progression, but expired on hospice, 48 months post diagnosis, 42 months post transplant.

#521733. 70 year old male with past medical history significant for coronary artery disease, atrial fibrillation, hypertension, diabetes mellitus, and hyperlipidemia presented with epistaxis and was diagnosed with AML. Blood counts were WBC 1500 cells/mm3, hemoglobin 9.4 g/dl, and platelets 9000 cells/m3, with 18% circulating blasts. A bone marrow biopsy demonstrated 60%

cellularity, with 48% blasts consistent with AML M2. Cytogenetics showed a complex monosomal karyotype: 39~43,XY,-Y,-5,?dic(7;11)(q36;p15),add(8)(q24.3),-9,-11,-13,add(14)(p13),-17,-18,add(18)(p11.2),?der(18)t(11;18)(?q11.2;?q22),-20,add(20)(q13.3),-21,-22,+r,+1~6mar[cp14]/46,XY[6]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, CEBPA negative, and NPM1 negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy at midcycle demonstrated 70% cellularity with 54% blasts. Repeat bone marrows after completing cycles 1 and 2, respectively, demonstrated similar findings. Due to persistent cytopenias and infectious complications, deitabine was reduced to 5 days per cycle, with which blood counts improved and a repeat bone marrow biopsy after 2 additional cycles demonstrated complete remission with normal cytogenetics. He went on to receive 5 additional cycles until progression, at which time he was treated with cladribine, cytarabine, and mitoxantrone (CLAM) without response after one cycle, and expired on hospice, 14 months post diagnosis.

#530962. 76 year old male with past medical history significant for coronary artery disease and hypertension, presented with fatigue, weight loss, and pancytopenia and was diagnosed with AML. Blood counts were WBC 3300 cells/mm3, hemoglobin 9.6 g/dl, and platelets 13,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 90% cellularity, with 33% blasts consistent with “AML with megakaryocytic features.” Cytogenetics showed 45,X,-Y[3]/46,XY[17]. Molecular diagnostic studies were not performed. Initial therapy consisted of decitabine on a clinical trial, administered days 1-5. Bone marrow biopsies after 2, 4, and 6 cycles, respectively demonstrated complete remission, prior to development of recurrent cytopenias and demonstration of relapse 8 months post diagnosis. He received no further therapy and expired 10 months diagnosis.

#537017. 69 year old male with past medical history significant for diabetes mellitus, hypothyroidism, and gastroespoageal reflux, presented with progressive fatigue, dyspenea, and a presyncopal episode, and was diagnosed with AML. Blood counts were WBC 3500 cells/mm3, hemoglobin 7.7 g/dl, and platelets 38,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, comprised of >80% erythroid lineage and 68% erythroblasts, consistent with AML M6. Cytogenetics showed a complex karyotype: 74<3N>,XXY,+1,?add(1)(p22),+2,+3,+6,-19,+21,+22[1]/82<4N>,XXYY,-1,?add(1)(p22),-2,-3,-4,-5,-7,-11,add(11)(q13),-12,-13,-14,-15,-16,-17,-18,-18,-19,add(19)(q13.3),-21,-22,+8mar[1]/46,XY[18]. Molecular diagnostic studies included: TP53 positive, Flt3 ITD negative, Flt3 D835 negative, and NPM1 negative. B12 was 224 pg/ml and methylmalonic acid was 0.7 nmol/ml. Initial therapy consisted of B12 injections without response, followed by 2 cycles of azacytidine and venetoclax. Bone marrow biopsies repeated after 1 and 2 cycles, respectively, demonstrated persistent disease. He received no further therapy and expired on hospice, 3 months post diagnosis.

#632378. 61 year old male with past medical history significant for gout and obstructive sleep apnea, presented with progressive weakness and fatigue and was diagnosed with MDS. Blood counts were WBC 1300 cells/mm3, hemoglobin 7.9 g/dl, and platelets 29,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 90% cellularity, with 11% blasts consistent with MDS/RAEB2. Cytogenetics showed a complex monosomal karyotype: 43~45,XY,-Y,-4,del(5)(q13q33),-13,add(13)(p11.2),add(15)(p11.2),-16,-17,add(20)(q11.2),-21,+22,+r,+1~3mar[cp20]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, IDH1 negative, IDH2 negative, and JAK2 negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy at midcycle demonstrated 90% cellularity with 8% blasts. A repeat bone marrow biopsy prior to cycle 2 demonstrated 60-70% cellularity with multilineage dysplasia and 1% blasts. Repeat bone marrow biopsies after cycles 2 and 4, respectively, demonstrated normocellularity with mild dyspoiesis and no excess blasts, following which decitabine was reduced to days 1-5. Relapse was demonstrated with 5-10% blasts on a repeat bone marrow biopsy at 10 months post diagnosis and decitabine was increased back to 10 days per cycle, despite which a repeat bone marrow biopsy 3 months later demonstrated 26% blasts, consistent with progression to AML with MDS changes. He expired one month later on hospice, 14 months post diagnosis.

#639691. 70 year old female with past medical history significant for breast cancer treated with lumpectomy and radiation, as well as gastroespoageal reflux, presented with progressive fatigue and was diagnosed with MDS (and CLL). Blood counts were WBC 31,600 cells/mm3, hemoglobin 8.5 g/dl, and platelets 63,000 cells/m3, with 86% mature lymphocytes and no circulating blasts. A bone marrow biopsy demonstrated multilneage dysplasia with 19% blasts consistent with MDS/RAEB2, as well 42% mature lymphocytes consistent with CLL. Cytogenetics showed a complex monosomal karyotype: 44~46,XX,del(5)(q12q33),del(7)(q22q34),add(12)(p13),dic(12;18)(p13;p11.3),del(13)(q12q14),del(17)(p11.2),-19[cp19]/46,XX[1]. Molecular diagnostic studies were not performed. Initial therapy consisted of azacytidine. A bone marrow biopsy after cycle 2 demonstrated 90% cellularity with 6% blasts and 45% mature lymphocytes. She subsequently underwent a matched unrelated donor stem cell transplant following reduced intensity conditioning with fludarabine, busulfan, and thymoglobulin. A repeat bone marrow biopsy one month post transplant demonstrated 5-10% blasts with 98% recipient chimerism. She was rapidly weaned off immunosuppression and underwent a second stem cell transplant from a different matched unrelated donor, following reduced intensity conditioning with fludarabine and melphalan. Repeat bone marrow biopsies at 1 and 3 months post transplant, respectively, demonstrated complete remission

with full donor chimerism. A repeat bone marrow biopsy at 6 months post transplant demonstrated multlineage dysplasia without excess blasts, and reappearance of del 5q, del 7q, and del 17p abnormalities on FISH, despite full donor engraftment based on based on both CD3- and CD15-enriched STR studies. She was treated with decitabine and a repeat bone marrow biopsy following 2 cycles demonstrated complete remission with full donor chimerism and disappearance of prior FISH abnormalities. Decitabine was continued thereafter with gradual spacing of cycles from every 4 weeks to every 12 weeks until it was held in the face of worsening cytopenias, at 56 months post transplant, and a repeat bone marrow biopsy at 58 months post transplant demonstrated relapse with progression to AML. Decitabine was then restarted, followed by a donor lymphocyte infusion, complicated by nausea, anorexia, and diarrhea presumed secondary to GVHD and treated with resumption of steroids. A repeat bone marrow biopsy one month later demonstrated 10% blasts and she was started on azacytidine and venetoclax. A bone marrow biopsy after 3 cycles demonstrated complete remission with full donor chimerism, but after 6 cycles a repeat bone marrow biopsy demonstrated relapsed AML. She received no further treatment and expired one month later, 75 months post diagnosis, 69 months post second transplant.

#679540. 74 year old female with past medical history significant for hypothyroidism, hypertension, coronary artery disease, chronic renal insufficiency, and urothelial papillary carcinoma (status post nephrectomy), presented with progressive fatigue and was diagnosed with AML. Blood counts were WBC 2800 cells/mm3, hemoglobin 7.5 g/dl, and platelets 144,000 cells/m3, with 2% circulating blasts. A bone marrow biopsy demonstrated 70% cellularity, with 74% blasts consistent with AML M1. Cytogenetics showed a MECOM rearrangement as part of a complex monosomal karyotype: 46,XX,inv(3)(q21q26.1)[3]/45,sl,der(16;17)(p10;q10)[4]/46,sdl,+13[5]/46,XX[8]. Molecular diagnostic studies included: SF3B1 positive, NF1 positive, TP53 positive, Flt3 ITD negative, Flt3 D835 negative,and NPM1 negative. Initial therapy consisted of decitabine, administered days 1-5, and venetoclax. A bone marrow biopsy after 2 cycles demonstrated a complete hematologic remission with normal cytogenetics, with flow cytometry-based minimal residual disease (MRD) undetectable. A repeat bone marrow biopsy following 6 ccyles demonstrated complete hematologic and cytogenetic remission, but flow based MRD showed re-emergence of the malignant clone at 1.2%. A repeat bone marrow biopsy one month later demonstrated increase in MRD to 6.8% with low level re-emergence of inversion 3 (MECOM) and del 16q by FISH, but no excess blasts. She was subsequently lost to followup and expired 6 months later, 14 months post diagnosis.

#708869. 66 year old female with past medical history significant for breast cancer treated with lumpectomy, radiation, and adjuvant chemotherapy with

carboplatin, taxotere, and Herceptin, presented with fatigue and was diagnosed with MDS. Blood counts were WBC 3000 cells/mm3, hemoglobin 9.1 g/dl, and platelets 35,000 cells/m3, with 16% circulating blasts. A bone marrow biopsy demonstrated 60-70% cellularity, with 11% blasts consistent with MDS/RAEB/2. Cytogenetics showed a complex monosomal karyotype: 43,XX,del(5)(q22q35),-7,+3mar[cp2]/46,XX[2]. Molecular diagnostic studies included: Flt3 ITD positive/negative, Flt3 D835 positive/negative,and NPM1 positive/negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy at midcycle cycle demonstrated persisitent dysmegakaryopoiesis with 7% blasts and low levels of del 5q and del 7 by FISH (5-7%). A repeat bone marrow biopsy after cycle 1 demonstrated <10% cellularity with 5% blasts. FISH studies demonstrated persistence of del 5q and del 7 (15-17%). A repeat bone marrow biopsy following cycle 2 demonstrated multilineage dysplasia without excess blasts, while FISH studies demonstrated low level persistence of del 5q and del (3.7%). Decitabine was reduced to days 1-5 thereafter, however a repeat bone marrow biopsy after 3 cycles demonstrated progression to AML, with 49% blasts, and increase in del 5q and del 7 FISH clones to 23% and 60% respectively. She subsequently underwent 7 + 3 induction chemotherapy with with cytarabine and idarubicin. A bone marrow biopsy at midcycle cycle however demonstrated persistent disease and she transitioned to hospice. She expired 8 months post diagnosis.

#729805. 67 year old male with past medical history significant for colon cancer presented with leukopenia in the setting of pneumonia and melena and was simultaneously diagnosed with AML and colon cancer (which was subsequently resected with negative margins). Blood counts were WBC 4000 cells/mm3, hemoglobin 12.4 g/dl, and platelets 50,000 cells/m3, with 24% circulating blasts. A bone marrow biopsy demonstrated 30% cellularity, with 59% blasts consistent with AML M4. A population of kappa-restricted plasma cells felt to represent concurrent multiple myeloma was also observed. Cytogenetics showed a complex monosomal karyotype: 44~47,XY,del(5)(q22q35)[20],-7[14],-8[6],der(12)t(10;12)(p11.2;q21)[2],add(14)(p12)[11],-17[13],der(17)t(10;17)(q11.2;p13)[14],-18[7],add(18)(p11.2)[7],-21[10],i(21)(q10)[4],-22[4],+mar[10],+mar1x2[6][cp20]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, and BCR/ABL neagtive. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. He expired in the setting of sepsis with multiorgan failure prior to formal assessment for response, one month post diagnosis.

#794178. 73 year old male with past medical history significant for resected colon cancer, deep venous thrombosis, and pulmonary embolism and presented with leukocytosis noted in the wake of a fall and was diagnosed with AML. Blood counts were WBC 66,800 cells/mm3, hemoglobin 15.1 g/dl, and platelets 15,000 cells/m3, without circulating blasts (90% neutrophils). A bone marrow biopsy demonstrated 90% cellularity, with % blasts unquantified, but felt consistent with AML. Cytogenetics showed 2 distinct clones: one with a Philadelphia

chromosome and a second with a complex monosomal karyotype: 46,XY,t(9;22)(q34;q11.2)[13]/34~37,idem,-3,del(4),-4,-5,-7,-9,-10,t?(11;12),-12,-13,-14,-16,-17,-22[cp6]/46,XY[1]. Molecular diagnostic studies were not performed. On the basis of rapid subsequent clinical deterioration, he received no therapy and expired one week later on hospice.

#806794. 70 year old female with past medical history significant for hyperthyroidism presented with incidentally noted pancytopenia on routine bloodwork and was diagnosed with AML. Blood counts were WBC 700 cells/mm3, hemoglobin 7.6 g/dl, and platelets 82,000 cells/m3, with 6% circulating blasts. A bone marrow biopsy demonstrated 50% cellularity, with 32% blasts consistent with AML M1. Cytogenetics showed a complex monosomal karyotype: 46,XX,del(5)(q11.2q33)[1]/48~52,idem,+1,+?del(5)(q15q33),+11,+11,?t(12;22)(p13;q12),-13,-17,+i(22)(q10),+i(22)(q10),+mar[cp19]. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, JAK2 negative, and NPM1 negative. Initial therapy consisted of decitabine on a clinical trial, administered days 1-5. A bone marrow biopsy after 2 cycles demonstrated persistent disease, and she was subsequently treated with 7 + 3 induction with cytarabine and daunorubicin. She did not undergo a midcycle bone marrow biopsy, but was noted to have rapid rise in circulating blasts upon count recovery and received no further therapy. She expired 4 months post diagnosis.

#809653. 60 year old female with past medical history significant for diabetes mellitus, hypertension, hypothyroidism, and atrial fibrillation, presented with fever, cough, and dyspnea and was diagnosed with AML. Blood counts were WBC 15,200 cells/mm3, hemoglobin 8.6 g/dl, and platelets 92,000 cells/m3, with 87% circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, with 62% blasts consistent with AML M1. Cytogenetics showed a complex monosomal karyotype: 44~47,XX,t(1;15)(q32;q26)[14],del(5)(q13q33)[19],-7[20],+8[7],del(12)(p11.2p11.2)[15],del(17)(q21)[8],der(22)t(1;22)(p13;p11.2)[20],+mar[13][cp20. Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated persistent disease with 70% cellularity and 55% blasts. She was subsequently reinduced with mitoxantrone, cytarabine, and etoposide (MitoEC), but expired prior to formal response assessment, 2 months post diagnosis.

#812077. 73 year old female with past medical history significant for early stage breast cancer treated with bilateral mastectomies and tamoxifen, diabetes, mellitus, and childhood polio, presented with incidental note of circulating blasts on routine screening labs and was diagnosed with MDS. Blood counts were WBC 4000 cells/mm3, hemoglobin 9.8 g/dl, and platelets 57,000 cells/m3, with 3% circulating blasts. A bone marrow biopsy demonstrated 50% cellularity, with 14% blasts consistent with MDS/RAEB2. Cytogenetics showed a complex

monosomal karyotype: 4~45,XX,-2,del(5)(q13q33),-7,add(7)(p21),add(7)(q11.1),+8,-16,-17,-19,+der(21)t(17;21)(q11.2;p13),add(22)(q12),+mar[cp12]/46,XX[8]. Molecular diagnostic studies were not performed. Initial therapy consisted of decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy at midcycle demonstrated multilineage dysplasia with 14 % blasts. Her second cycle was delayed by febrile neutropenia, following which a repeat bone marrow was of poor quality but felt to be without significant change. FISH studies showed persistence of del 5q, del 7, trisomy 6, and del 16q (36-57%). Repeat bone marrow biopsies after cycle 3 and 5, respectively, demonstrated no excess blasts, and no evidence of prior FISH abnormalities. After completion of 5 cycles of decitabine, she underwent a 9/10 B antigen mismatched unrelated donor transplant following reduced intensity conditioning with fludarabine, cyclophosphamide, and single dose total body irradiation, followed by post transplant cyclophosphamide for GVHD prophylaxis. A repeat bone marrow biopsy one month post transplant demonstrated complete remission with full donor engraftment. A repeat biopsy 3 months post transplant however demonstrated relapse with 10-15% blasts, following which immunosuppression was rapidly withdrawn and a donor lymphocyte infusion was administered. A repeat bone marrow biopsy one month later was unchanged, and 10 day decitabine was initiated. A repeat bone marrow biopsy one month later demonstrated progression to AML with 36% blasts. She subsequently underwent salvage chemotherapy with cladribine and cytarabine (CLAG), followed by a second donor lymphocyte infusion, however, a subsequent marrow showed persistent disease and she was transitioned to hospice. She expired 17 months post diagnosis, 9 months post transplant.

#884262. 54 year old male with past medical history significant for deep venous thrombosis, pulmonary embolism, and “MDS” (details unavailable), presented with fatigue and pancycopenia and was diagnosed with AML. Blood counts were WBC 2800 cells/mm3, hemoglobin 6.0 g/dl, and platelets 14,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 100% cellularity, with 8% myeloblasts and 59% erythroblasts, consistent with AML M6. Cytogenetics showed a complex monosomal karyotype: 42,XY,-5,-7,add(12)(p13),t(14;15)(q10;q10),der(17)t(5;17)(p12;p11.2),-18[6]/40,iformal dem,-11,-add(12)(p13),der(12)t(?;12)(?;p13),-19[6]/41,idem,-der(17)[3]/41,idem,-der(17),+mar1,+mar2[3]/41,idem,der(1)del(1)(p12)add(1)(p12),+der(1)del(1)(q21)add(1)(q21),-3,-8[2]. Molecular diagnostic studies were not performed. Initial therapy consisted of cytarabine, daunorubicin, and etoposide. A bone marrow biopsy at midcycle demonstrated an ablated marrow. A subsequent bone marrow biopsy at count recovery demonstrated complete remission, with persistence of initial karyotypic abnormalities in a single metaphase cell. He subsequently underwent 1 cycle of high dose cytarabine consolidation, prior to matched

unrelated donor stem cell transplantation following myeloablative conditioning with cyclophosphamide and total body irradiation. A repeat bone marrow one month post transplant demonstrated complete remission with full donor engraftment, but also showed persistence of his prior karyotypic abnormalities in 2 metaphases. His post-transplant course was notable for mild skin GVHD treated with steroids. A repeat bone marrow biopsy 3 months post transplant demonstrated relapse, treated with rapid withdrawl of immunosuppression and subsequent mitoxantrone, etoposide, and cytarabine (MitoEC) and a donor lymphocyte infusion, complicated by acute GVHD and sepsis, with prolonged pancytopenia and persistence of circulating blasts at count recovery. A repeat bone marrow was not performed. He expired 11 months diagnosis, 6 months post transplant.

#888204. 79 year old female with past medical history significant for deep venous thrombosis, hypertension, and atrial fibrillation, presented with fatigue and dypnea in the setting of recurrent atrial fibrillation and was diagnosed with MDS. Blood counts were WBC 11,200 cells/mm3, hemoglobin 7.8 g/dl, and platelets 175,000 cells/m3, with 3% circulating blasts. A bone marrow biopsy demonstrated 80-90% cellularity, with 13% blasts consistent with MDS/RAEB2. A 7% population of kappa-restricted plasma cell was also observed, felt to represent a monoclonal gammopathy of uncertain significance (MGUS). Cytogenetics showed a complex monosomal karyotype: 43,XX,der(3)t(3;8)(p11;q11.2),add(5)(q11.1),add(6)(p23),inv(7)(p21q22),add(9)(q34),add(11)(p11.1),-12,-16,-17,-17,-22,+mar1,+mar2,+mar3[21]. Molecular diagnostic studies included: TP53 positive, Flt3 ITD negative, Flt3 D835 negative, and NPM1 negative. The remainder of a 36 gene myeloid sequencing panel was negative. She was initially treated with transfusional support alone. A repeat bone marrow biopsy 6 weeks later demonstrated progression to AML with 90% cellularity, with 81% blasts consistent with consistent with AML M0. Initial therapy consisted of a single cycle of decitabine and venetoclax, complicated by extension of deep venous thrombosis, sacral decubitus ulcers, and E. coli sepsis. A repeat bone marrow biopsy was not performed due to clinical deterioration, and she expired on hospice, 2 months post diagnosis.

#898627. 26 year old female with past medical history significant for obesity and bipolar disorder, presented initially with pancytopenia in the setting of progressive weakness, night sweats, and 30 pound weight loss over 2 months. Blood counts were WBC 1200 cells/mm3, hemoglobin 5.5 g/dl, and platelets 95,000 cells/m3, without circulating blasts. Workup at that time included ruling out nutritional deficiencies (normal iron, copper, B12, folate), paroxysmal nocturnal hemoglobinuria (PNH), and parvovirus. A bone marrow biopsy demonstrated >90% cellularity with erythroid and megakaryocytic hyperplasia and mild atypia, but no excess blasts. Cytogenetics demonstrated a t(9;11)(q22;q23), trisomy 8, and monosomy 13 karyotype in a single metaphase cell. She was subsequently

non-compliant with followup until presenting 2 months later with worsening fatigue. Blood counts were WBC 115,800 cells/mm3, hemoglobin 12.3 g/dl, and platelets 84,000 cells/m3, with 86% circulating blasts. A bone marrow biopsy demonstrated >90% cellularity, with 89% blasts consistent with AML M4. Cytogenetics were non-diagnostic (only 5 metaphases), but FISH studies demonstrated trisomy 8 (82%) and an MLL rearrangement (86%). Molecular diagnostic studies included: Flt3 ITD negative, Flt3 D835 negative, NPM1 negative, IDH1 negative, IDH2 negative, DNMT3A negative, and CEBPA negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated an ablated marrow. A repeat bone marrow biopsy at count recovery demonstrated complete remission with normal cytogenetics. Post-remission therapy consisted of a single cycle of high dose cytarabine, complicated by nausea, initially attributed to chemotherapy, but subsequently determined secondary to CNS involvement following a lumbar puncture that demonstrated the presence of leukemia cells. She was subsequently treated with twice weekly intrathecal chemotherapy until clearance. A subsequent bone marrow biopsy demonstrated relapse, treated with cladribine and cytarabine on a clinical trial, complicated by pancreatitis and a seizure in the context of posterior reversible encephalopathy syndrome (PRES). A repeat bone marrow biopsy demonstrated persistent disease. She was subsequently treated with mitoxantrone, etoposide, and cytarabine (MitoEC), but had circulating blasts upon count recovery. She received no further therapy and expired 8 months post diagnosis.

#938150. 60 year old female with past medical history significant for hyperlipidemia, stroke, hypothyroidism, and osteoporosis presented with pancytopenia in the setting of fever, fatigue, nausea, vomiting, and diarrhea, and was diagnosed with AML. Blood counts were WBC 2700 cells/mm3, hemoglobin 10.5 g/dl, and platelets 45,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 70% cellularity, with 58% blasts consistent with AML with multilineage dysplasia. Cytogenetics showed a complex monosomal karyotype with two distinct clones: CloneA: 44,XX,t(4;11)(q21;q23),-5,-7,add(12)(q24),add(18)(q23),del(20)(q12)[3]/ CloneB: 43,XX,del(3)(p12),der(3)t(3;3)(p21;q2?7),psu dic(5;7)(q13;p22),-10,-15,-17,add(18)(p11.2),-21,+22,+mar[cp14]/46,XX[3]. Molecular diagnostic studies were not performed. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated an ablated marrow. A repeat bone marrow biopsy at count recovery demonstrated complete remission with normal cytogenetics. Post-remission therapy consisted of 3 cycles of high dose cytarabine, prior to undergoing matched sibling donor allogeneic stem cell transplant, following myeloablative conditioning with cyclophosphamide and single dose total body irradiation. Repeat bone marrow biopsies post transplant showed persistent mixed chimerism, prior to relapse 5 months post transplant. She was treated with salvage mitoxantrone, cytarabine, and etoposide (MitoEC), but expired 13 months post diagnosis, 6 months post transplant.

#971297. 85 year old male with past medical history significant for coronary artery disease, aortic valve replacement, hypertension, atrial fibrillation, and benign prostatic hypertrophy, presented with weakness and epistaxis and was diagnosed with MDS. Blood counts were WBC 3200 cells/mm3, hemoglobin 9.2 g/dl, and platelets 65,000 cells/m3, with 9% circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, with 11% blasts consistent with MDS/RAEB2. Cytogenetics showed a complex monosomal karyotype: 41~42,XY,del(5)(q13q33),dup(11)(q13q25),-12,del(16)(q11.2),der(17;21)(p10;q10),-18,dic(13;20)(p12;q11.2)[cp20]. Molecular diagnostic studies were not performed. Initial therapy consisted of a single cycle of azacytidine, following which a repeat bone marrow biopsy demonstrated persistent disease and he was started on decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy at midcycle demonstrated persistent disease with 8% blasts. A repeat bone marrow biopsy after one cycle demonstrated 50% celluarity with multilineage dysplasia with 3% blasts, and persistence of previously observed karyotypic abnormalities in 19/20 metaphases. A repeat bone marrow biopsy following cycle 2 demonstrated 30% cellularity with 3% blasts and normal cytogenetics. Repeat bone marrow biopsies following cycles 4, 6, and 8, respectively showed ongoing cytogenetic complete remission. A repeat bone marrow biopsy following cycle 10 showed no excess blasts, but reappearance of prior karyotypic abnormalities in 1/20 metapheses. A repeat bone marrow biopsy after cycle 16 demonstrated relapse, and he was switched to supportive care. He expired 21 months post diagnosis.

#976116. 59 year old male without significant past medical history presented with weakness and dyspnea and was diagnosed with AML. Blood counts were WBC 2200 cells/mm3, hemoglobin 4.6 g/dl, and platelets 14,000 cells/m3, with 24% circulating blasts. A bone marrow biopsy demonstrated 60-70% cellularity, with 45% blasts consistent with AML NOS. Cytogenetics showed a complex monosomal karyotype: 41~43,XY,der(1)t(1;17)(q12;q11.2),add(3)(p?13),add(5)(q11.2),add(5)(q11.2),-7,t(14;17)(q11.2;p13),-17,-18,add(19)(p13.3)add(21)(p11.2)[cp20]. Molecular diagnostic studies included: Flt3 ITD negative and Flt3 D835 negative. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated an ablated marrow. A repeat bone marrow biopsy at count recovery demonstrated 5% residual blasts with previously observed karyotypic abnormalities in 5/20 metaphases, consistent with residual disease. A repeat bone marrow biopsy one week later demonstrated no excess blasts and normal cytogenetics, consistent with complete remission. He subsequently transferred care to another facility where he received 2 cycles of consolidation chemotherapy with cladribine, idarubicin, and cytarabine (CLIA). A repeat bone marrow biopsy after cycle 2 demonstrated 1% blasts with 1.8% flow cytometry-based minimal residual disease (MRD), and

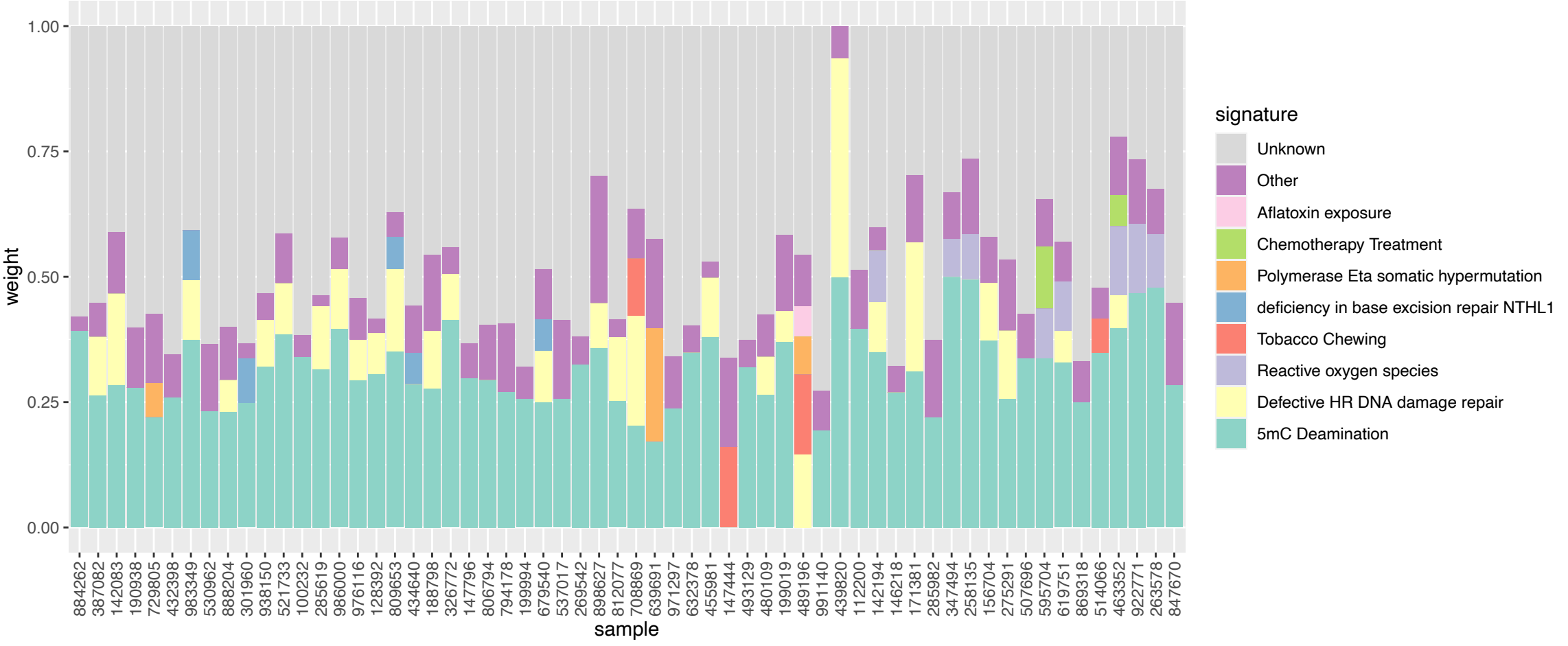
venetoclax was added to cycle 3. A subsequent bone marrow biosy demonstrated relapse with 23% blasts, and he was treated with 2 cycles of decitabine and venetoclax. A repeat bone marrow biopsy showed hematologic remission with 2% MRD, however further treatment, including a planned haploidentical stem cell transplant, was postponed due to the development of fungal pneumonia. A subsequent bone marrow biopsy one month later demonstrated second relapse with 14% blasts, and he was again started on decitabine and venetoclax. A repeat bone marrow biopsy one month later again showed persistent disease, and he expired 11 months post diagnosis.

#983349. 46 year old male with past medical history significant for hypertension and hyperlipidemia presented with dyspnea and was diagnosed with AML. Blood counts were WBC 2000 cells/mm3, hemoglobin 10.4 g/dl, and platelets 27,000 cells/m3, with 9% circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, with 48% blasts and significant erythroid dysplasia consistent with AML with MDS-related changes. Cytogenetics showed a complex monosomal karyotype: 42~43,XY,add(3)(q10),add(5)(q13),-7,-9,add(11)(p10),der(11)hsr(11)(q23),-12,add(16)(p11.2),add(16)(q12),-17,-18,+mar[cp20] . Molecular diagnostic studies included: TP53 positive, Flt3 ITD negative, Flt3 D835 negative, and NPM1 negative. The remainder of a 40 gene myeloid sequencing panel was unremarkable. Initial therapy consisted of 7 + 3 induction with cytarabine and idarubicin. A bone marrow biopsy at midcycle demonstrated <5% cellularity with 20% blasts based on flow cytometry. A repeat bone marrow biopsy one week later demonstrated 80% cellularity with 6% blasts, and he was started on decitabine on a clinical trial, administered days 1-10. A bone marrow biopsy at midcycle demonstrated 70% cellularity with 2% blasts, and normal cytogenetics. A repeat bone marrow biopsy after cycle 1 again demonstrated no excess blasts, however cytogenetics demonstrated persistence of prior karyotypic abnormalities in 2/20 metaphases. A repeat bone marrow biopsy following cycle 2 demonstrated complete remission with normal cytogenetics. He subsequently underwent a matched unrelated donor stem cell transplant following myeloablative conditioning with busulfan, cyclophosphamide, and thymoglobulin. A repeat bone marrow biopsy one month post transplant demonstrated a complete remission, flow-based minimal residual disease (MRD) negative, with full donor engraftment. A repeat bone marrow biopsy 2 ½ months post transplant demonstrated relapse, following which immunosuppression was rapidly withdrawn and he was restarted on a 5 day regimen of decitabine with venetoclax, complicated by a subdural hematoma. A repeat bone marrow biopsy after cycle 2 demonstrated persistent disease, following which he was transitioned to hospice and expired 10 months post diagnosis, 6 months post transplant.

#986000. 77 year old male with past medical history significant for hypertension, hyperlipidemia, coronary artery disease, and urolithiasis presented with pneumonia and was diagnosed with AML. Blood counts were WBC 1500 cells/mm3, hemoglobin 7.2 g/dl, and platelets 39,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 80% cellularity, with 47% blasts consistent with AML M7. There was also incidental note of 27% normal appearing plasma cells, and a small possible lambda restricted gamma region peak was observed on serum protein electropheresis that was not further evaluated. Cytogenetics showed a complex monosomal karyotype: 46,XY,-5,+8,del(9)(q22),add(10)(q26),der(15;19)(q10;q10),add(17)(p11.2),-20,-21,add(21)(p11),add(22)(q13),+3mar[20]. Molecular diagnostic studies were not performed. After extensive discussion regarding his poor prognosis and limited treatment options, he was discharged home to receive supportive care. He expired 5 months post diagnosis.

#991140. 60 year old male with past medical history significant for chronic lymphocytic leukemia (CLL) treated with fludarabine, cyclophosphamide, and rituximab (FCR) for 4 cycles with complete response, but complicated by subsequent development of pancytopenia and diagnosed with MDS. Blood counts were WBC 2500 cells/mm3, hemoglobin 7.7 g/dl, and platelets 79,000 cells/m3, without circulating blasts. A bone marrow biopsy demonstrated 50% cellularity, with 1% blasts and marked multilineage dysplasia with marked erythroid predominance, consistent with MDS/RA. There was also evidence of low level residual CLL. Cytogenetics showed a complex monosomal karyotype: 44,XX,-7,psudic(12;15)(p13;p13),-18,+mar[13]/44,Y,t(X;19)(q11.2;p13.1),add(3)(p?23),add(5)(q13),add(7)(p13),-18[3]/46,XY[4]. Molecular diagnostic studies were not performed. Initial therapy consisted of azacytidine. A hemodilute bone marrow biopsy after 2 cycles demonstrated no excess blasts and 25% residual CLL cells. Cytogenetics demonstrated persistence of prior karyotypic abnormalities in 9/20 metaphases. He subsequently underwent matched unrelated donor stem cell transplant following reduced intensity conditioning with fludarabine and busulfan. A repeat bone marrow biopsy one month post transplant showed complete remission with full donor engraftment and a normal 46 XX karyotype. Repeat bone marrow biopsies over the following 7 years demonstrated similar findings. His post transplant course was complicated by acute (skin) and chronic extensive (mouth, eyes, lungs, GI tract) GVHD treated with multiple agents and requiring frequent hospitalizations. He expired in multiorgan failure from complications of chronic GVHD and atypical HUS, nearly 9 years post diagnosis.

Supplementary Figure 1.



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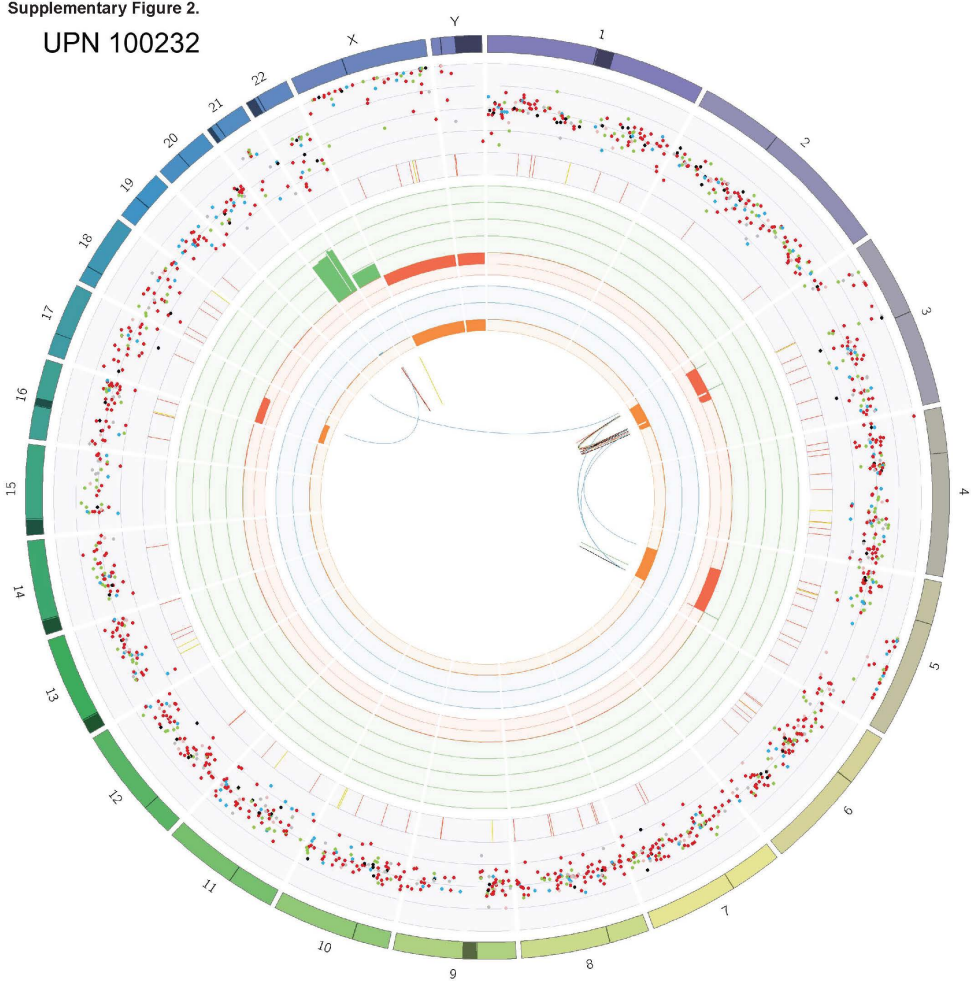

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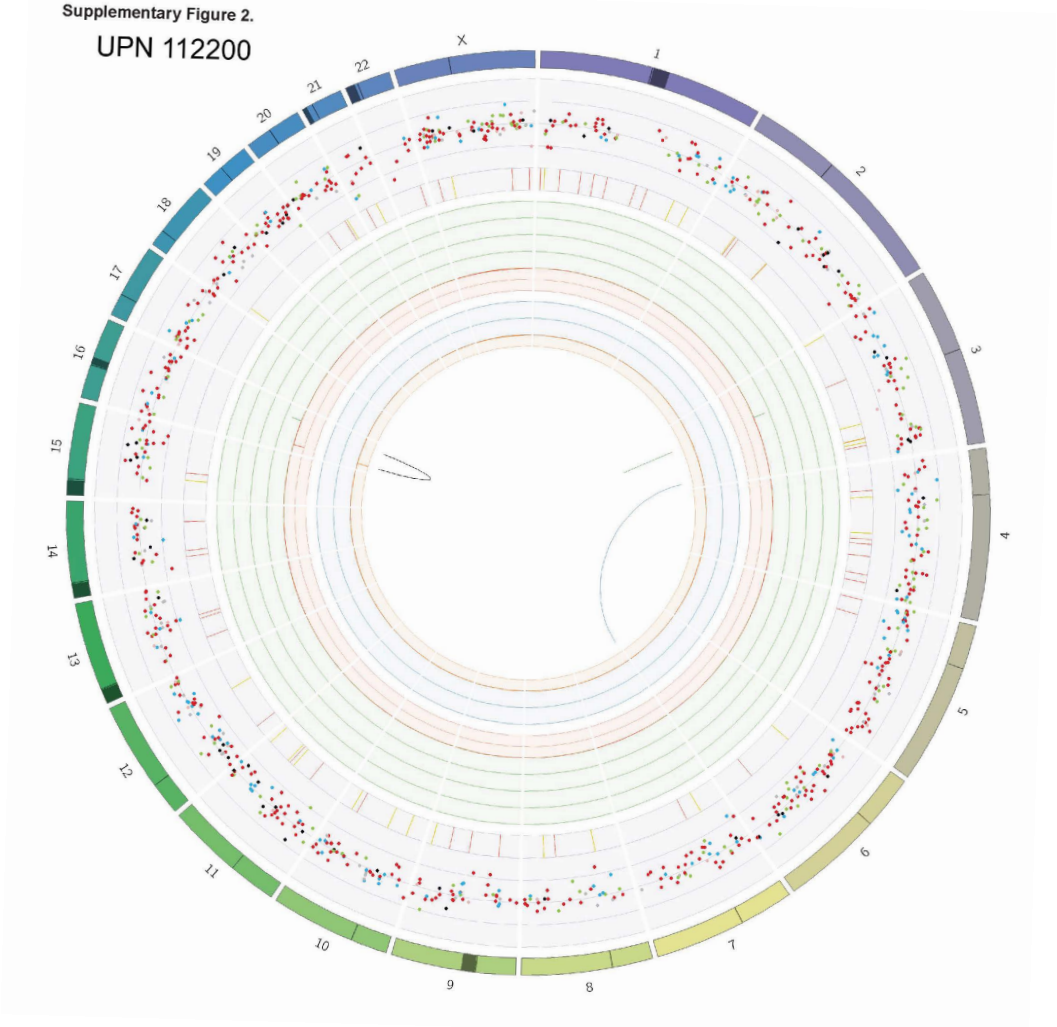

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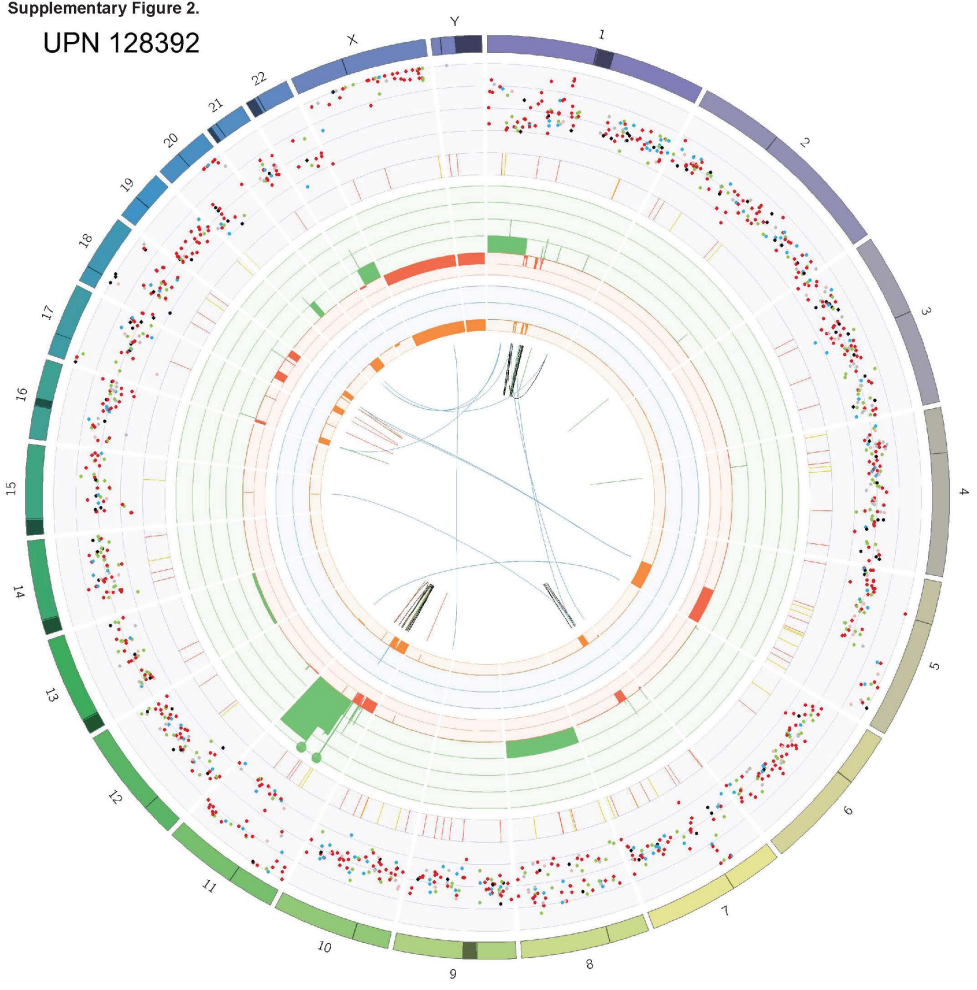

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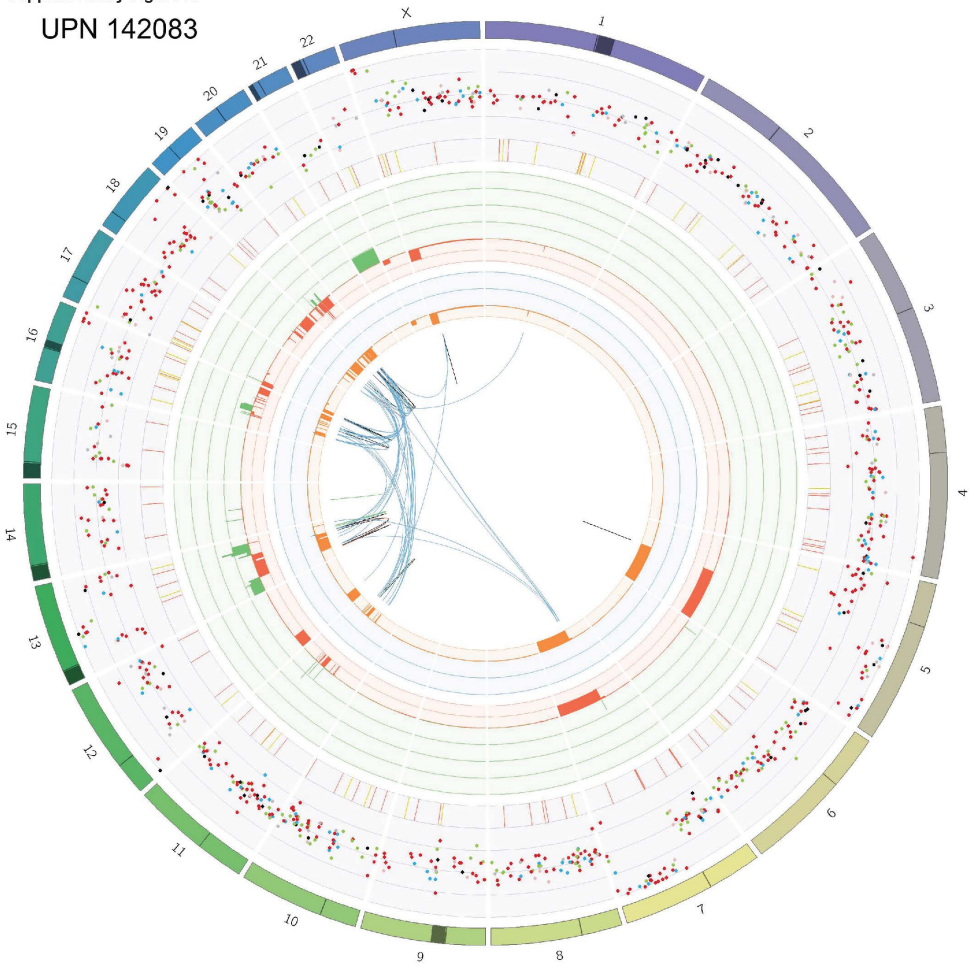

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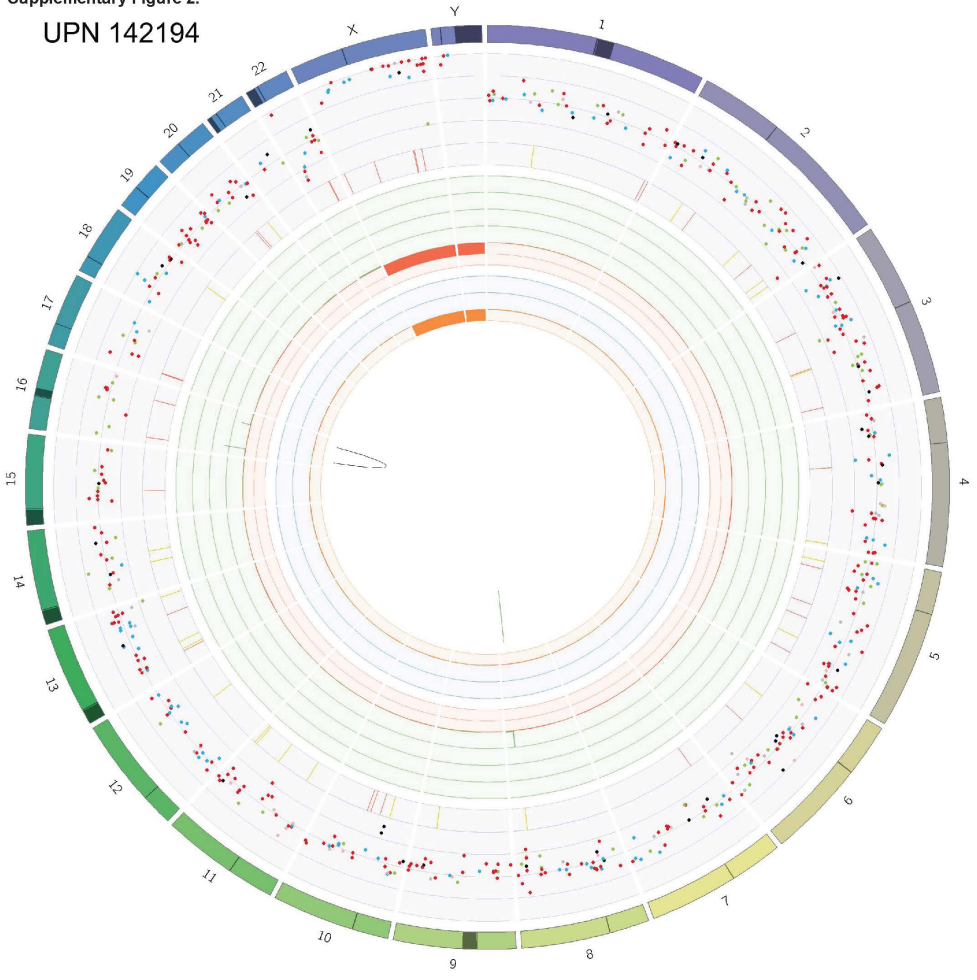

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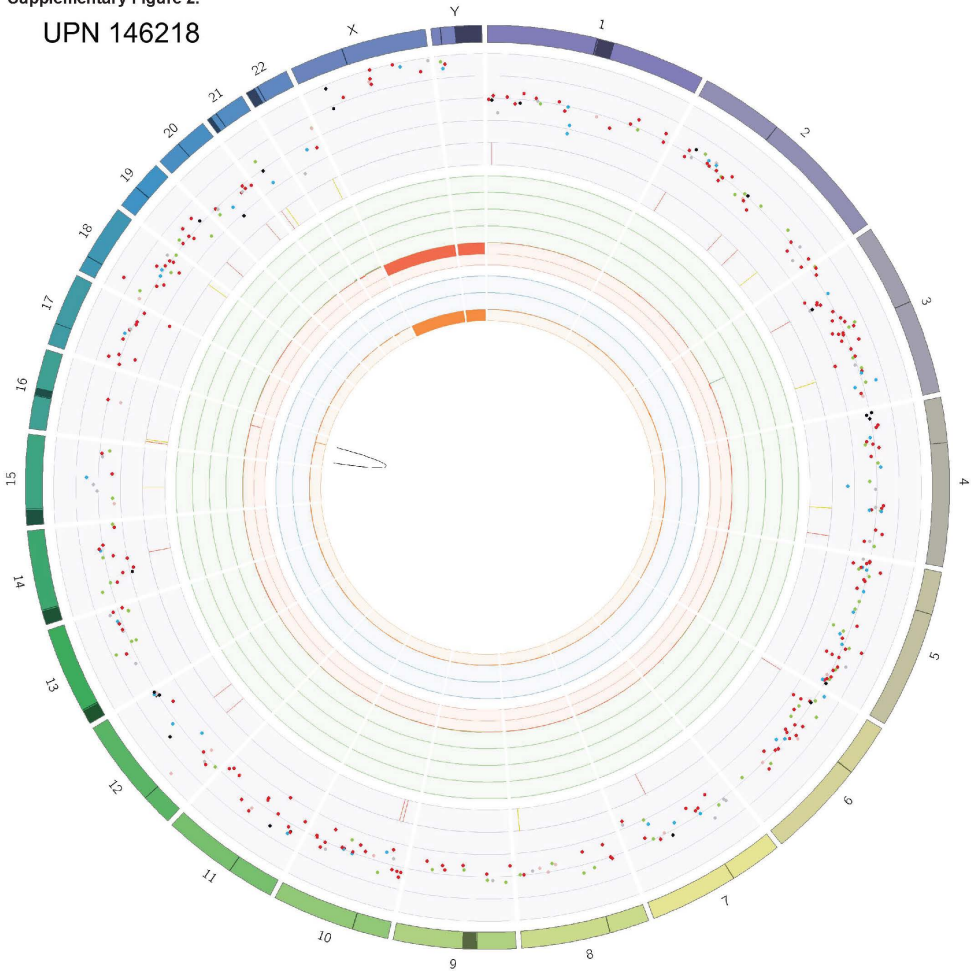

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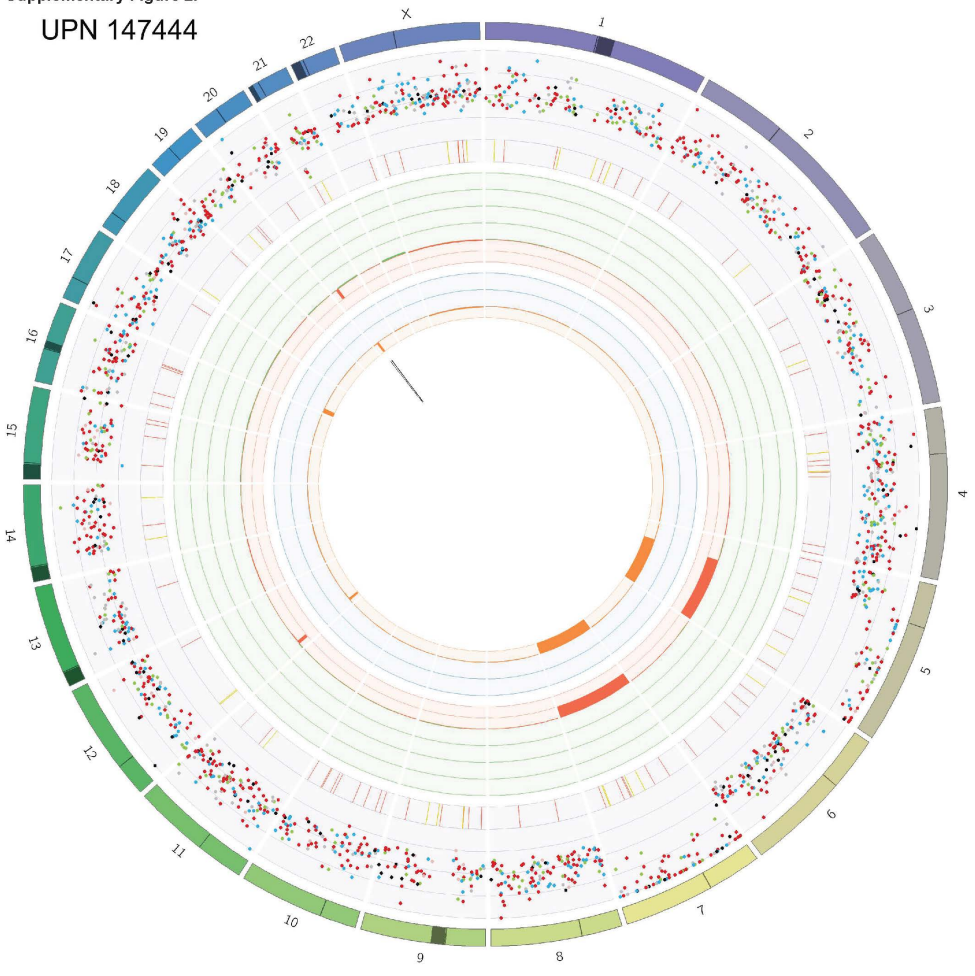

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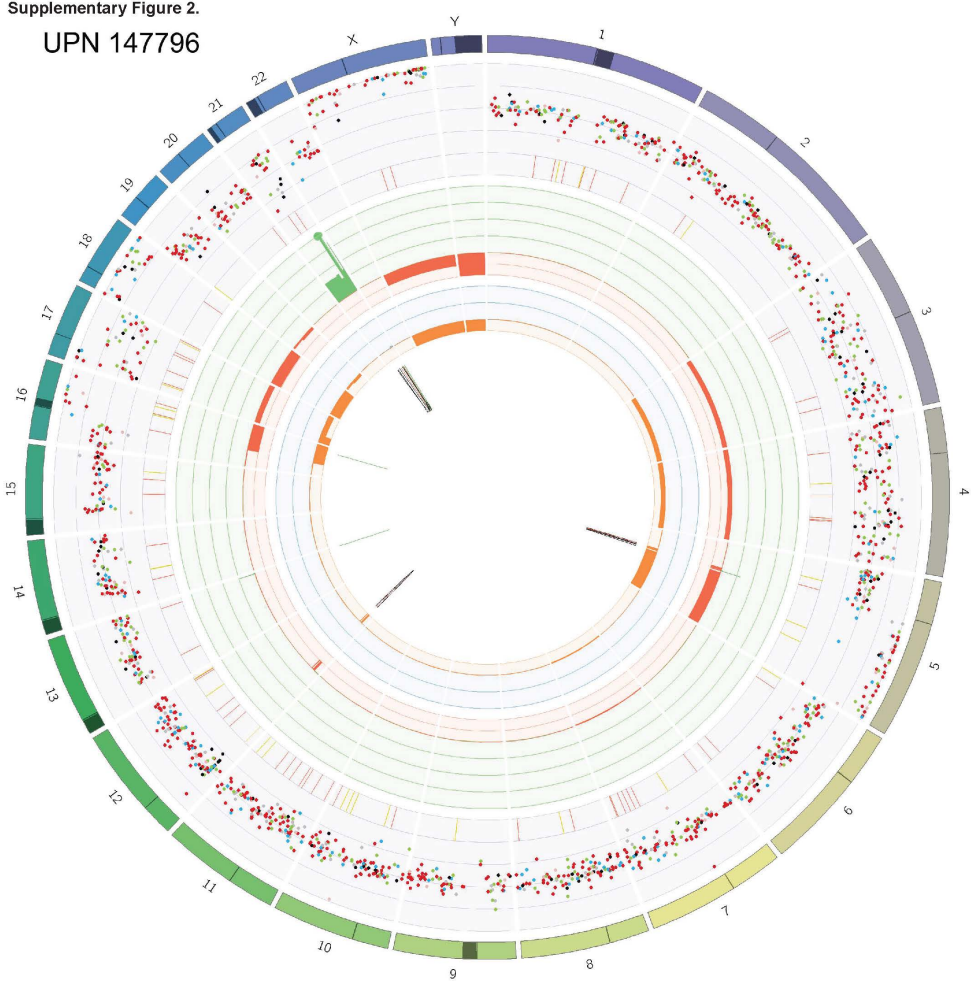

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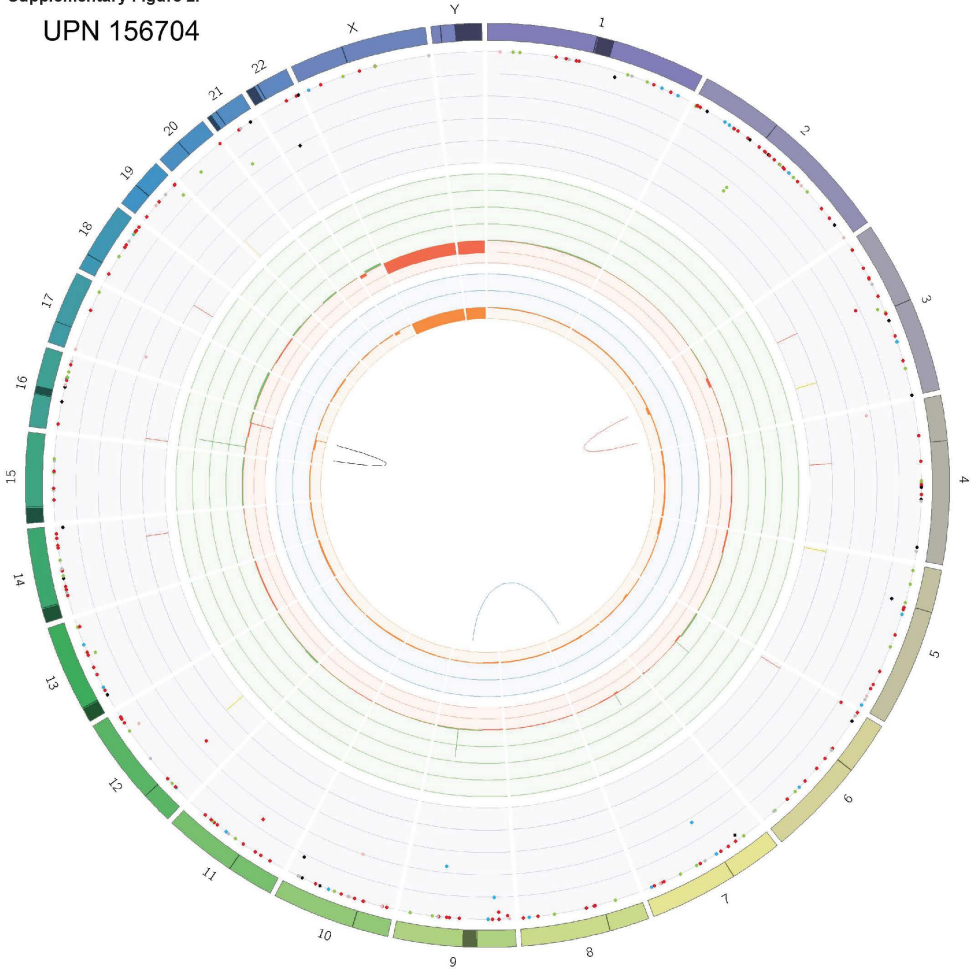

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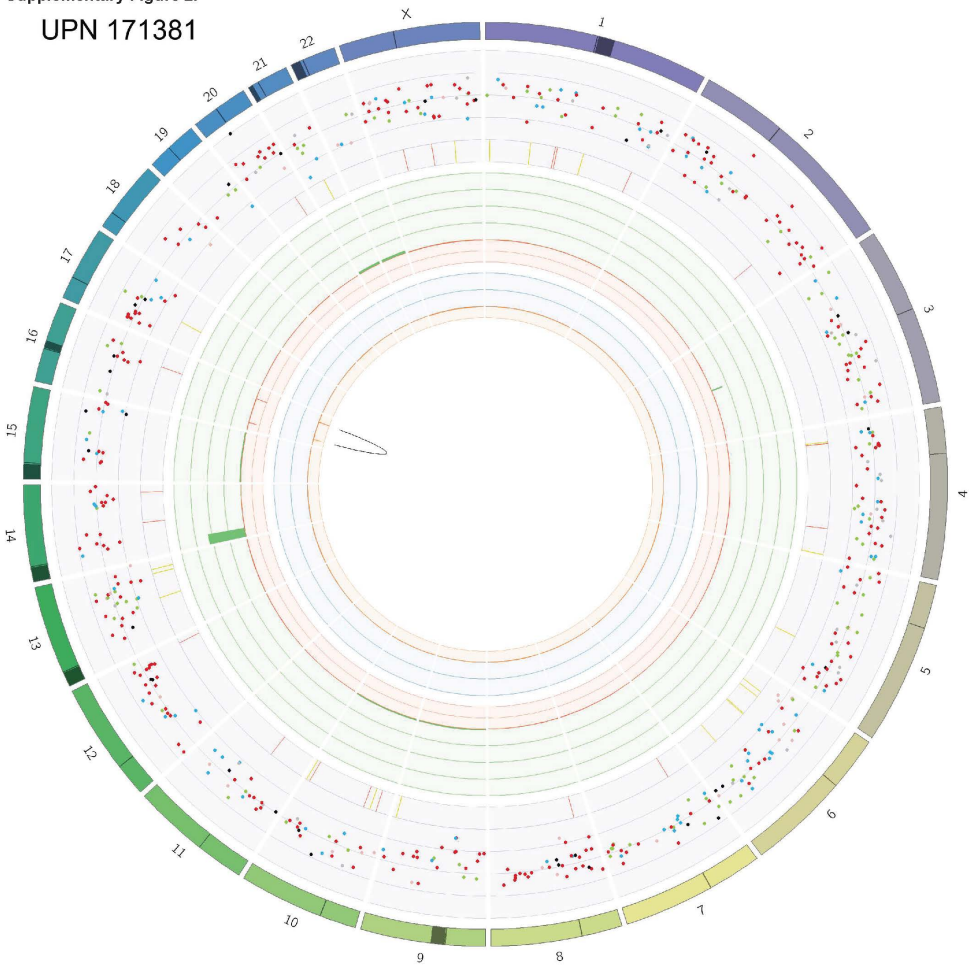

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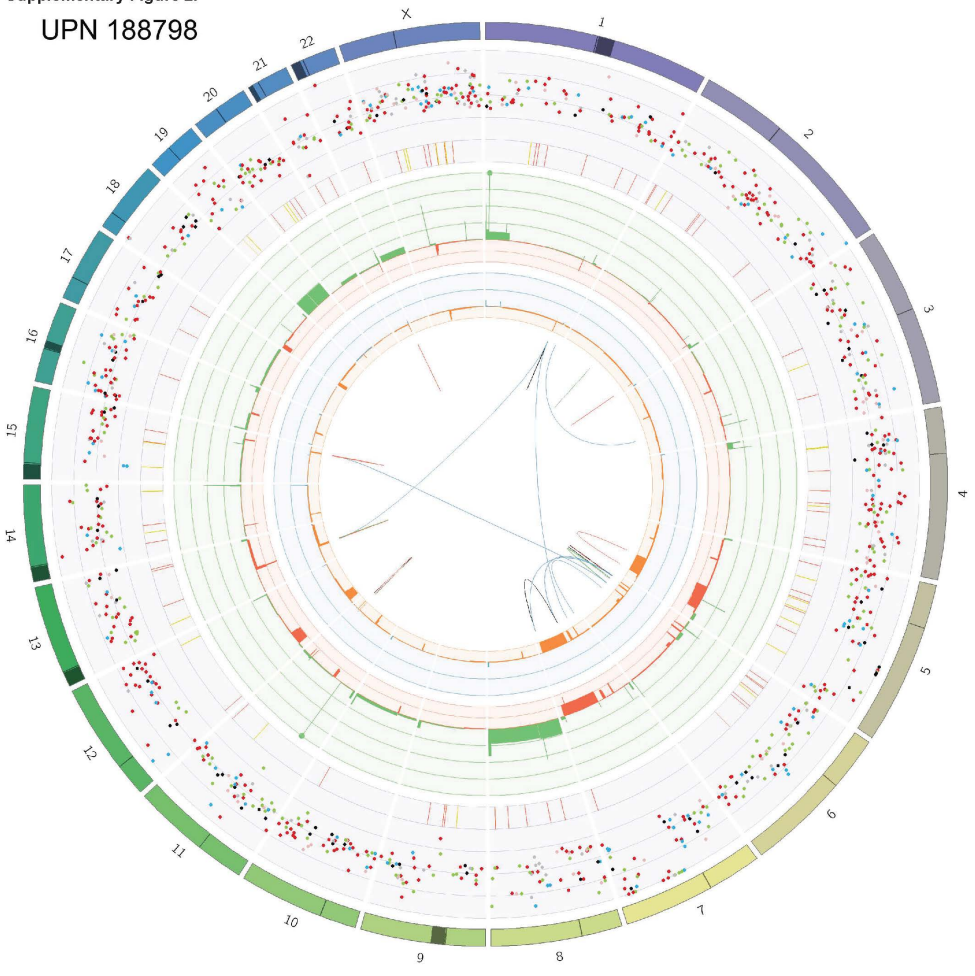

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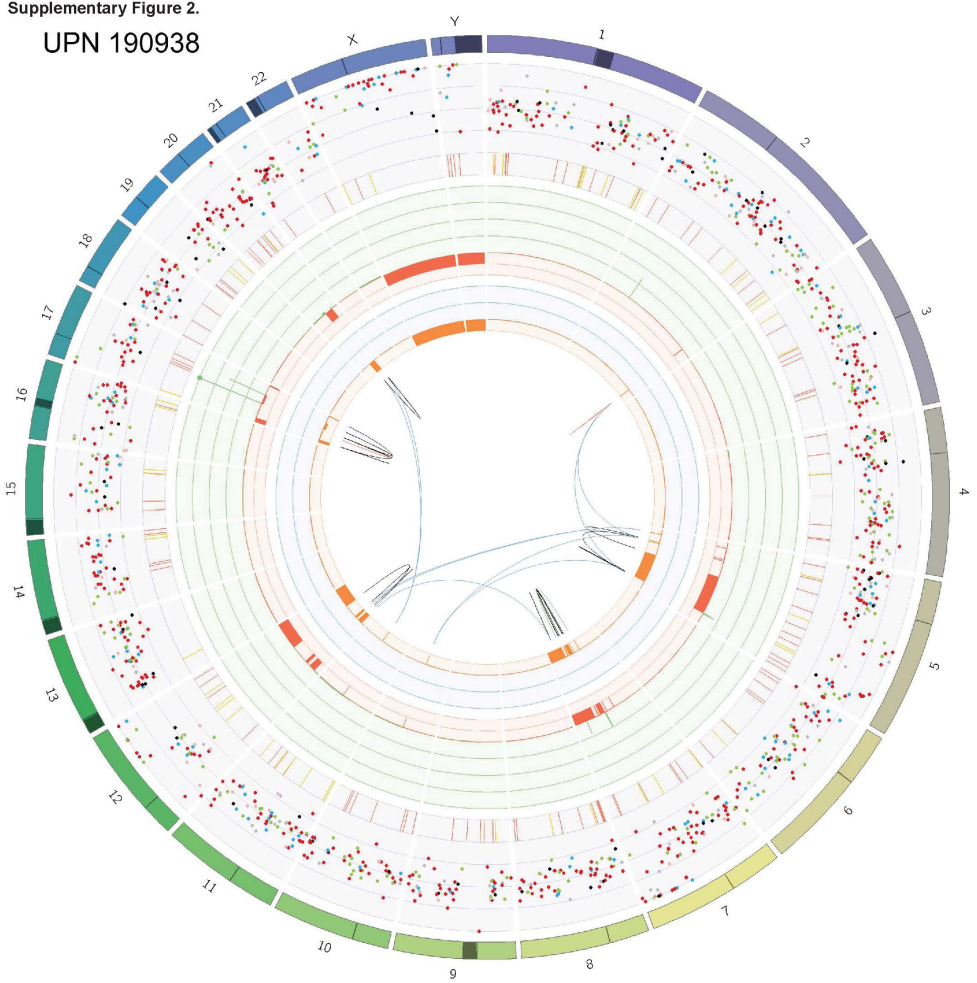

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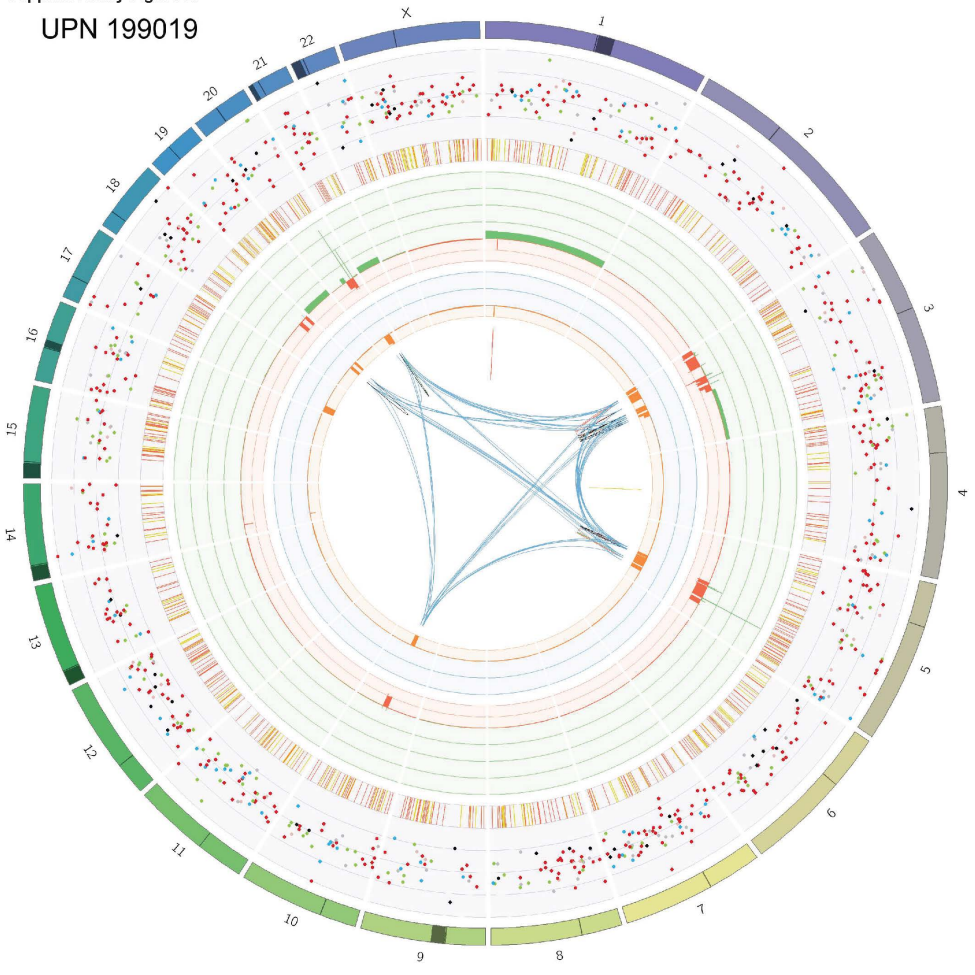

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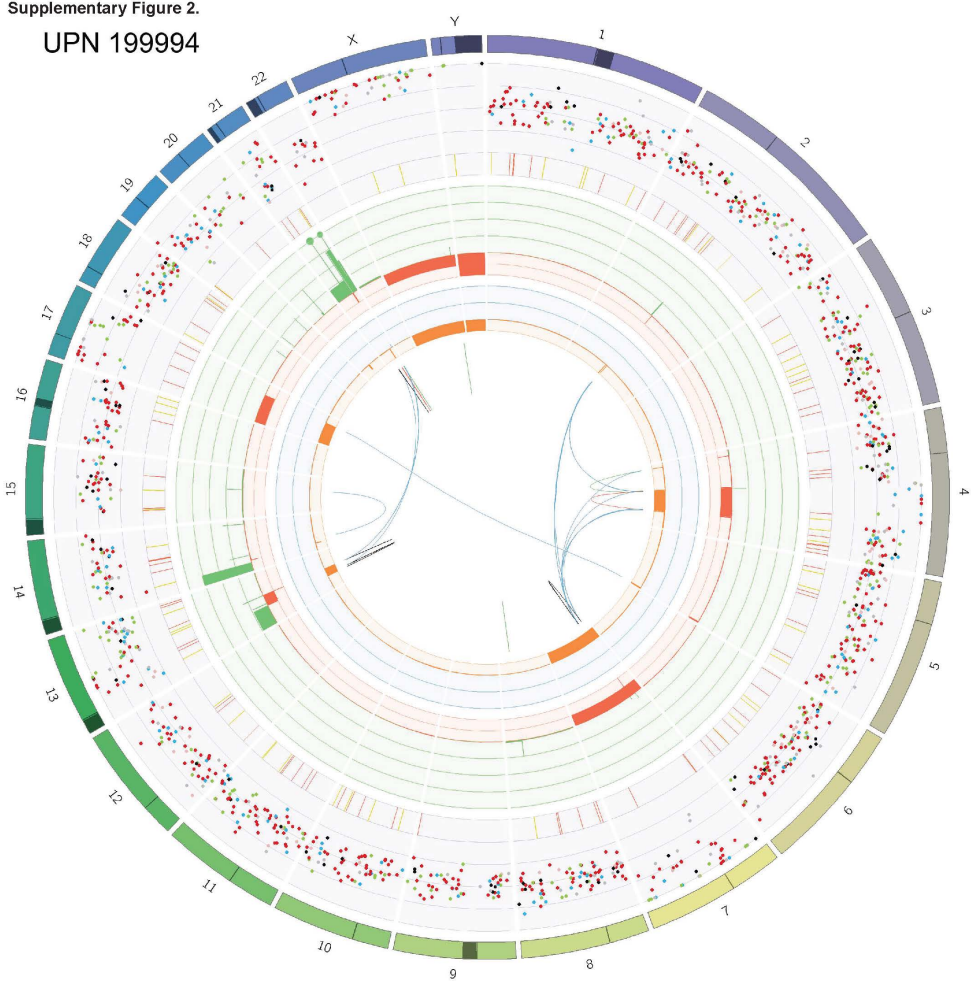

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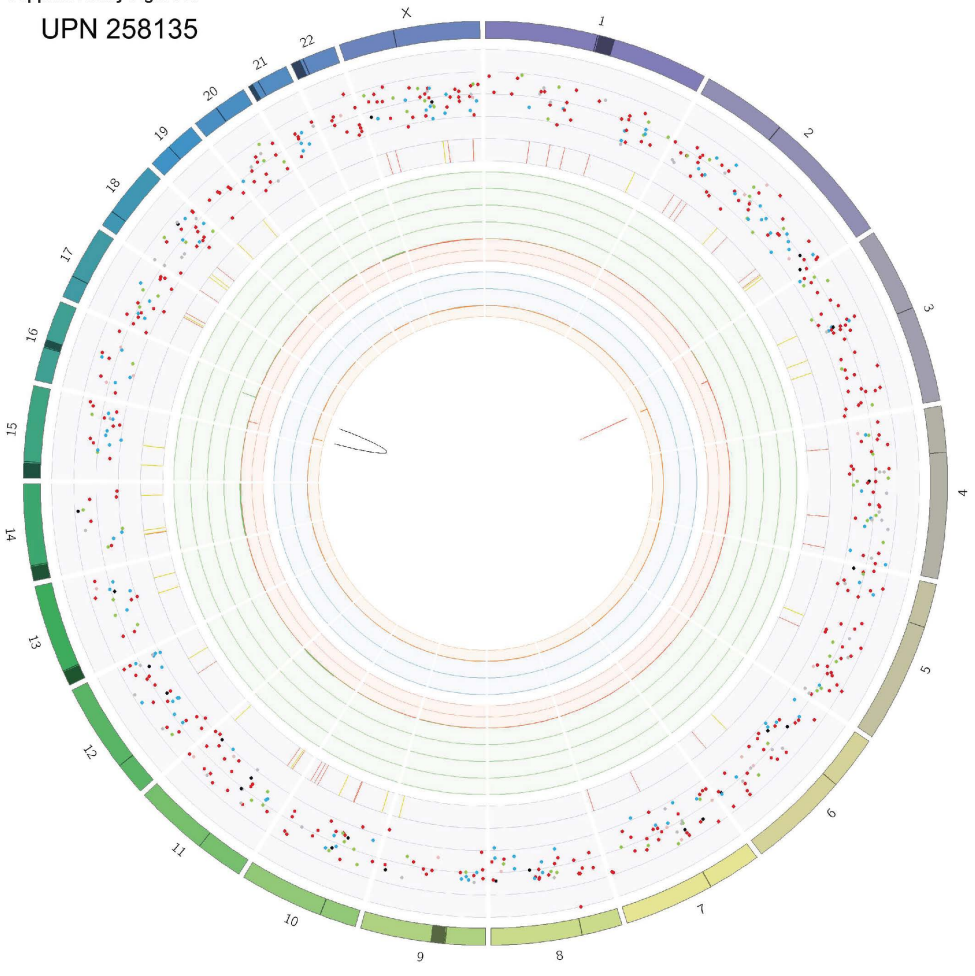

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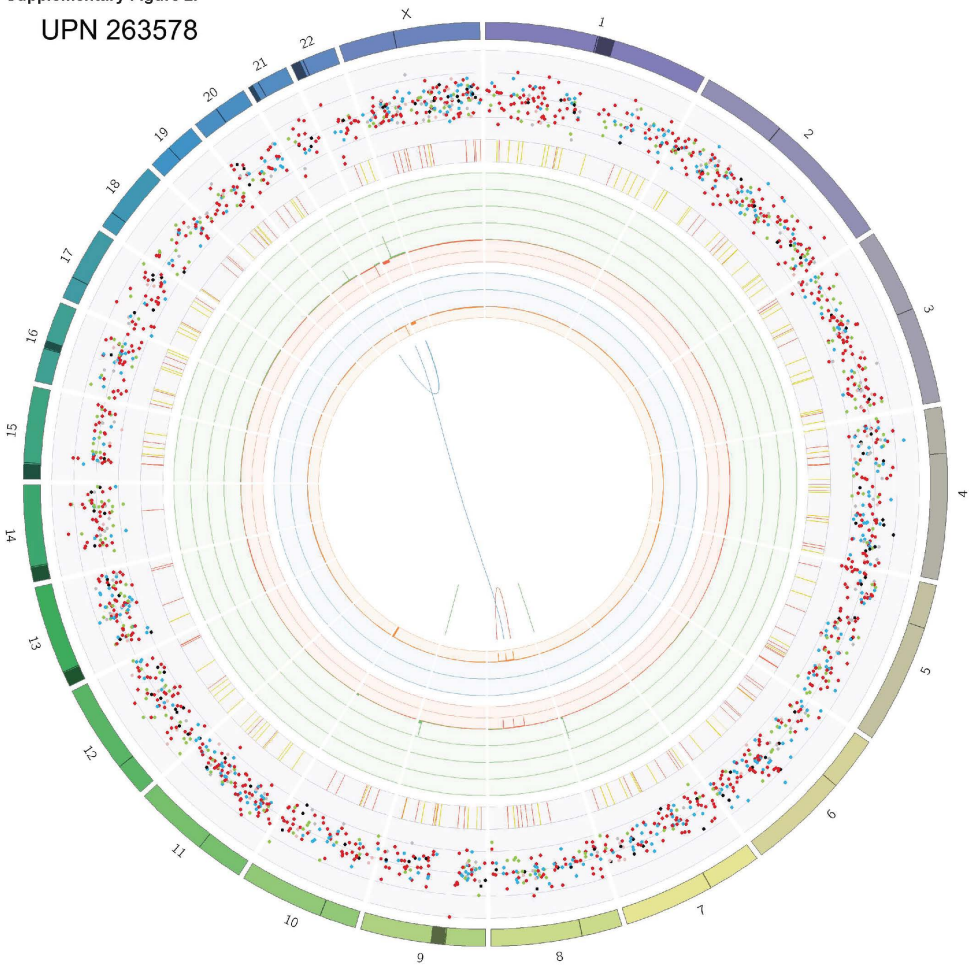

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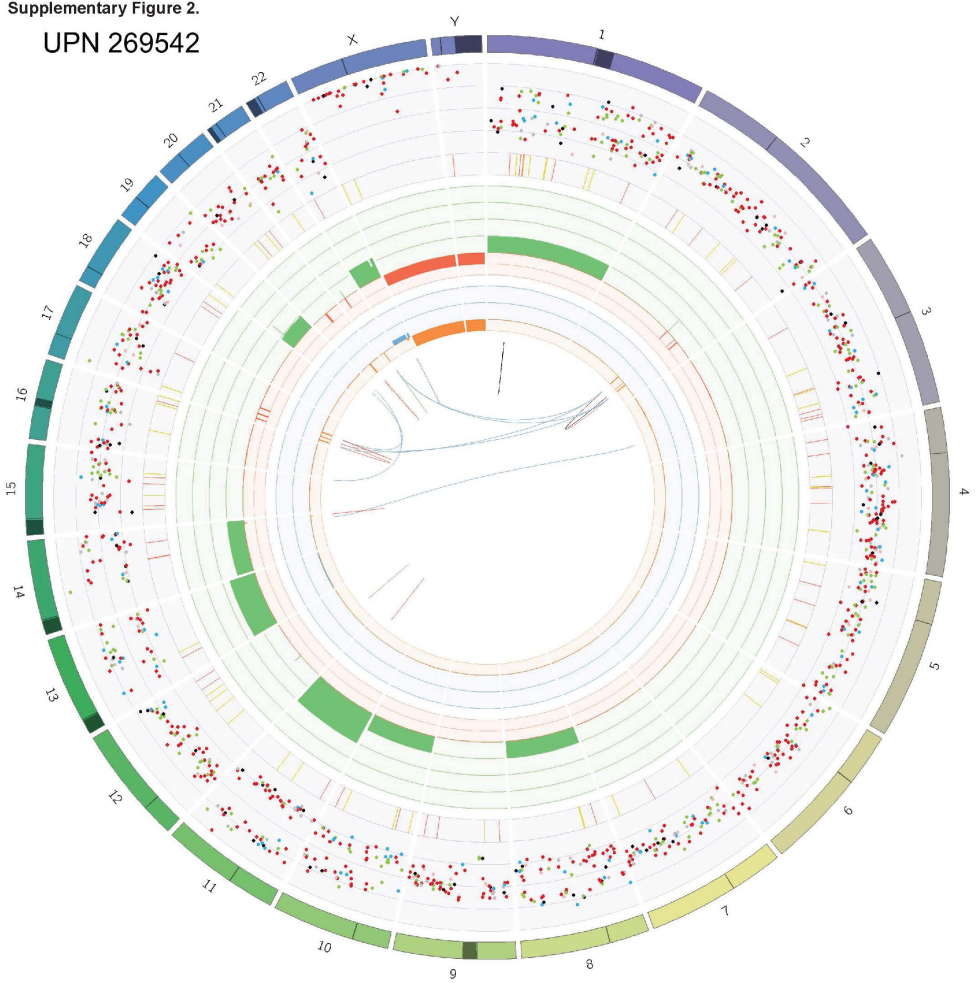

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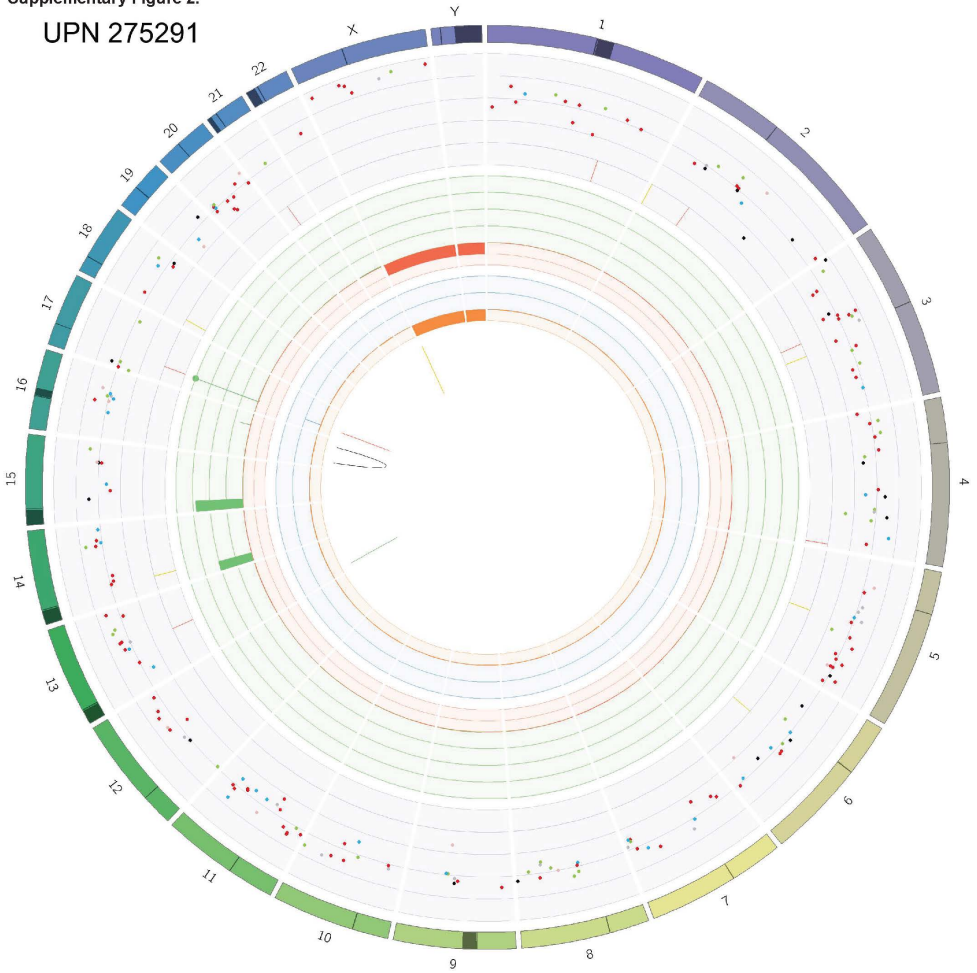

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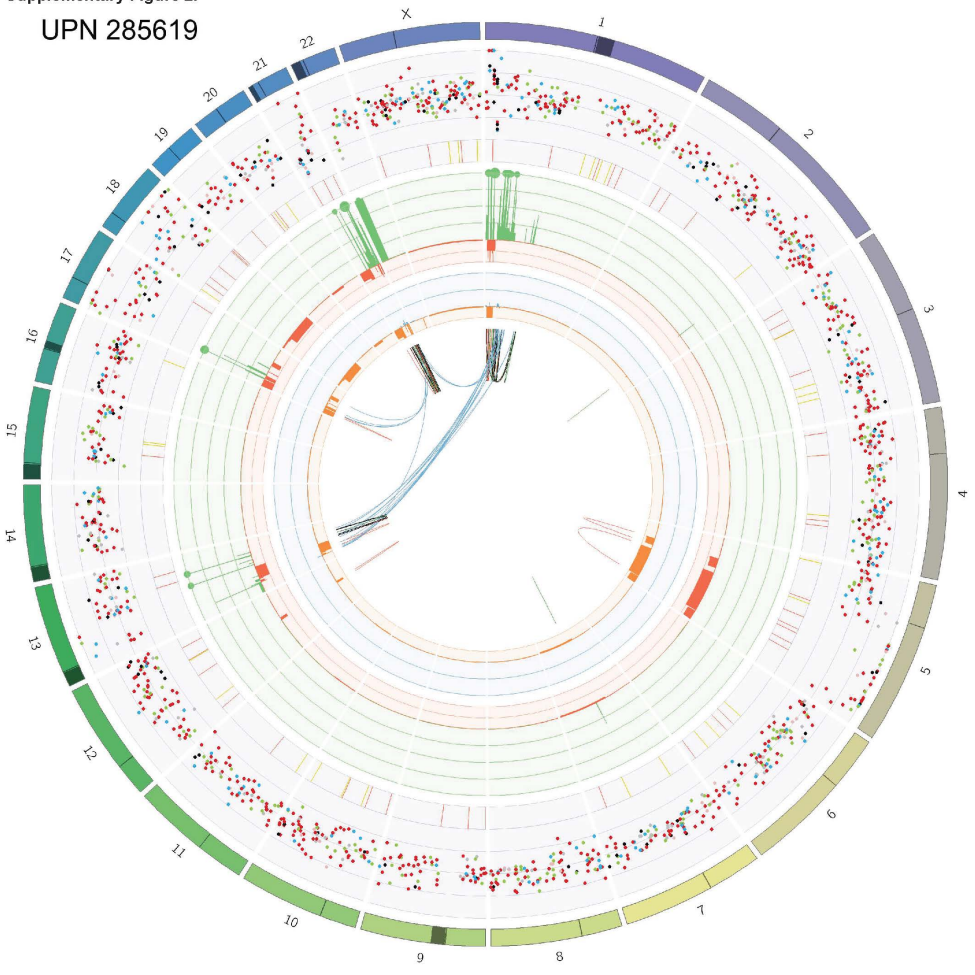

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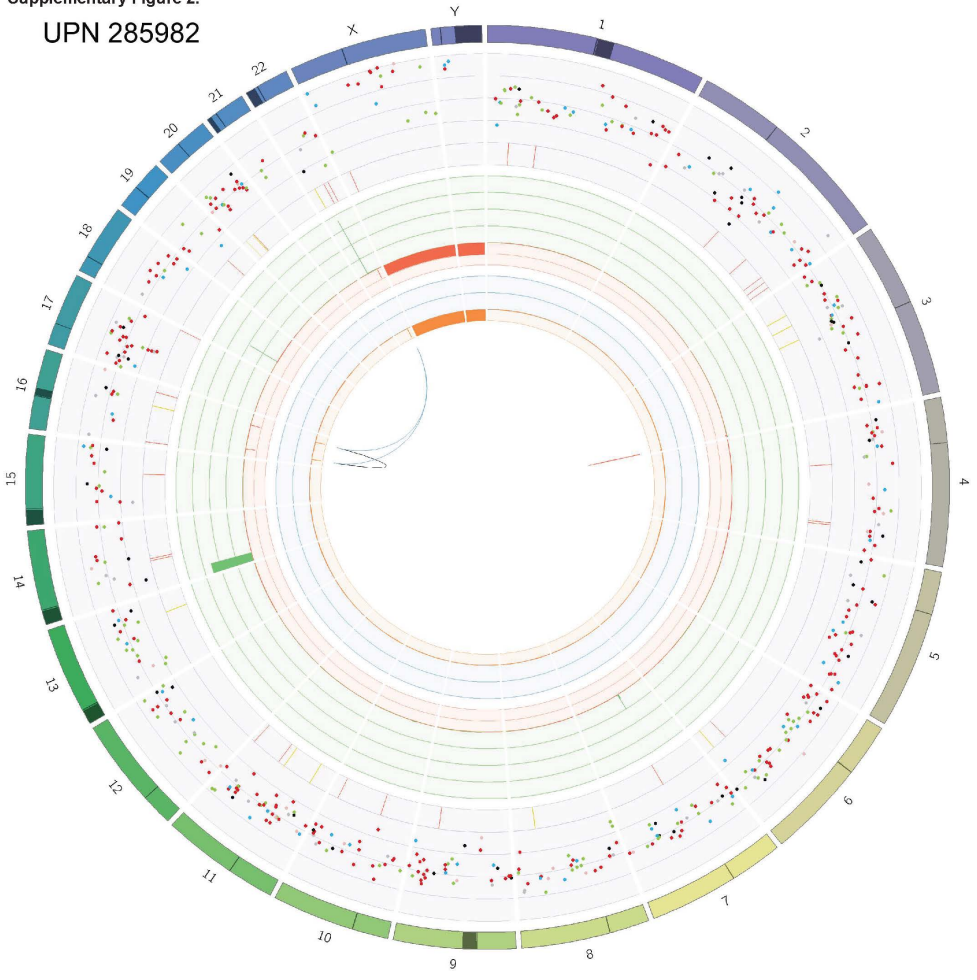

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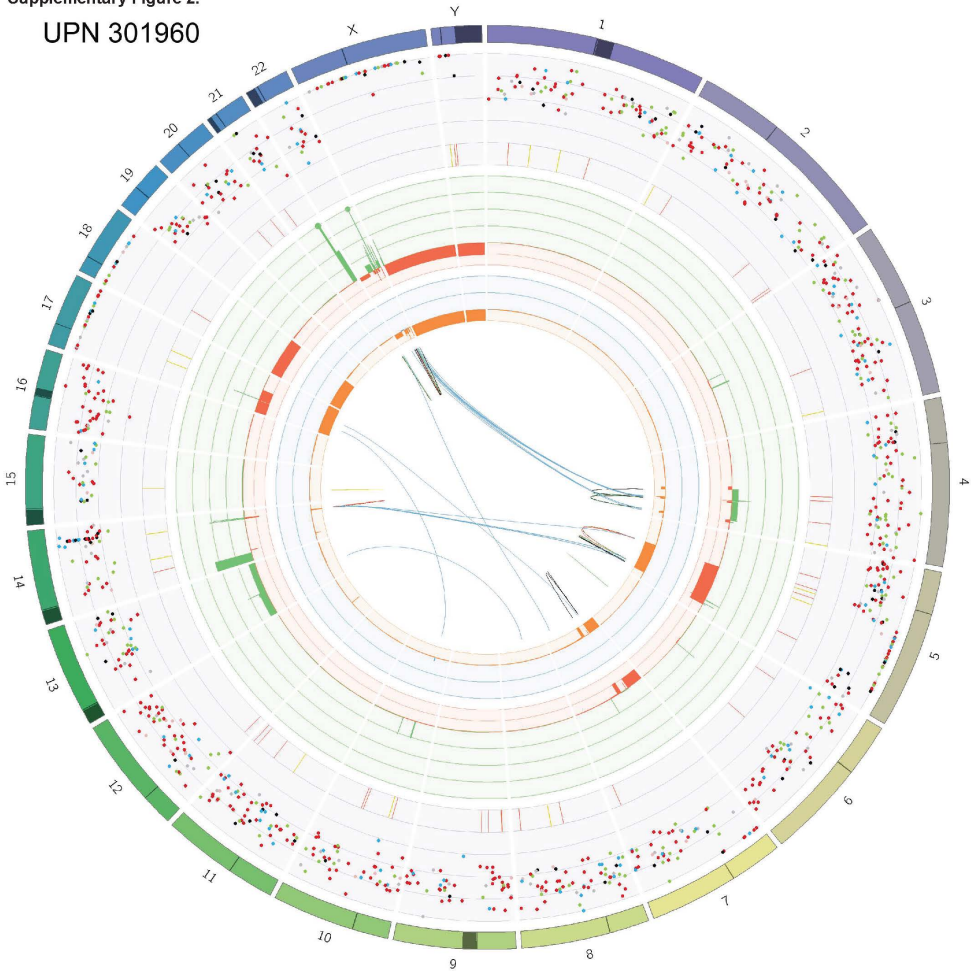

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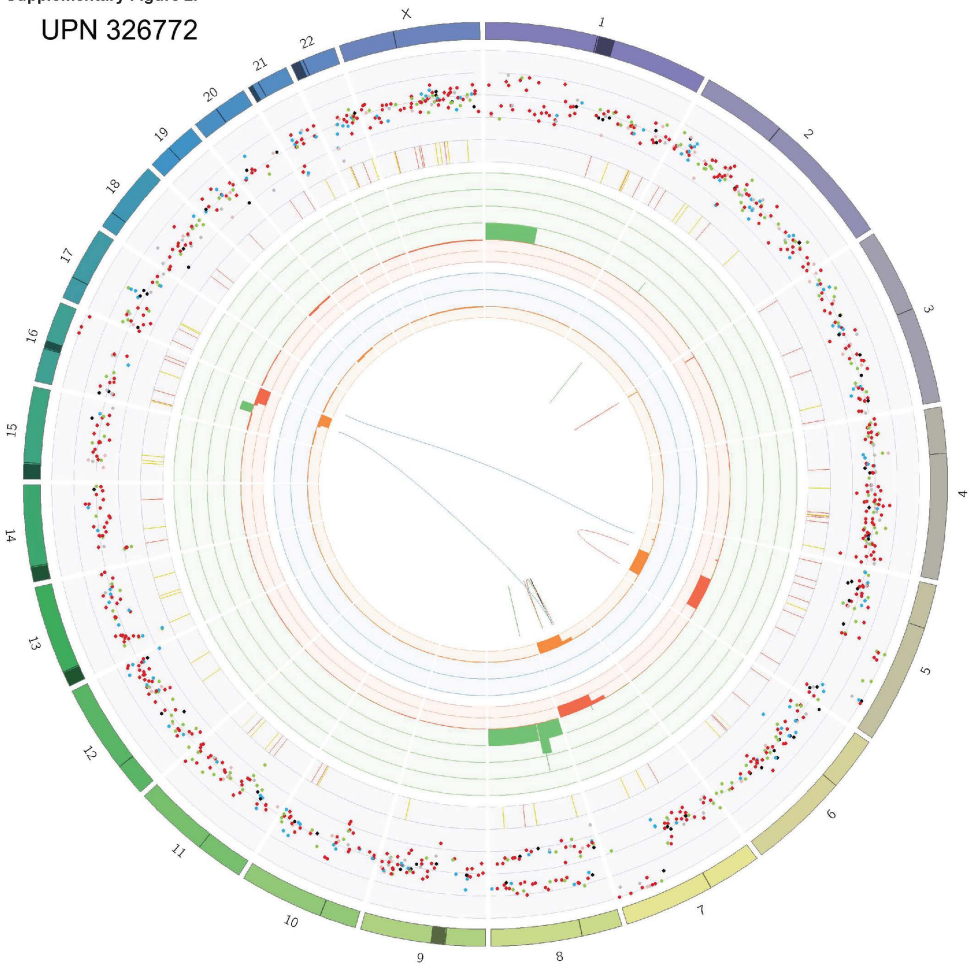

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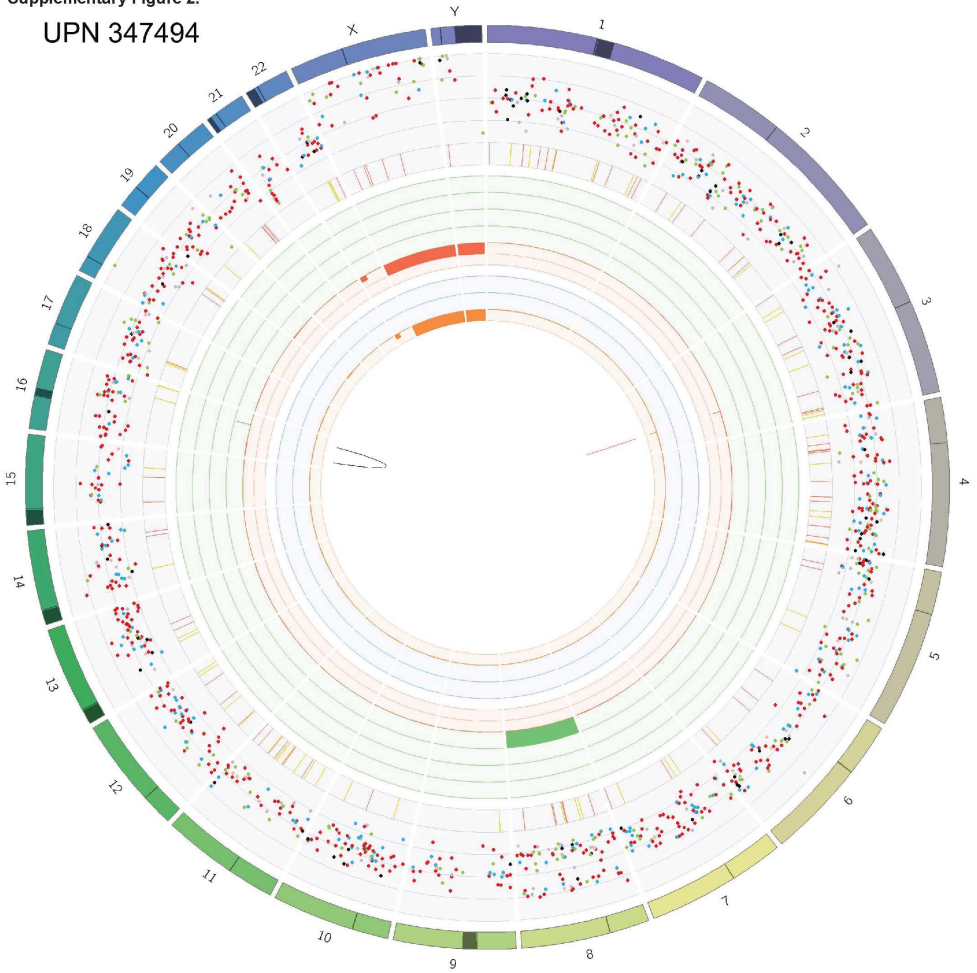

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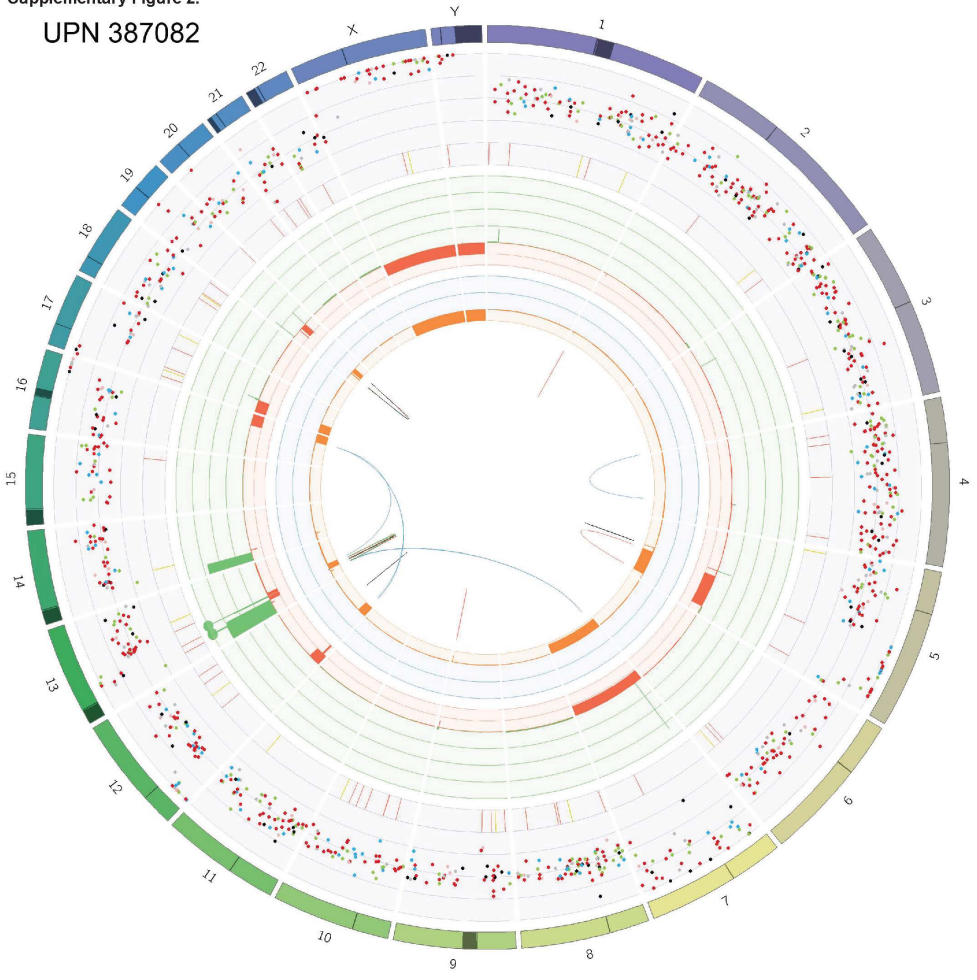

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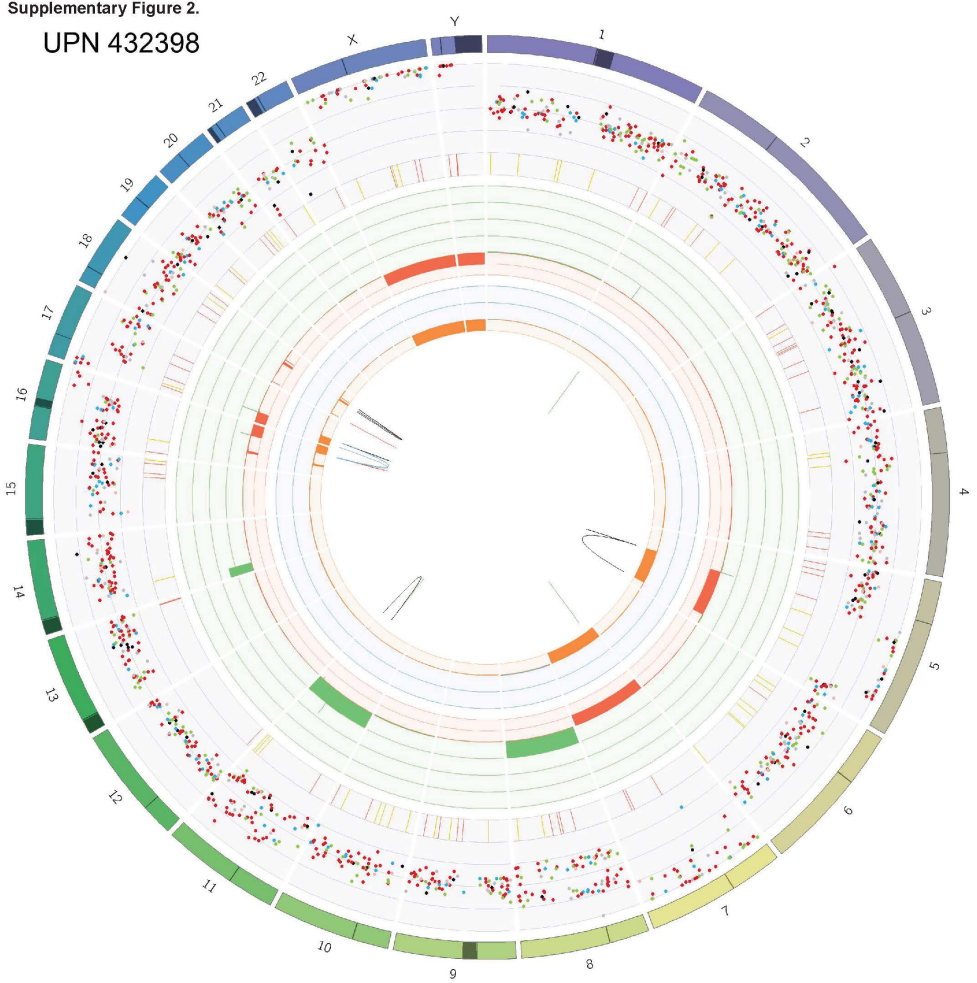

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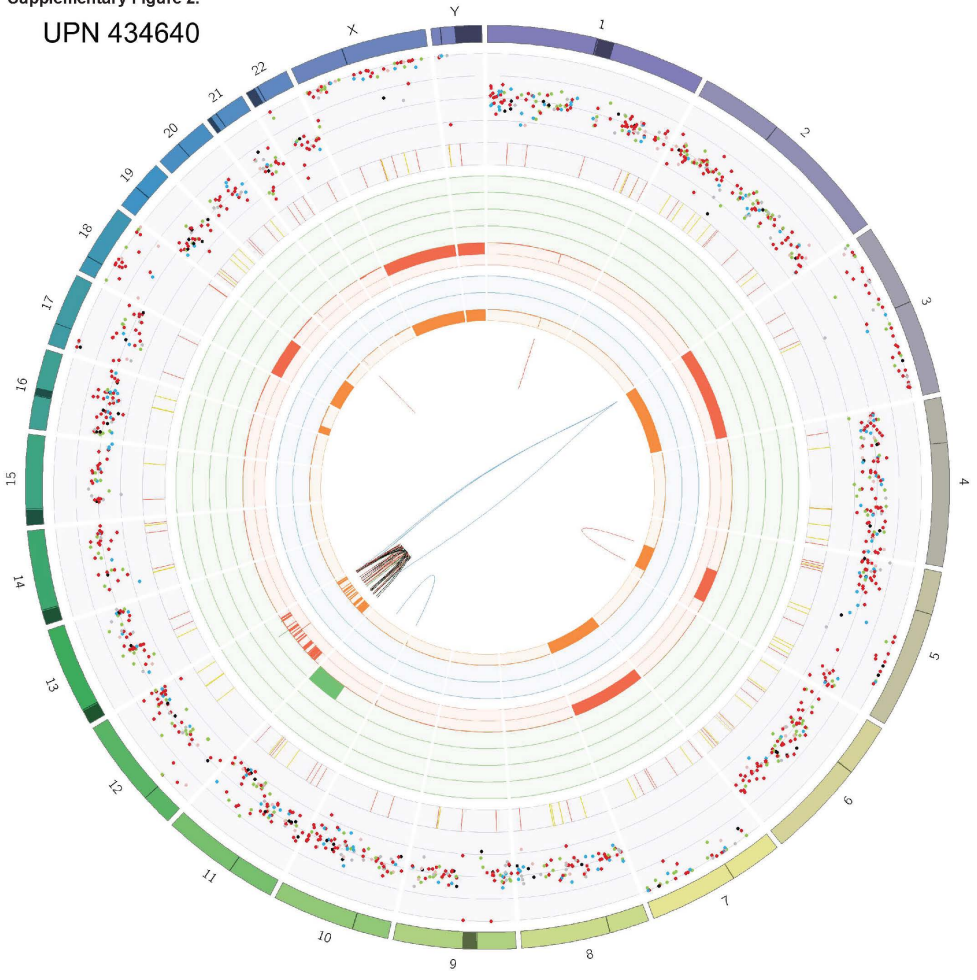

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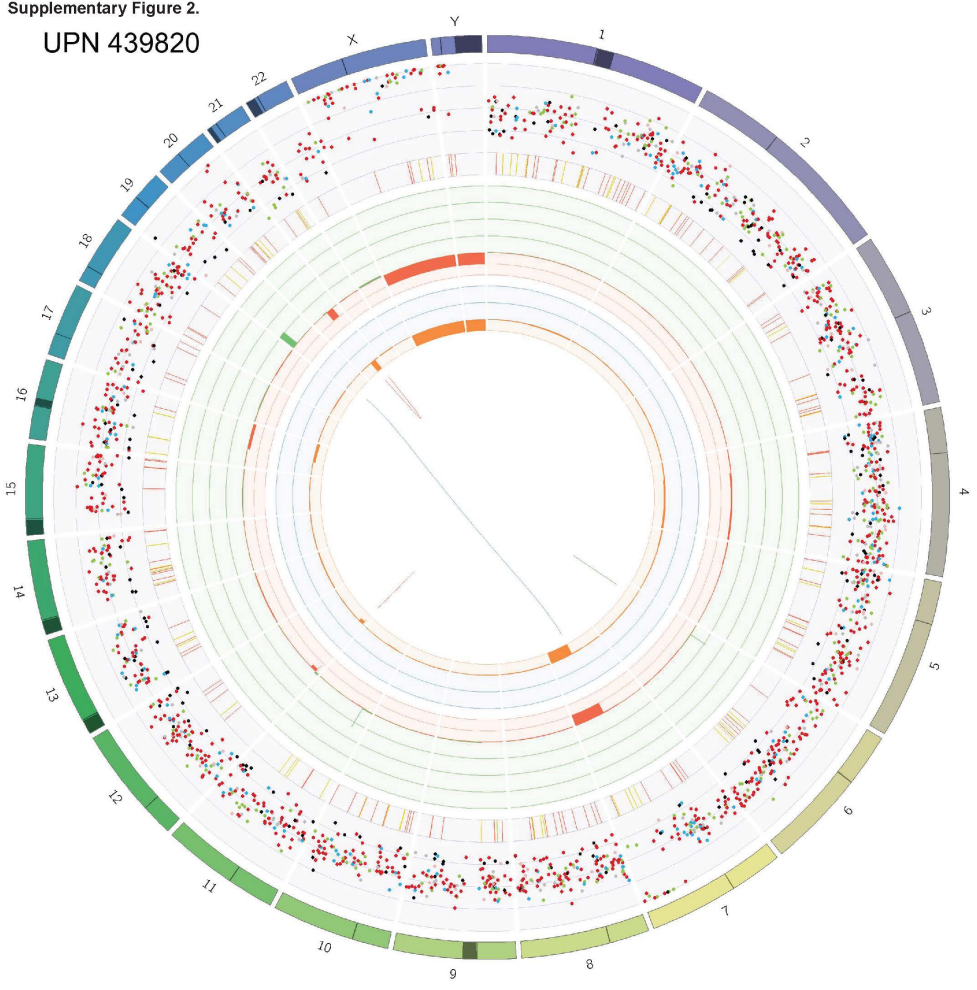

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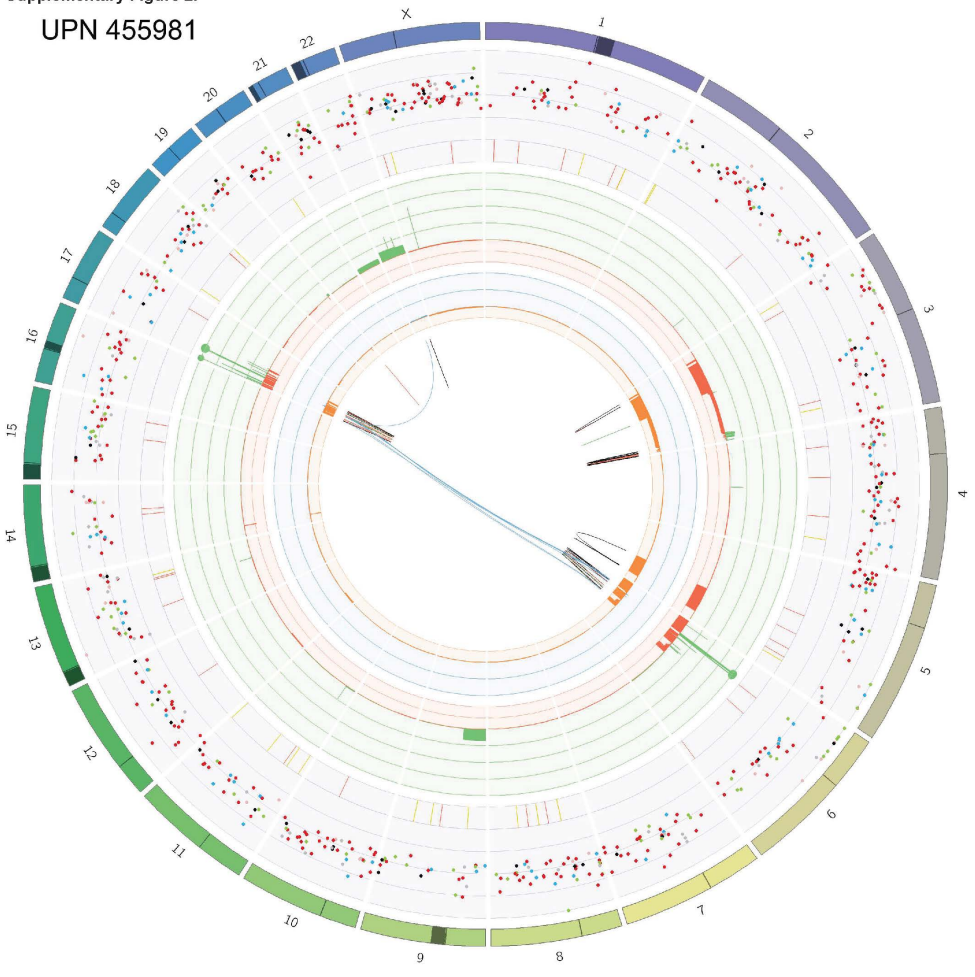

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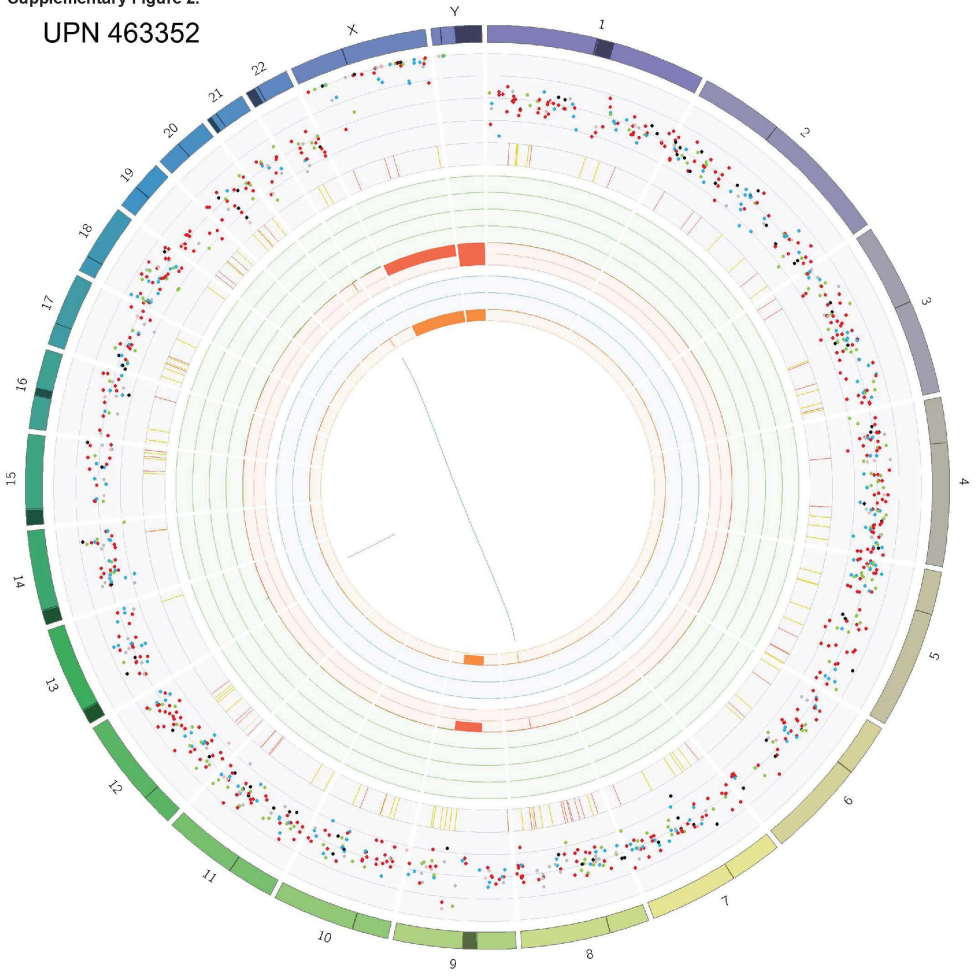

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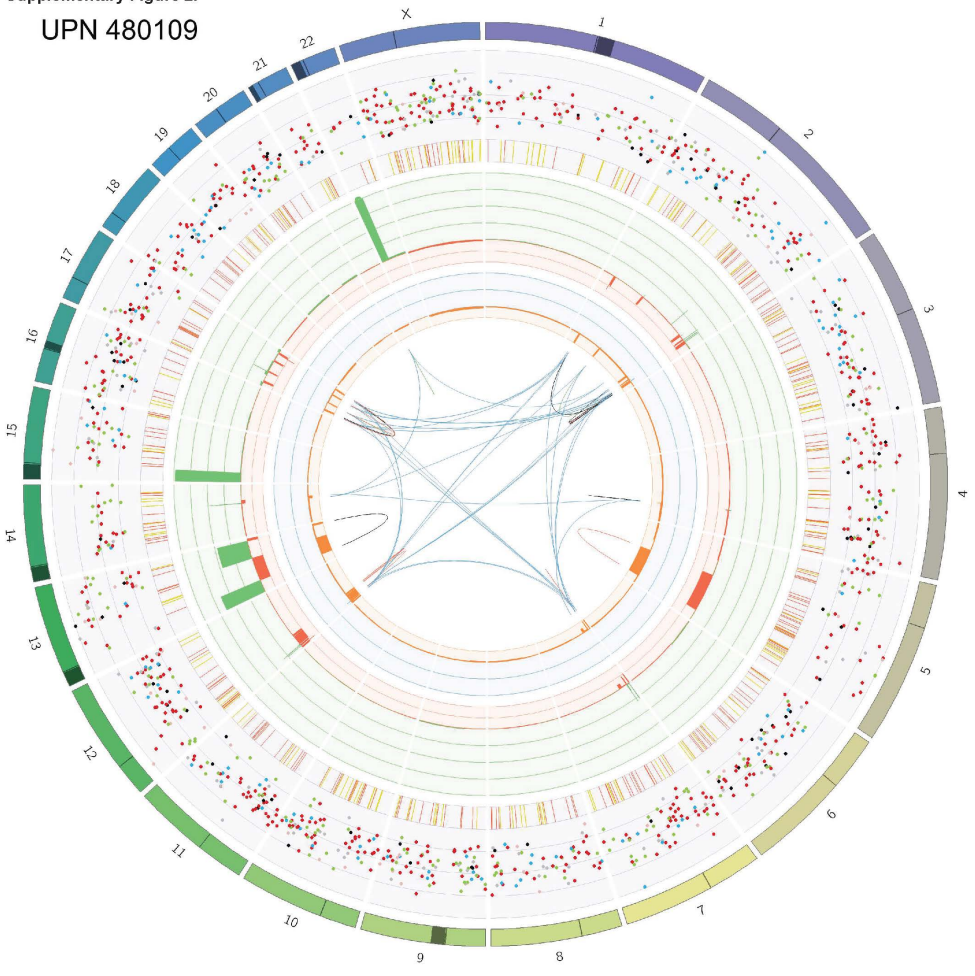

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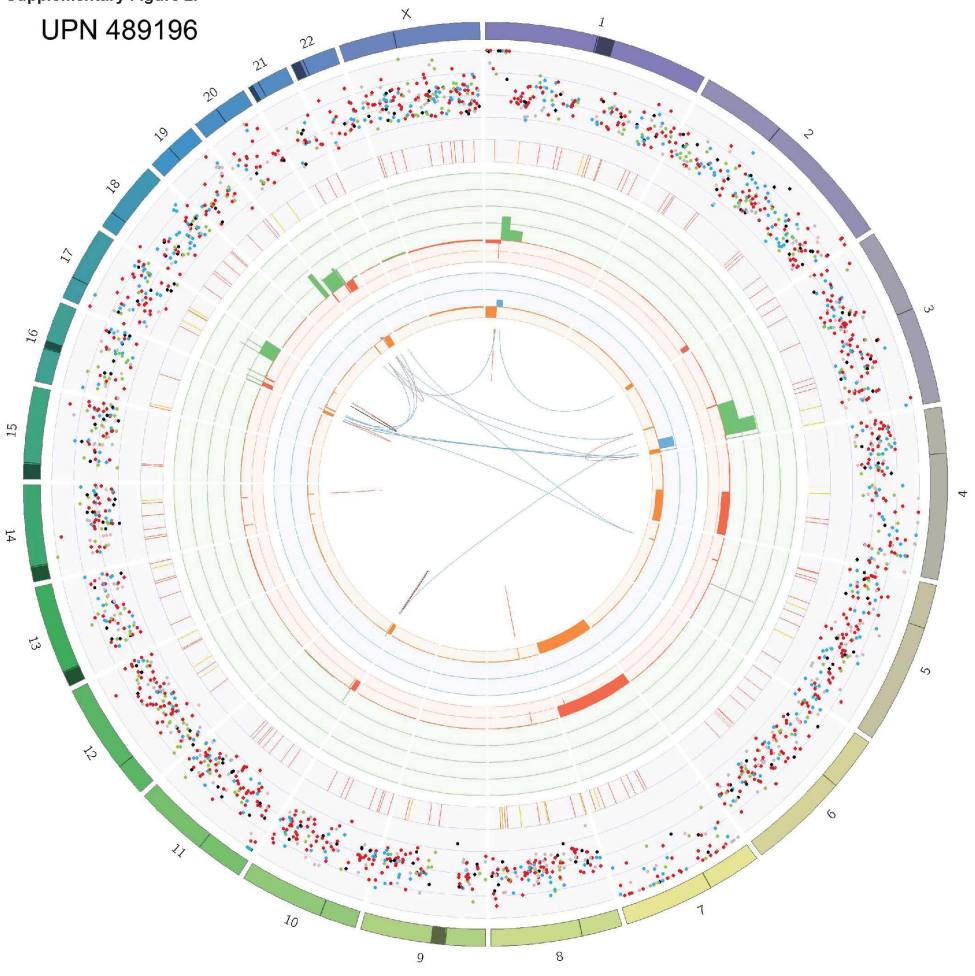

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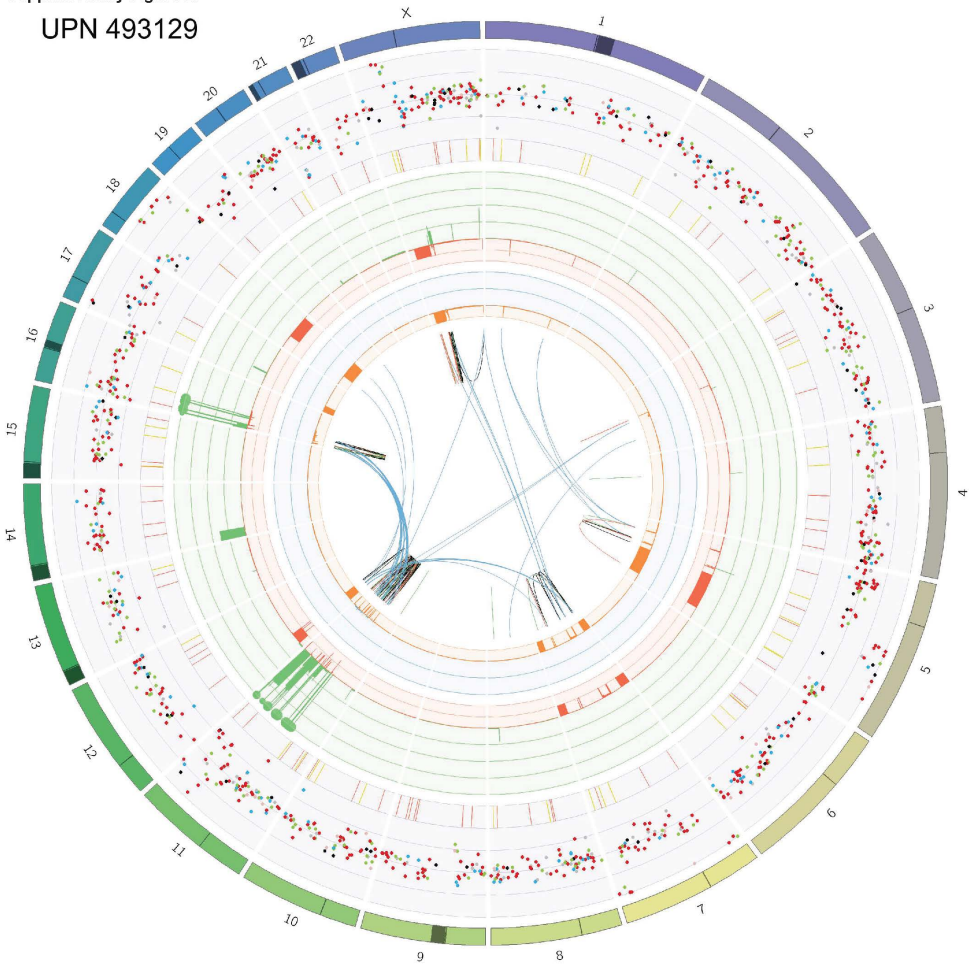

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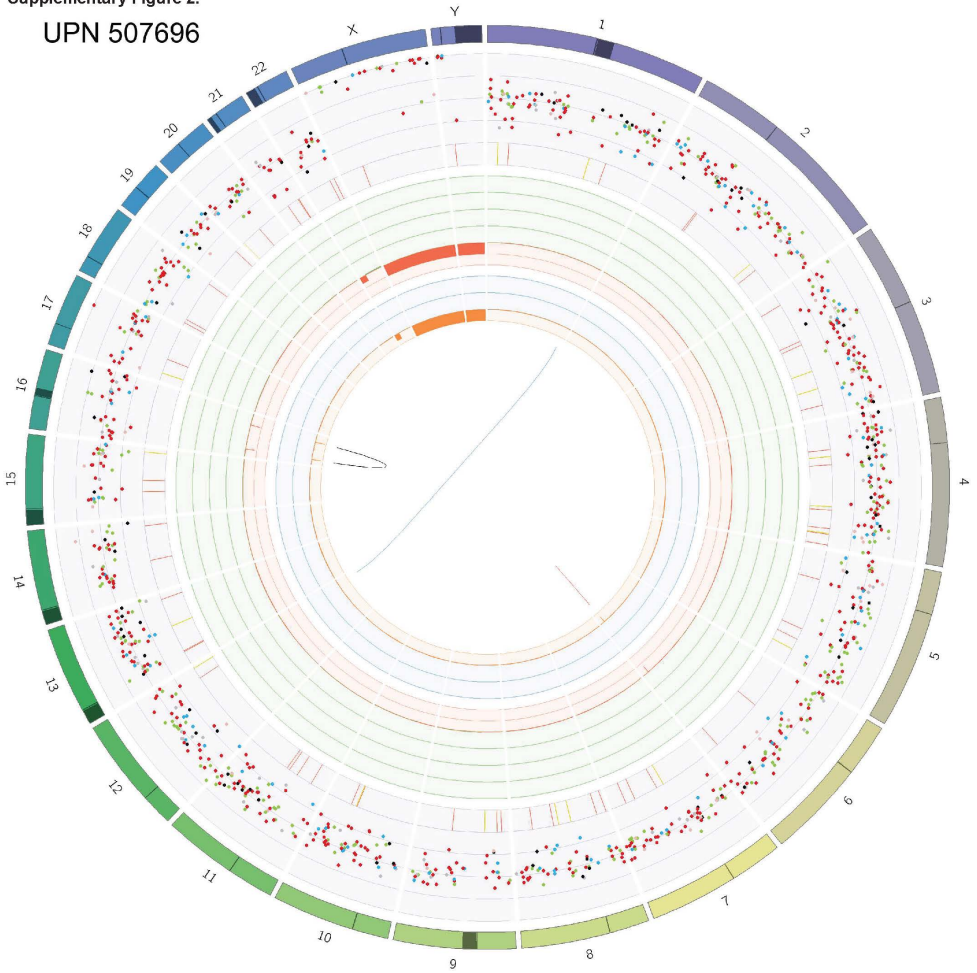

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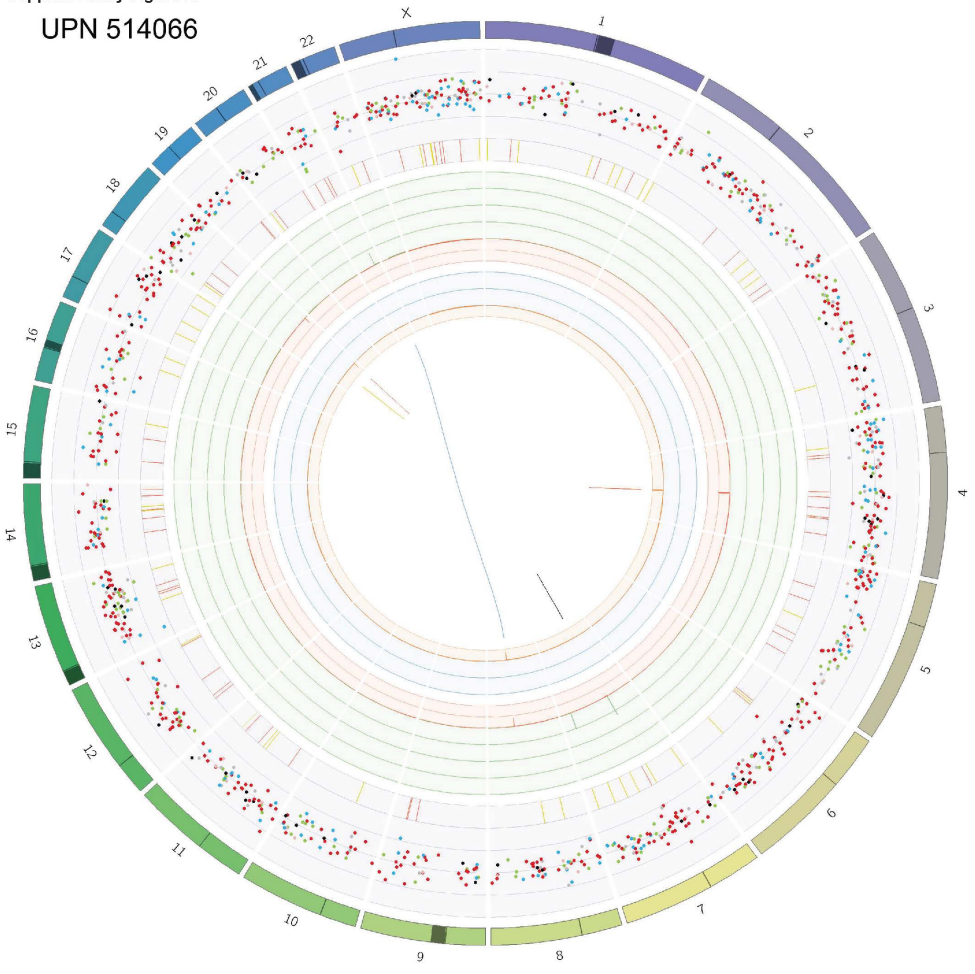

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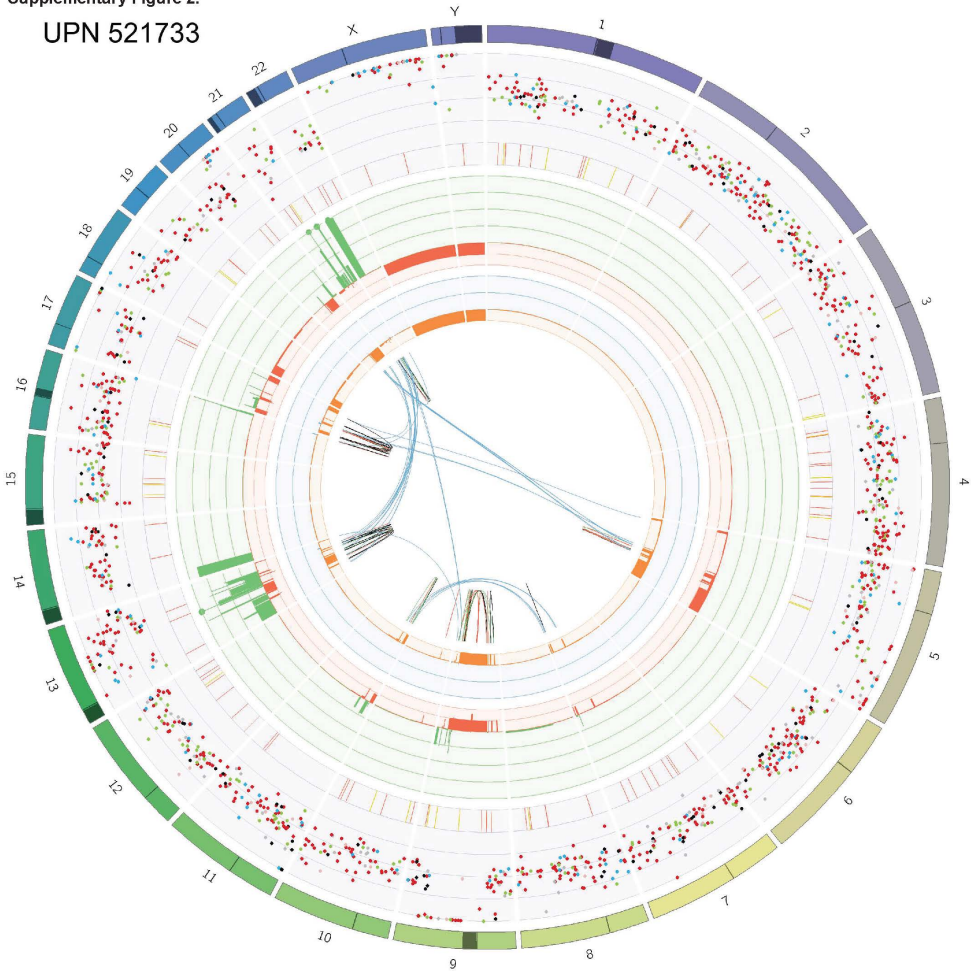

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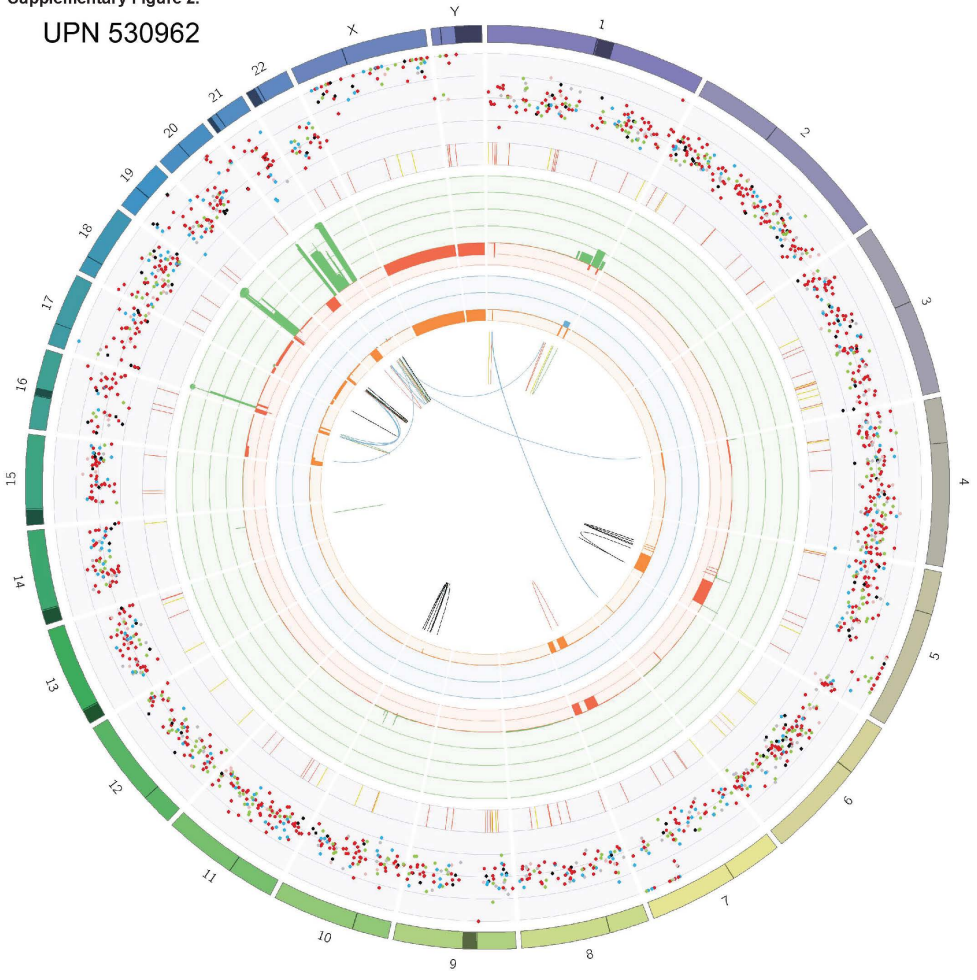

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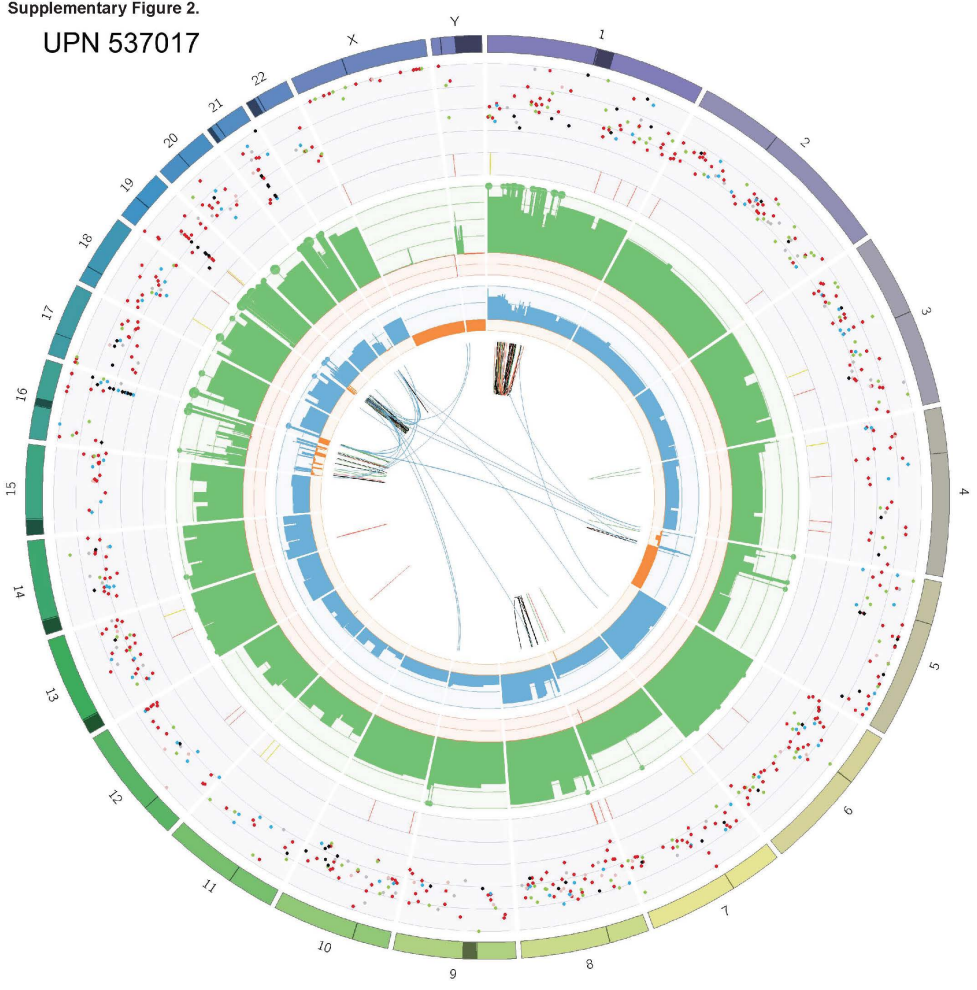

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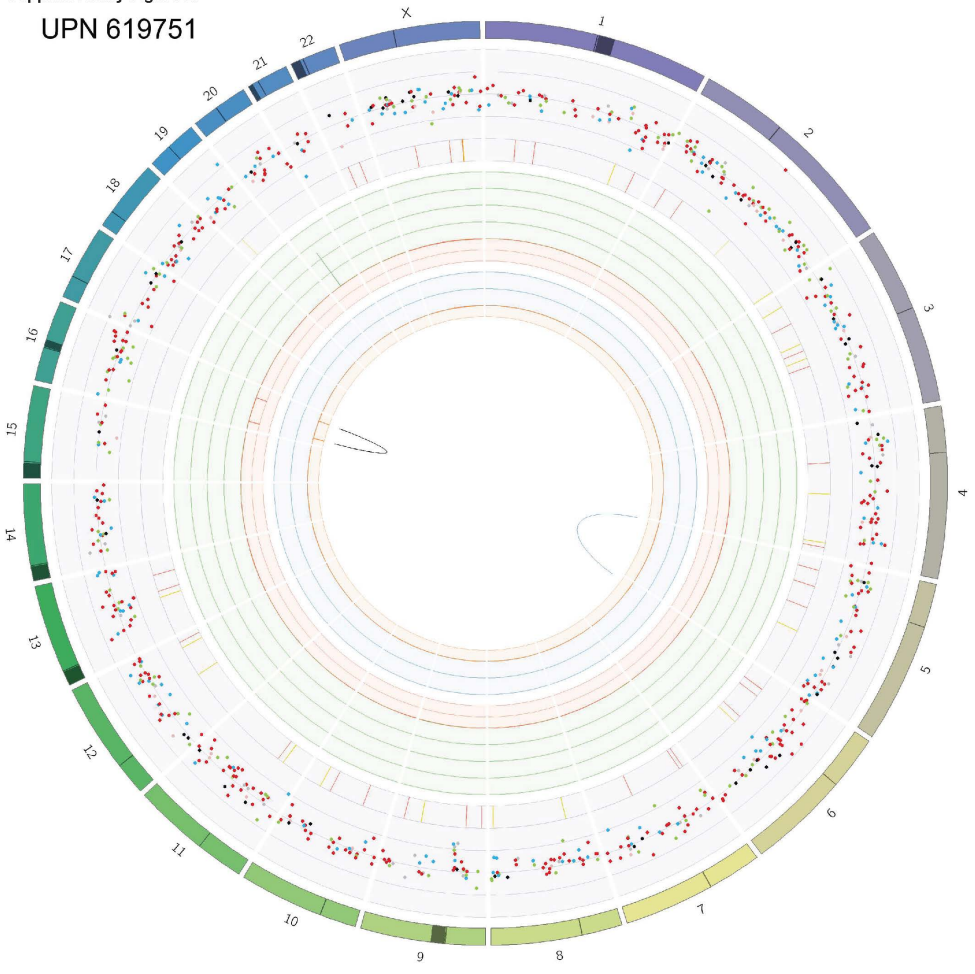

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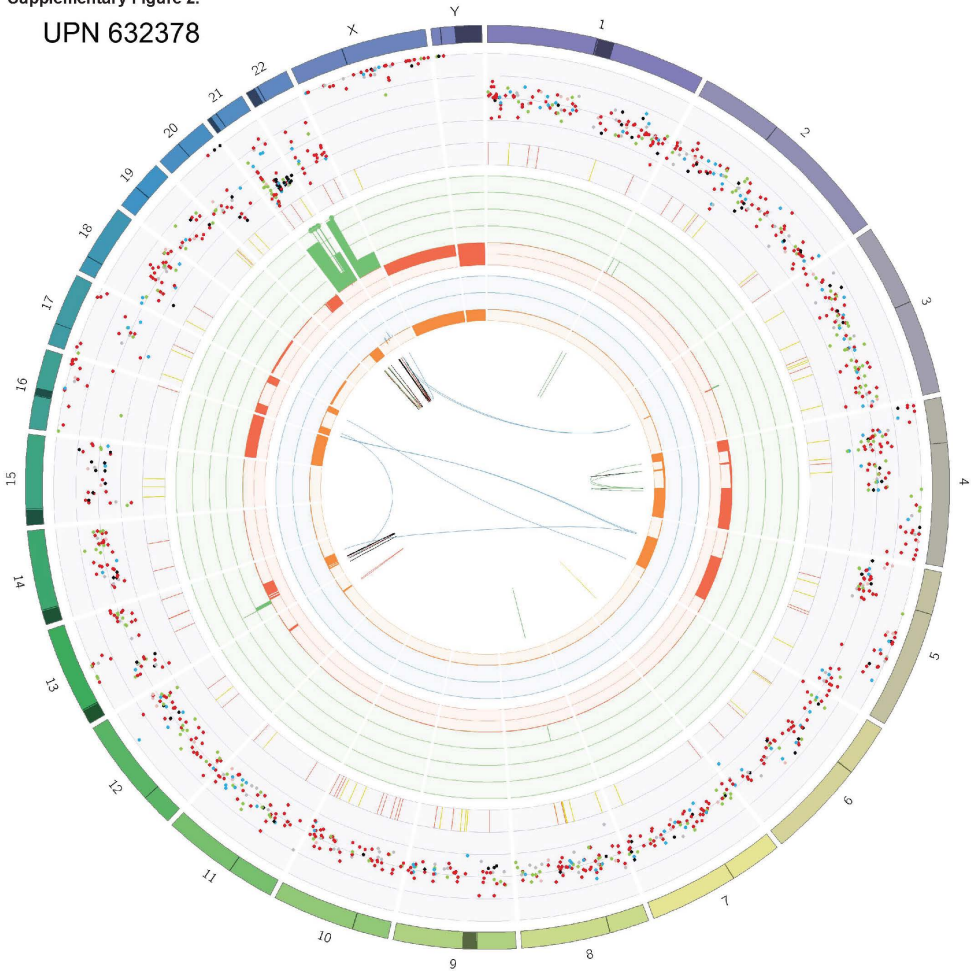

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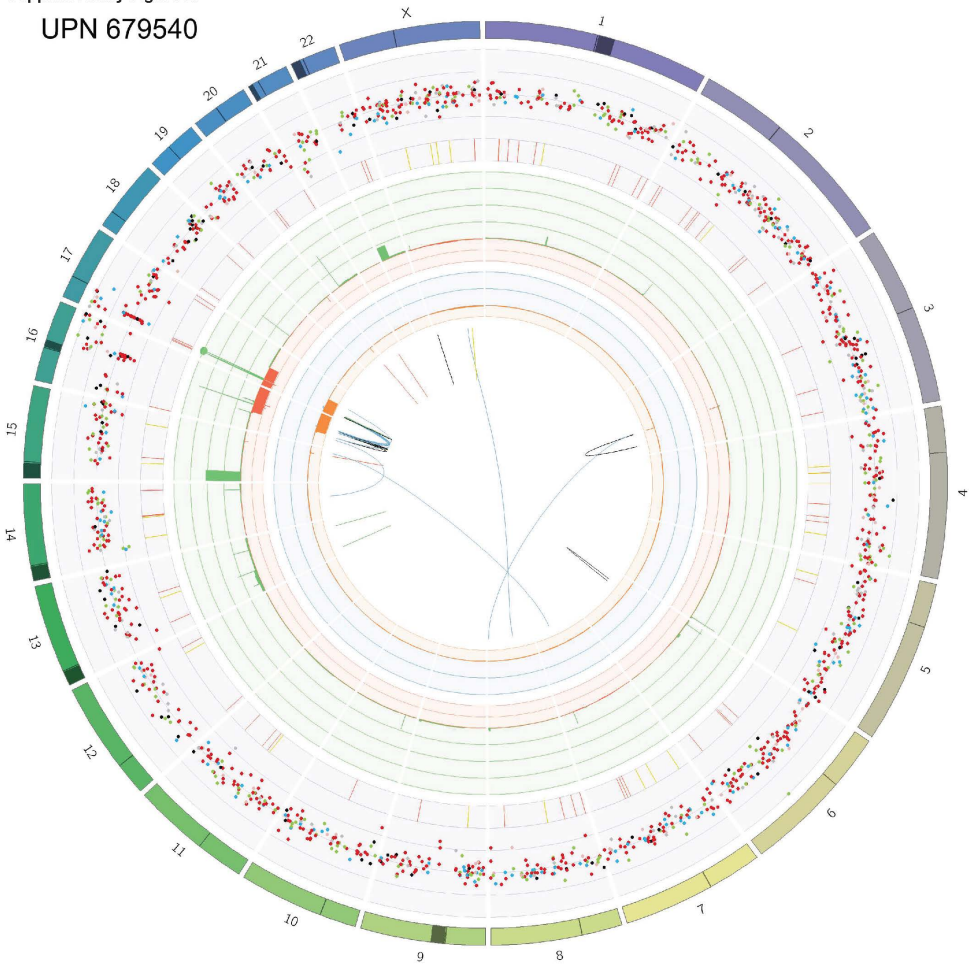

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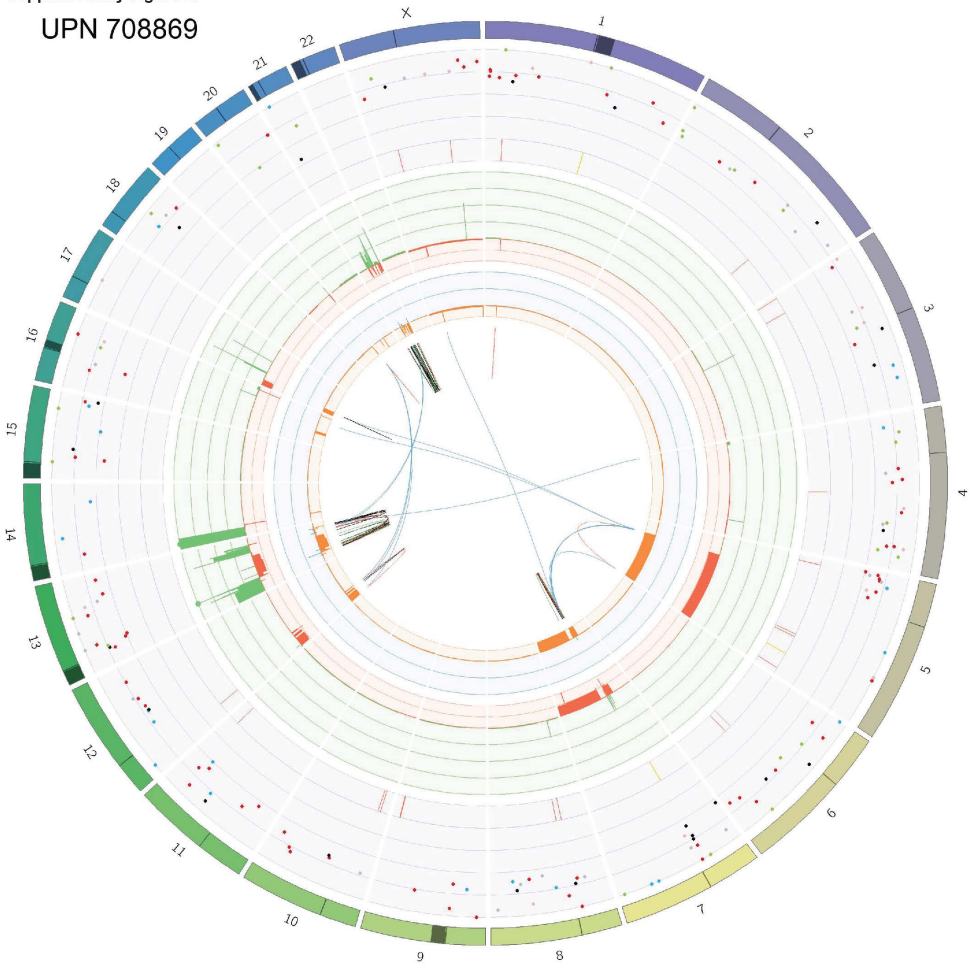

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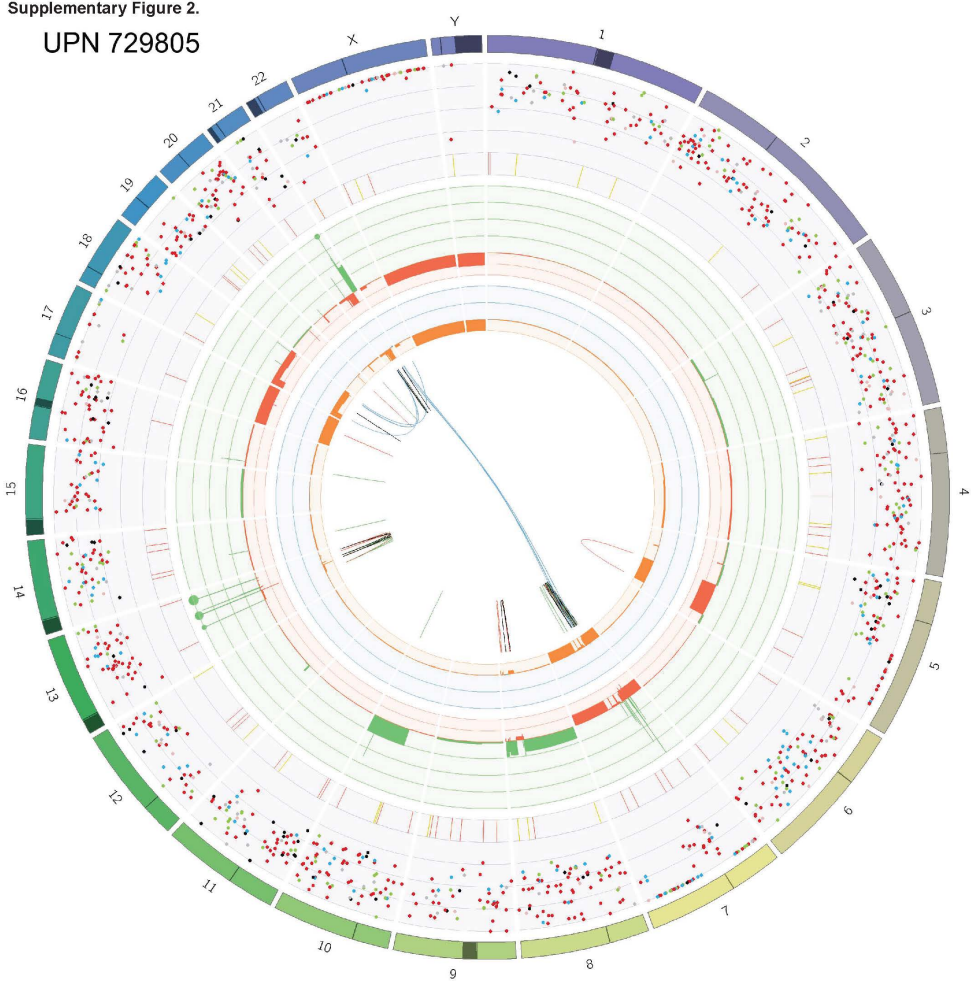

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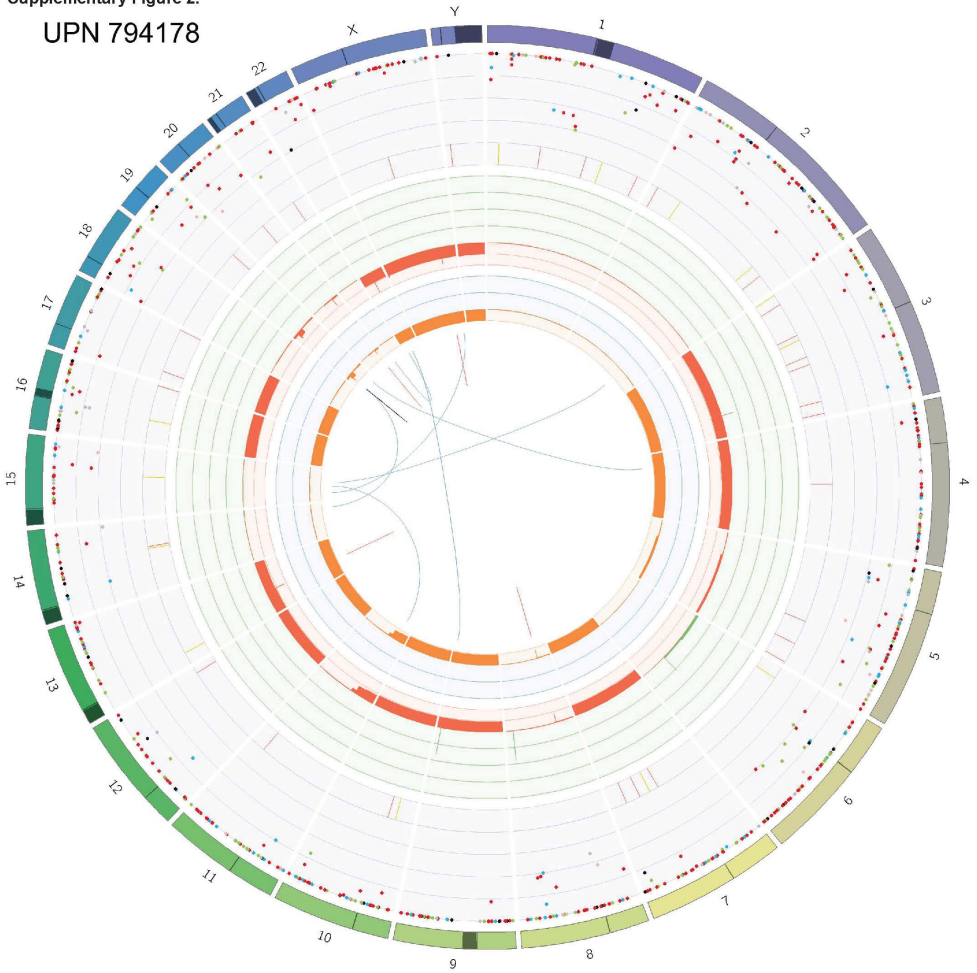

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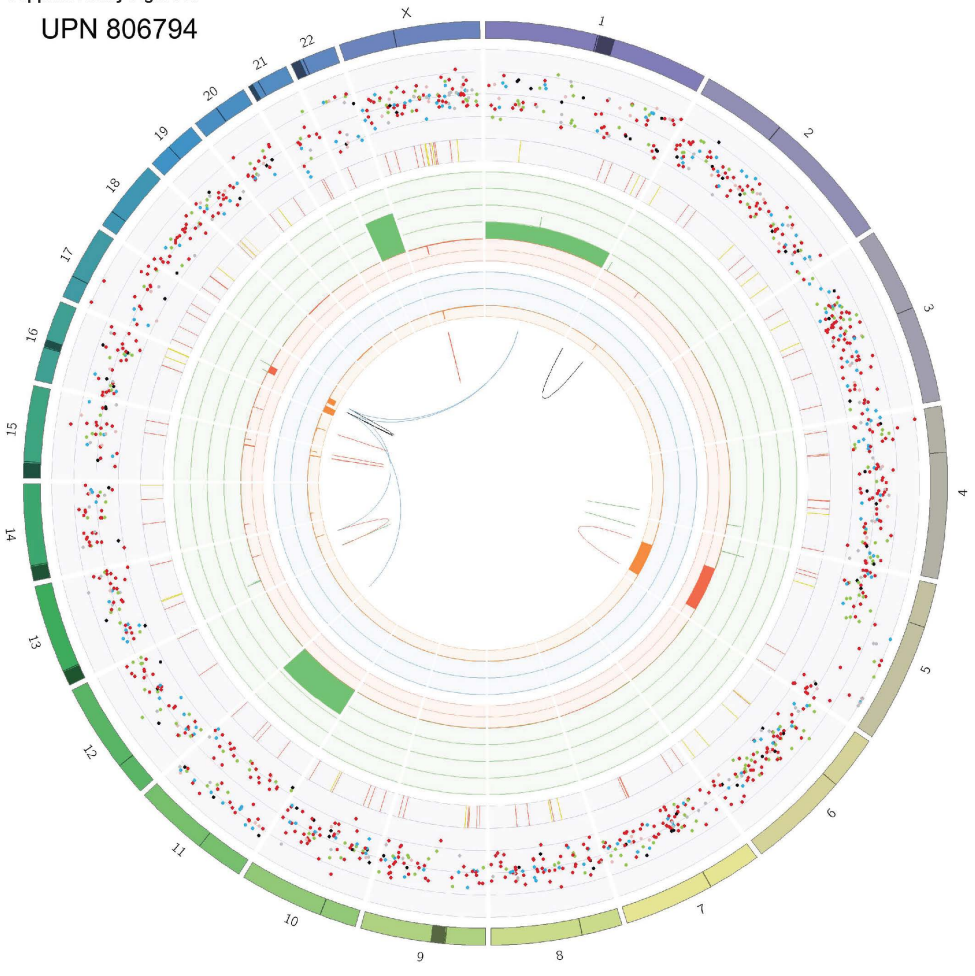

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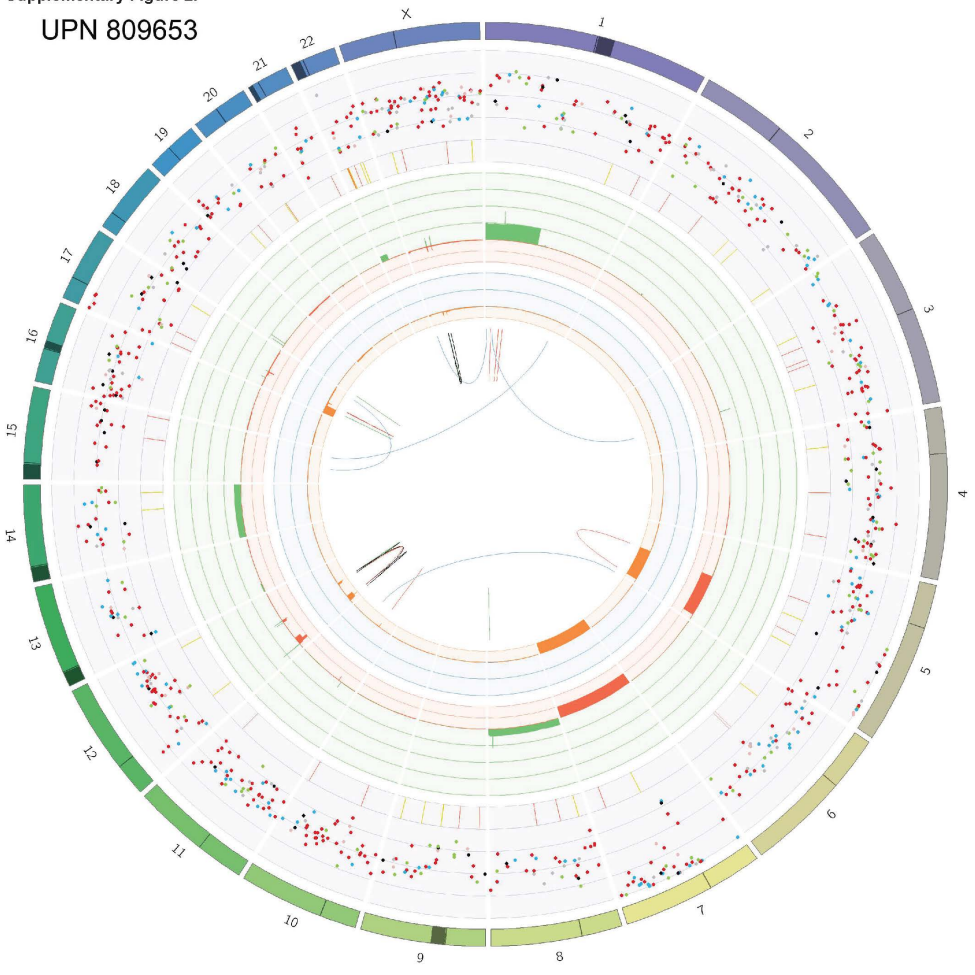

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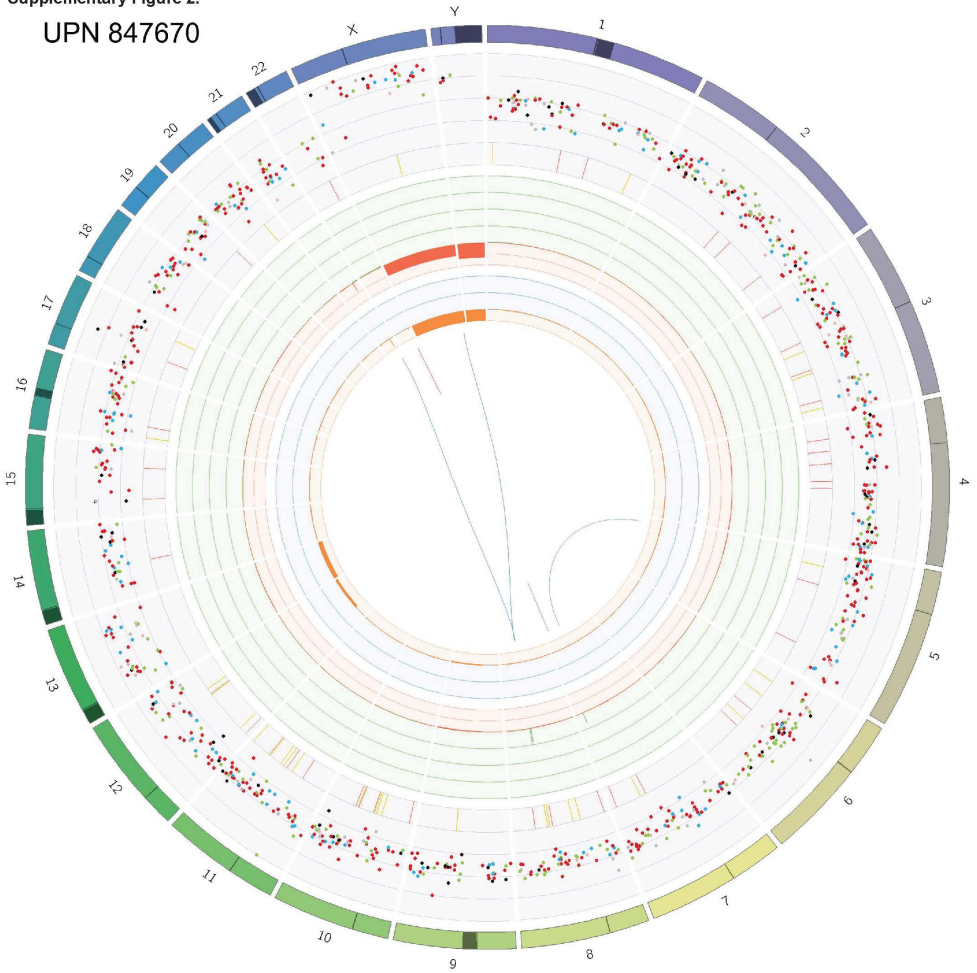

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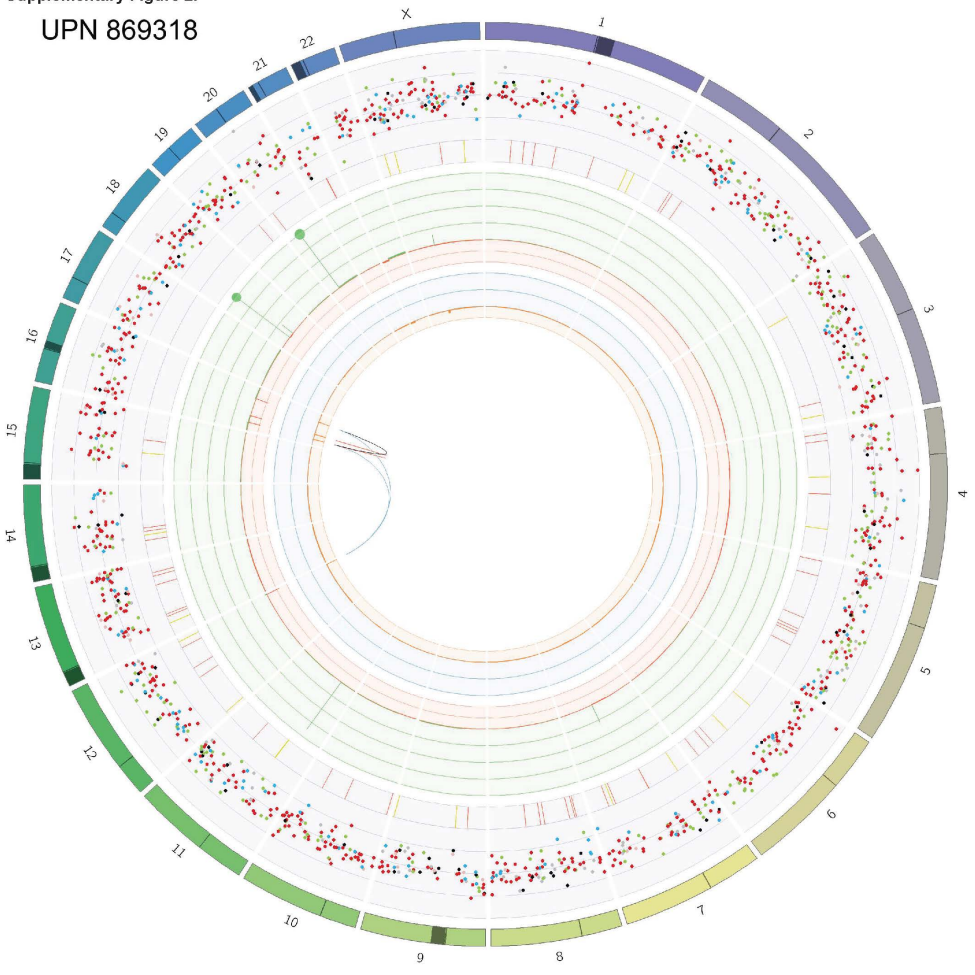

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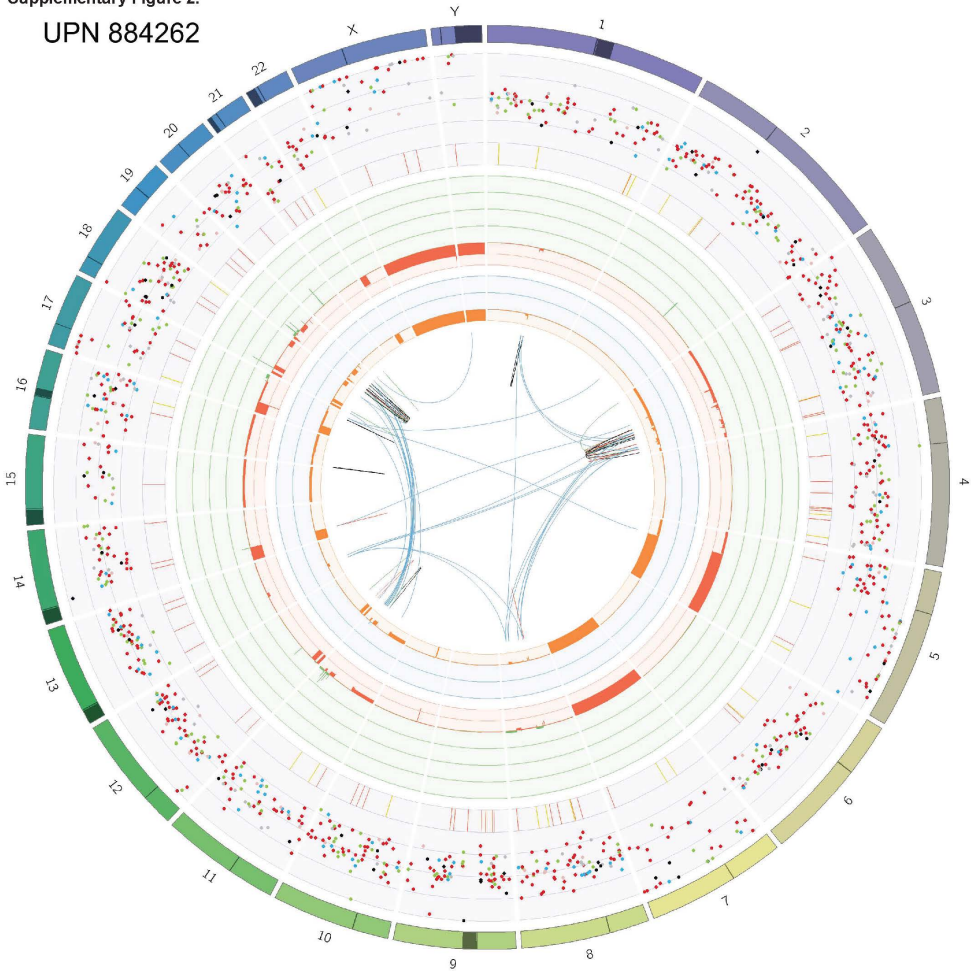

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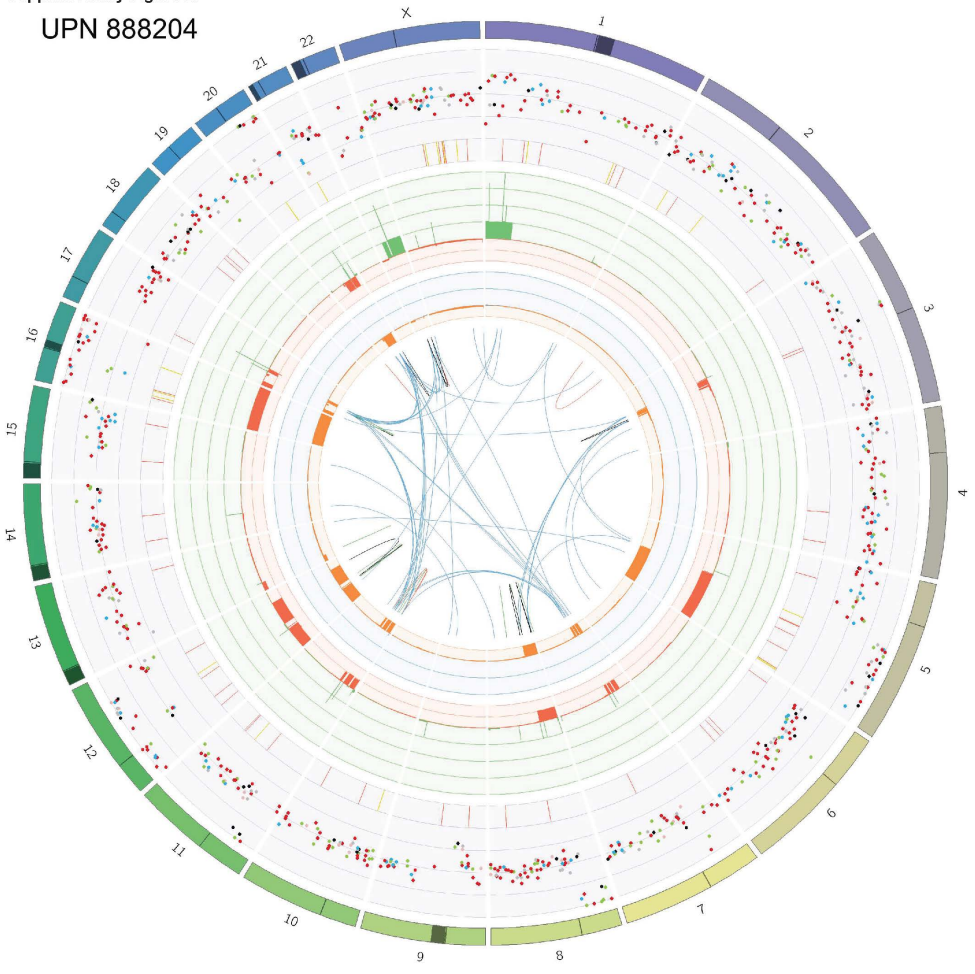

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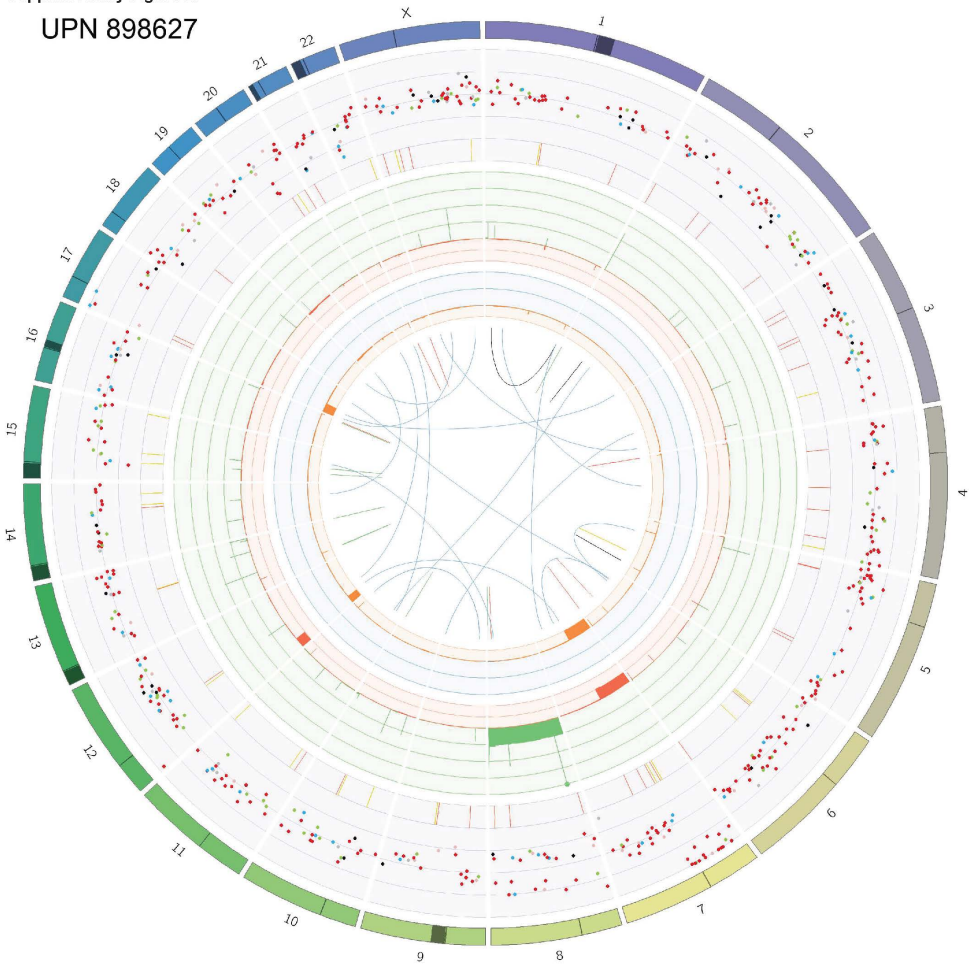

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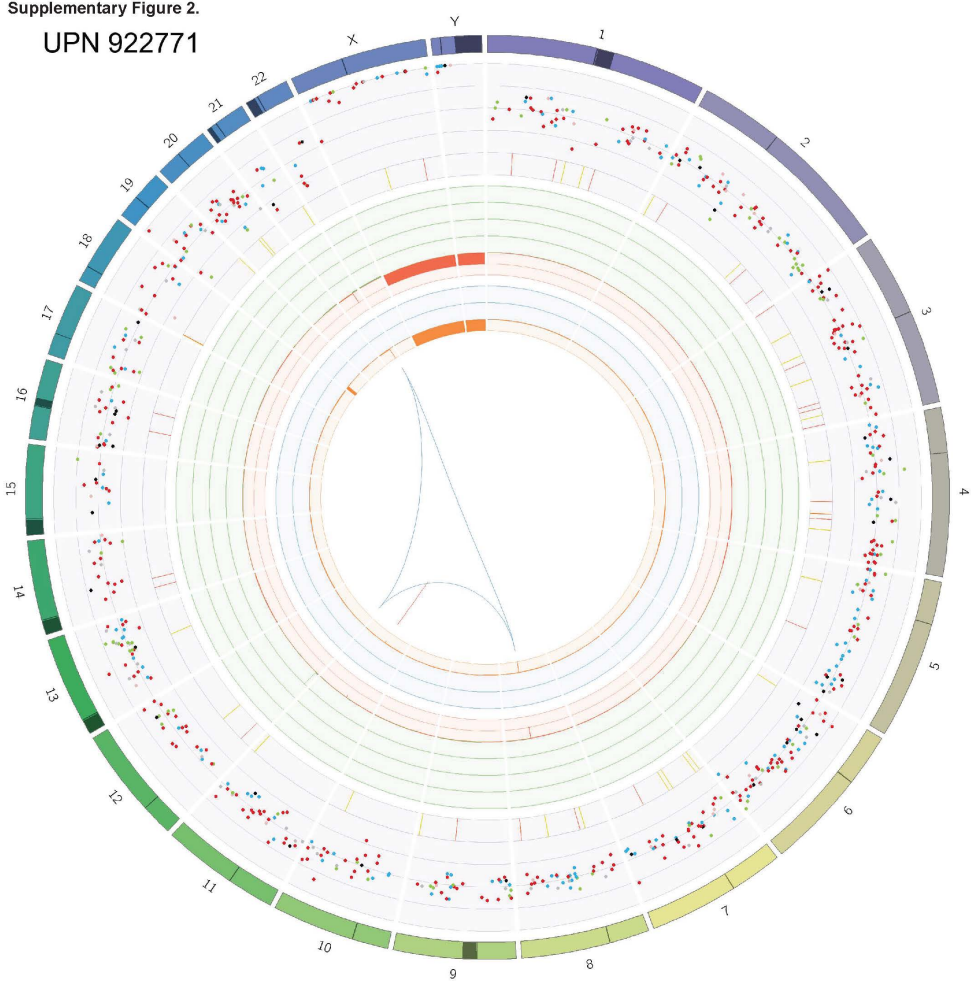

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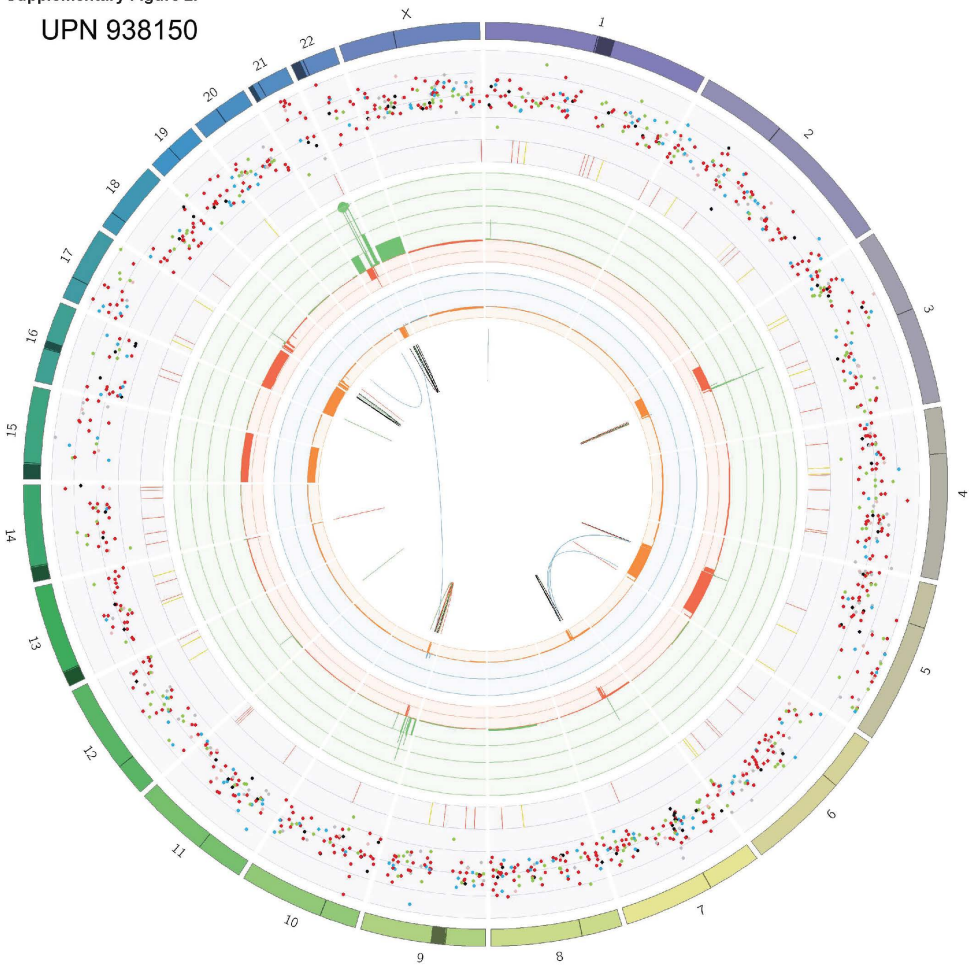

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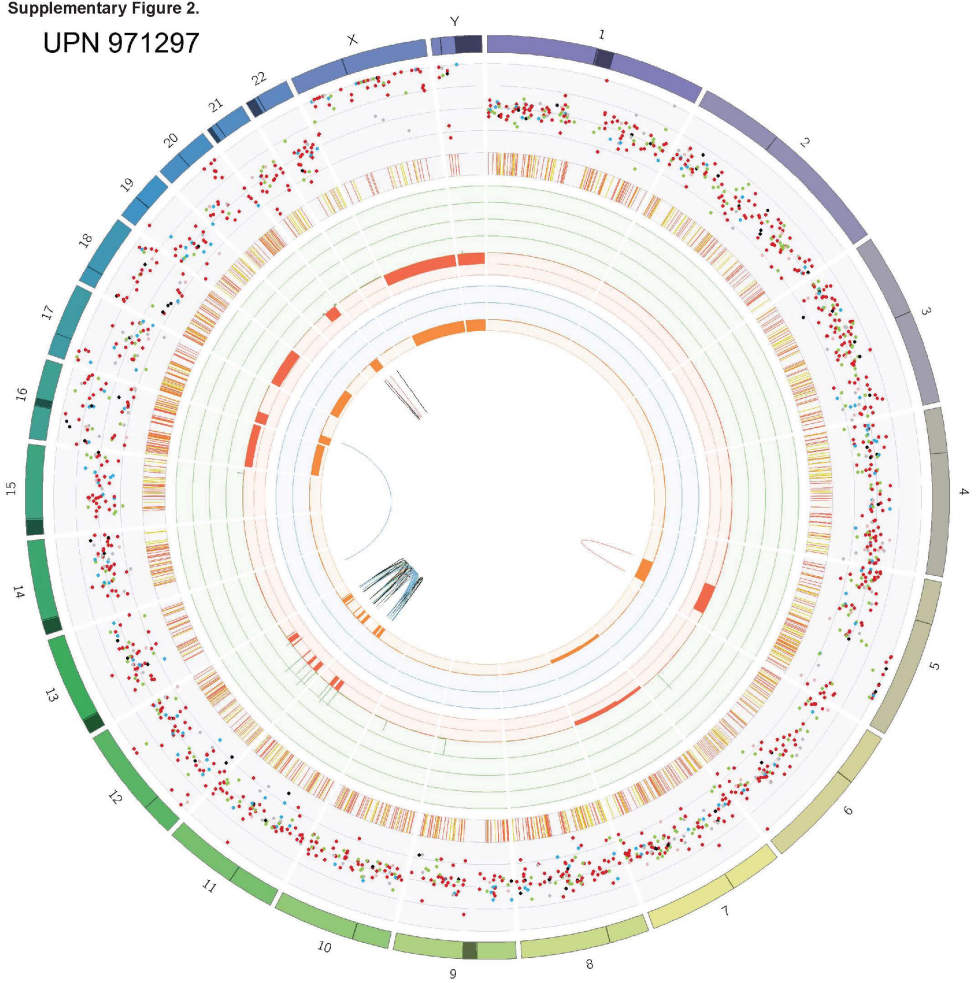

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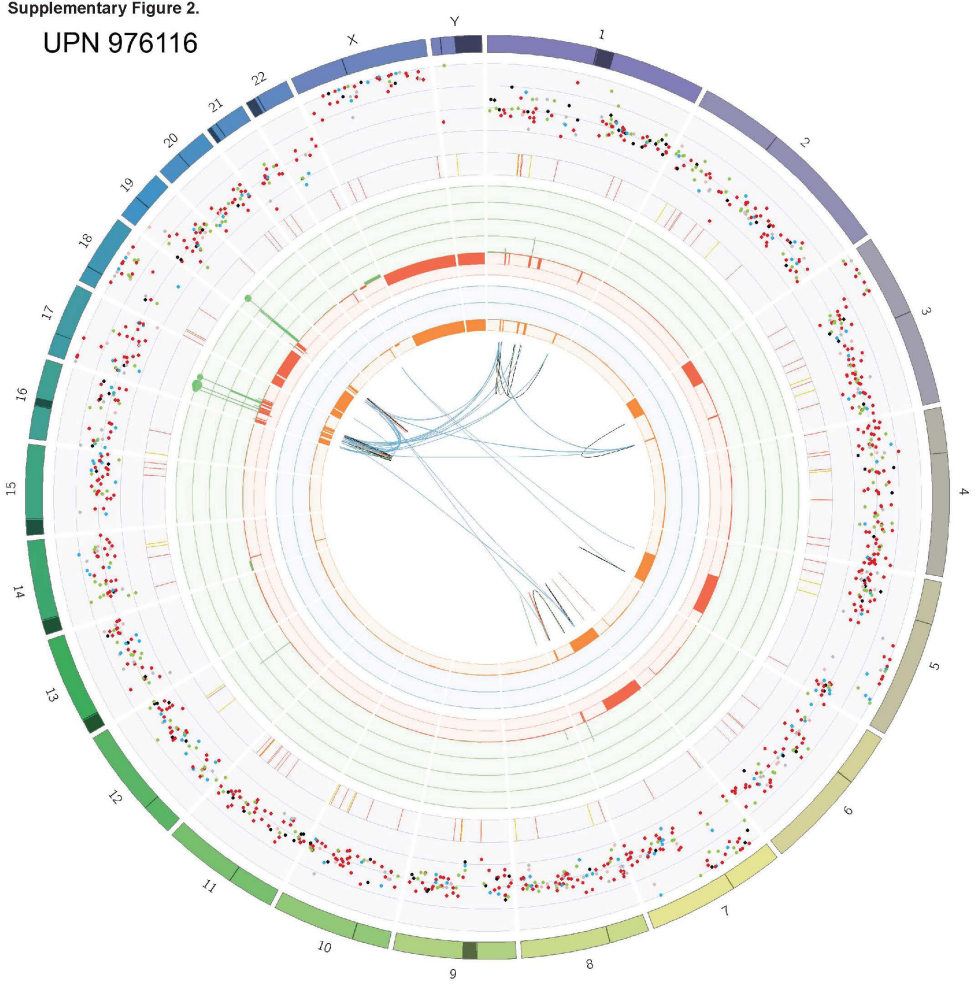

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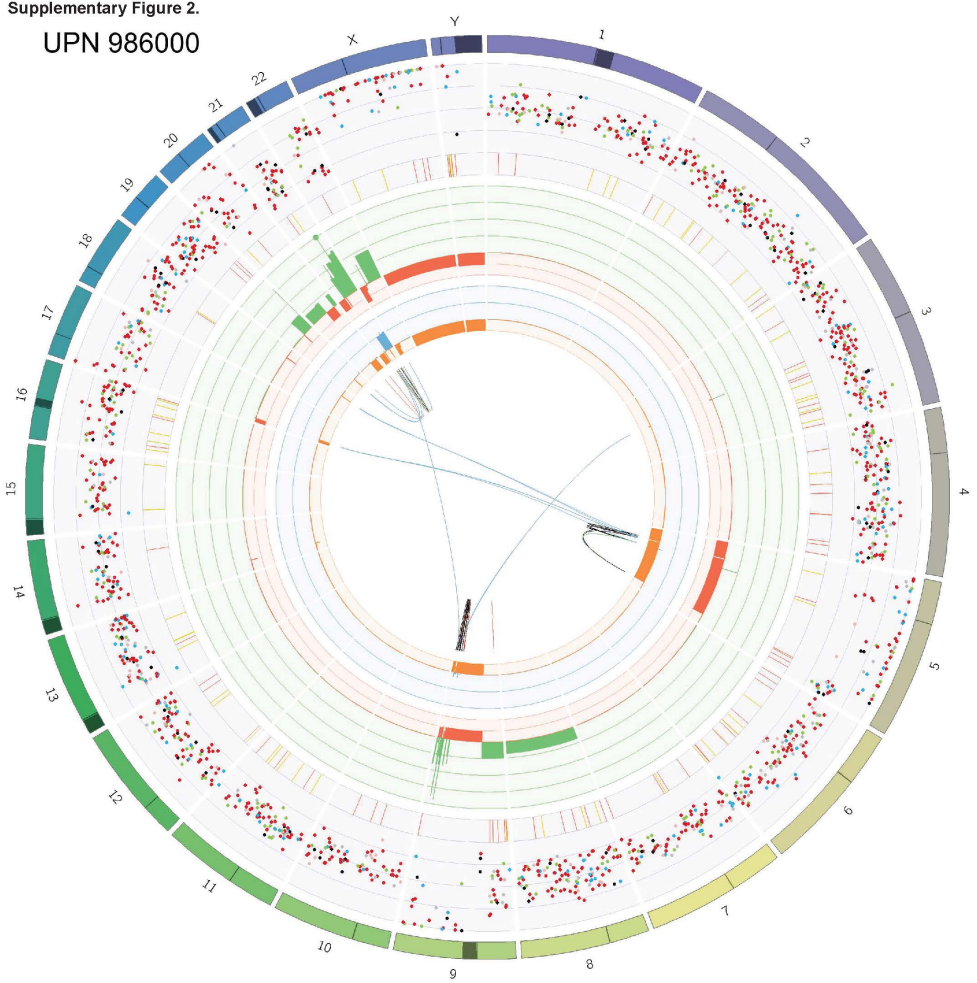

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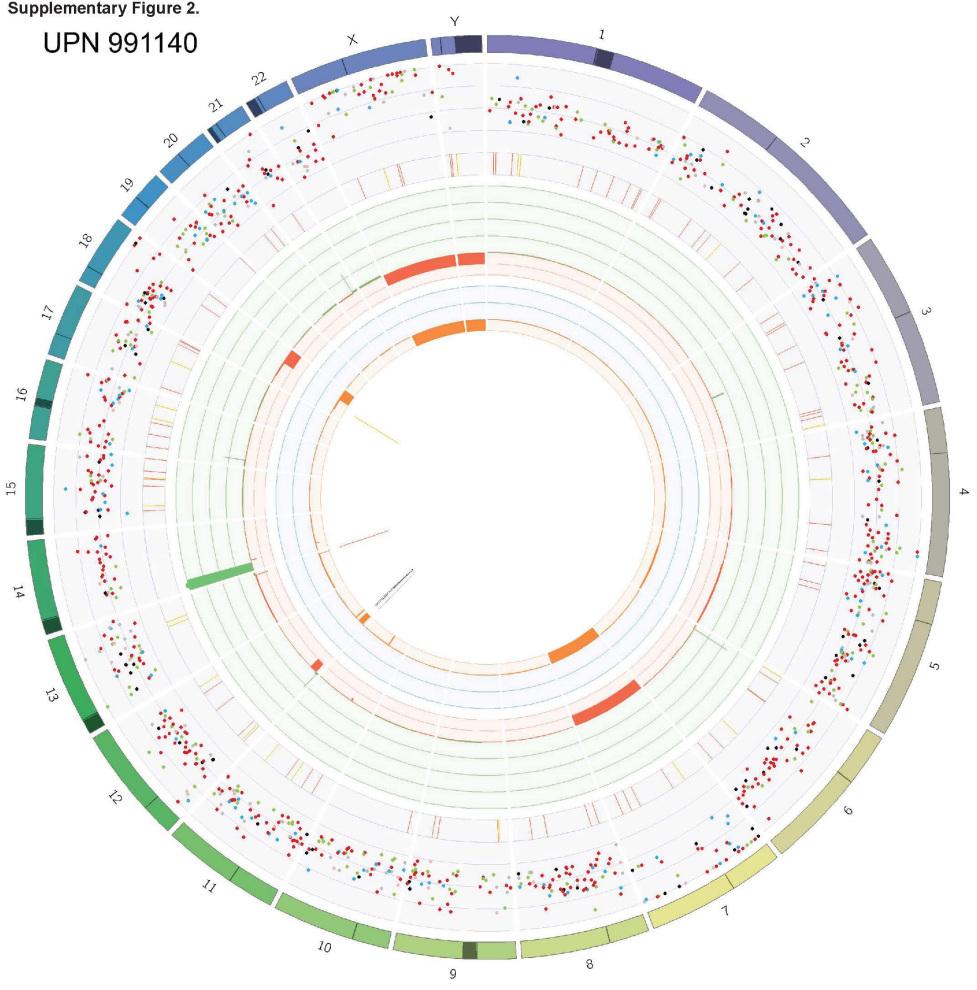

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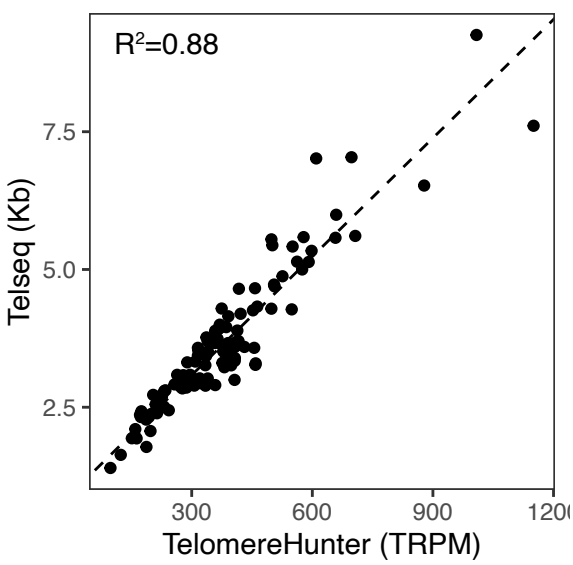

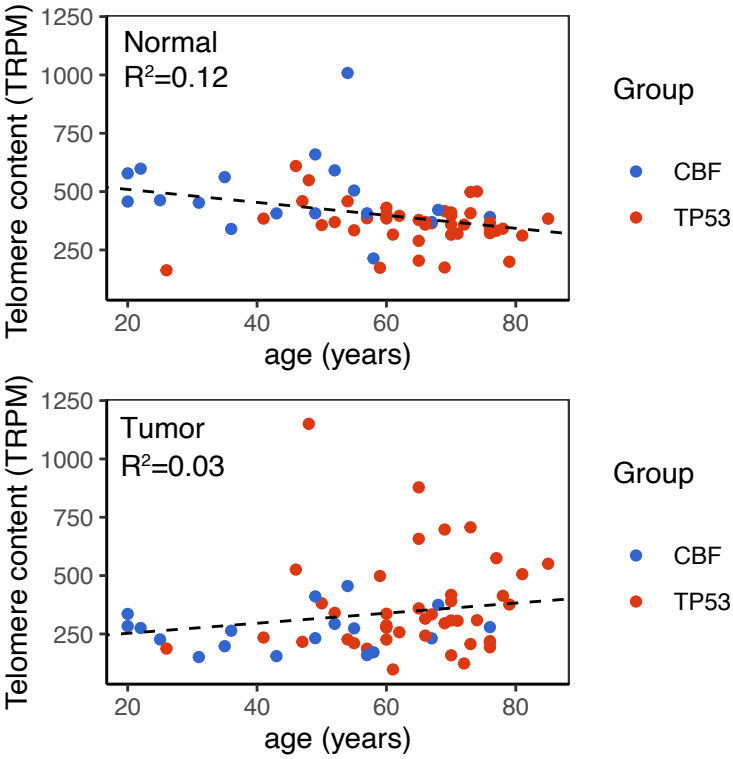

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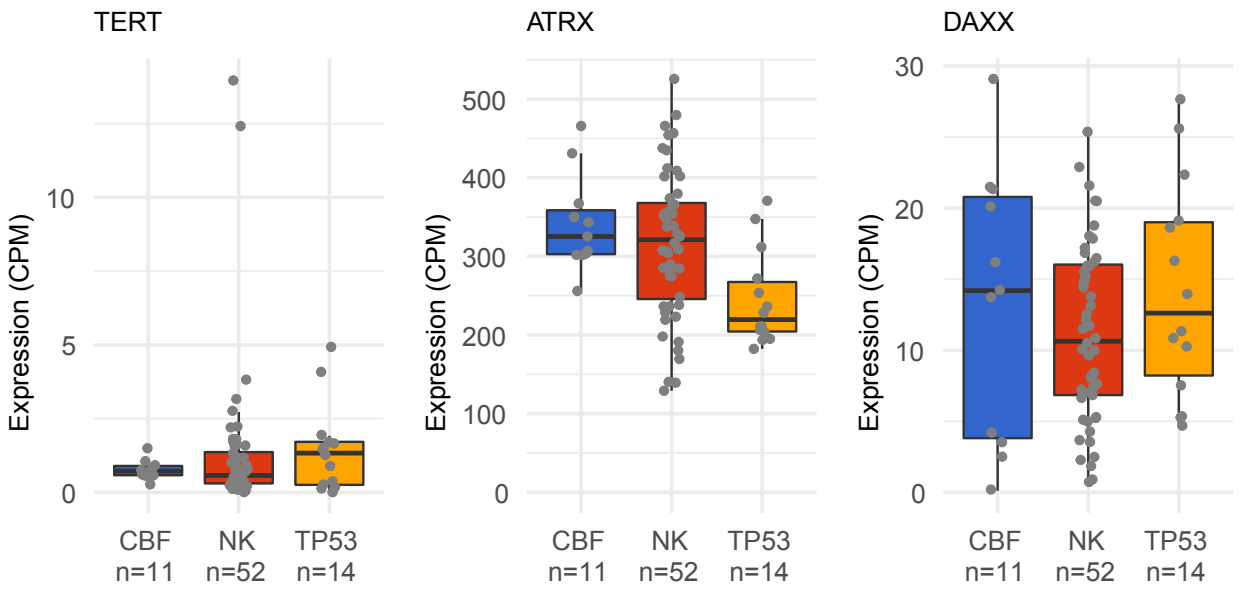

Supplementary Figure 5