Whole genome analysis of chordoma

4th International Research Workshop

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21 March 2013

Acknowledgements

- David Huntsman
- Torsten Nielsen
- Farzad Jamshidi
- Leah Prentice

The Terry Fox Research Institute
L'Institut de recherche Terry Fox

Chordoma Foundaion

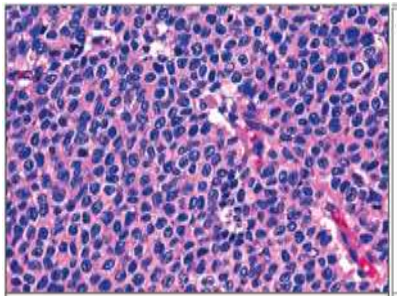
- Sohrab Shah
- Karey Shumansky

- Mt Sinai Hospital – Toronto
- UCSF (Joanna Phillips)
- Mayo Clinic
- MGH

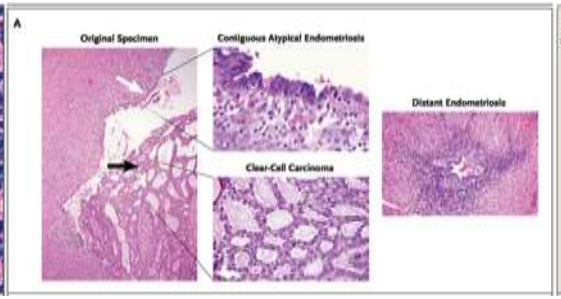
Forme Fruste Tumour Profiling

- TFRI/CIHR
- David Huntsman

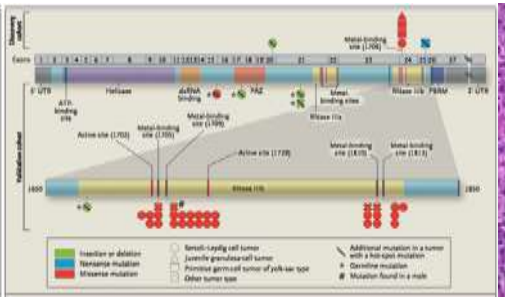
- “Clinically and pathologically homogenous tumour types, presumed to be driven by a limited number of genetic events”



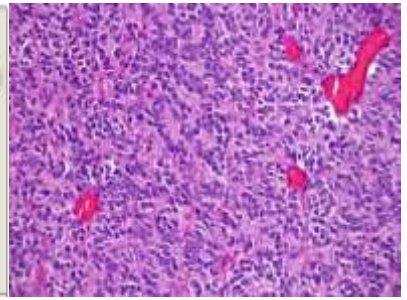
FOXL2
Granulosa Cell Tumour of the Ovary



ARID1A
Endometriosis associated Ovarian Ca



DICER1
Sex cord stromal tumour



CIC
Oligodendroglioma

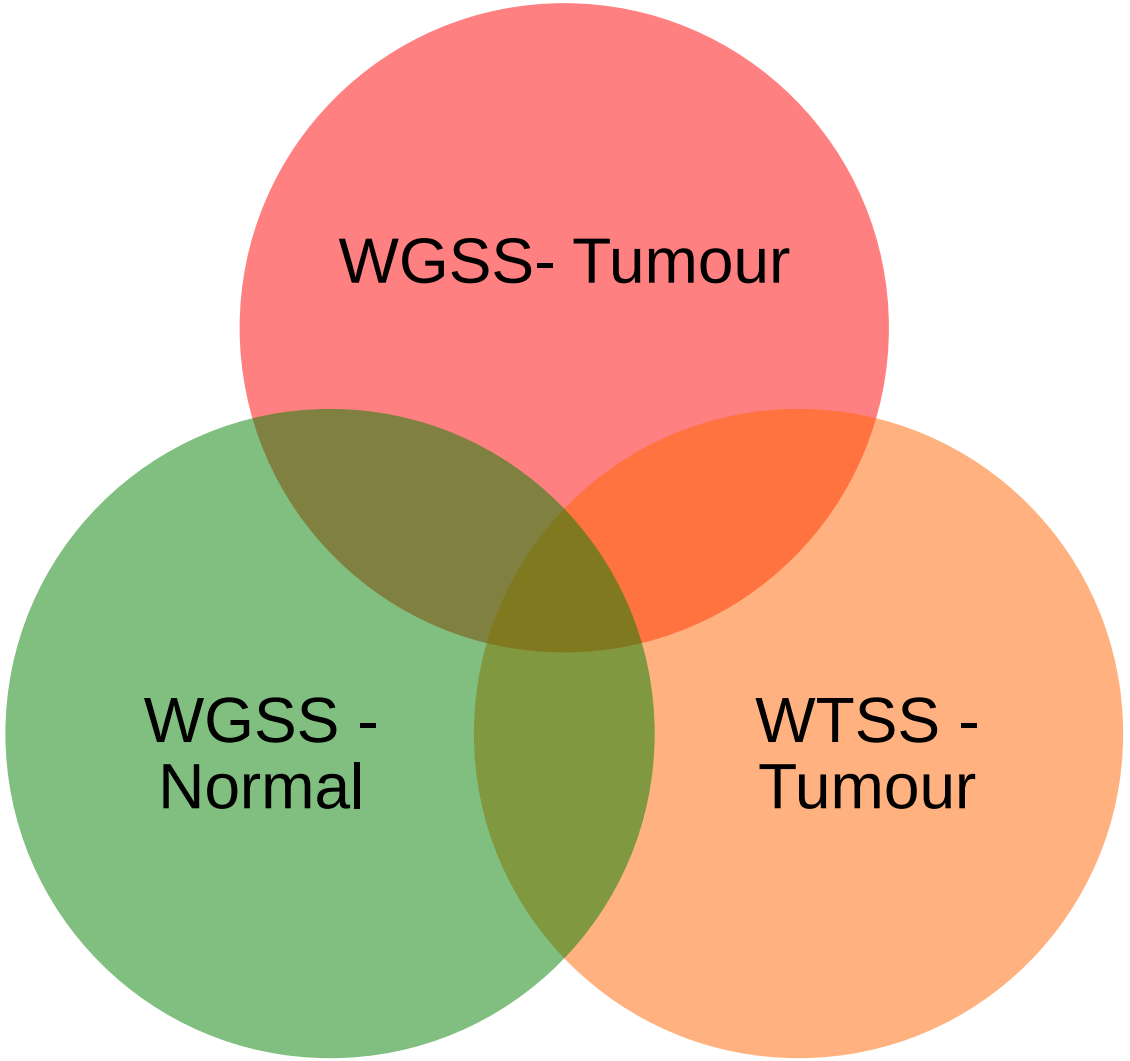
- Chordoma, Epithelial sarcoma, GI carcinoids

Update on BCCA sequencing of chordoma specimens

		Whole Transcriptome Sequencing				Exome Sequencing		Whole Genome Sequencing	
	SNP 6.0	SNV	INDEL	FUSION	RPKM	SNV	INDEL	SNV	INDEL
1T	Y	N	N	Y	N	n/a	n/a	Y	Y
1N	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Y	n/a
2T	Y	Y	N	Y	N	n/a	n/a	Y	Y
2N	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Y	n/a
3T	N	Y	Y	Y	Y	Y	Y	n/a	n/a
4T	Y	n/a	n/a	n/a	n/a	Y	Y	n/a	n/a
4N	n/a	n/a	n/a	n/a	n/a	Y	?	n/a	n/a
5T	Y	n/a	n/a	n/a	n/a	Y	Y	n/a	n/a
5N	n/a	n/a	n/a	n/a	n/a	?	?	n/a	n/a
6T	Y	n/a	n/a	n/a	n/a	Y	Y	n/a	n/a
6N	n/a	n/a	n/a	n/a	n/a	Y	?	n/a	n/a
7T	Y	n/a	n/a	n/a	n/a	Y	Y	n/a	n/a
7N	n/a	n/a	n/a	n/a	n/a	Y	?	n/a	n/a
8T	Y	n/a	n/a	n/a	n/a	Y	Y	n/a	n/a
8N	n/a	n/a	n/a	n/a	n/a	Y	?	n/a	n/a

Farzad Jamshidi

“Holy Trinities”



Metrics of WGSS

Tumour coverage = 60X
Normal coverage = 30X

- Single Nucleotide Variants
- Copy Number Variants
- Fusion/Translocations

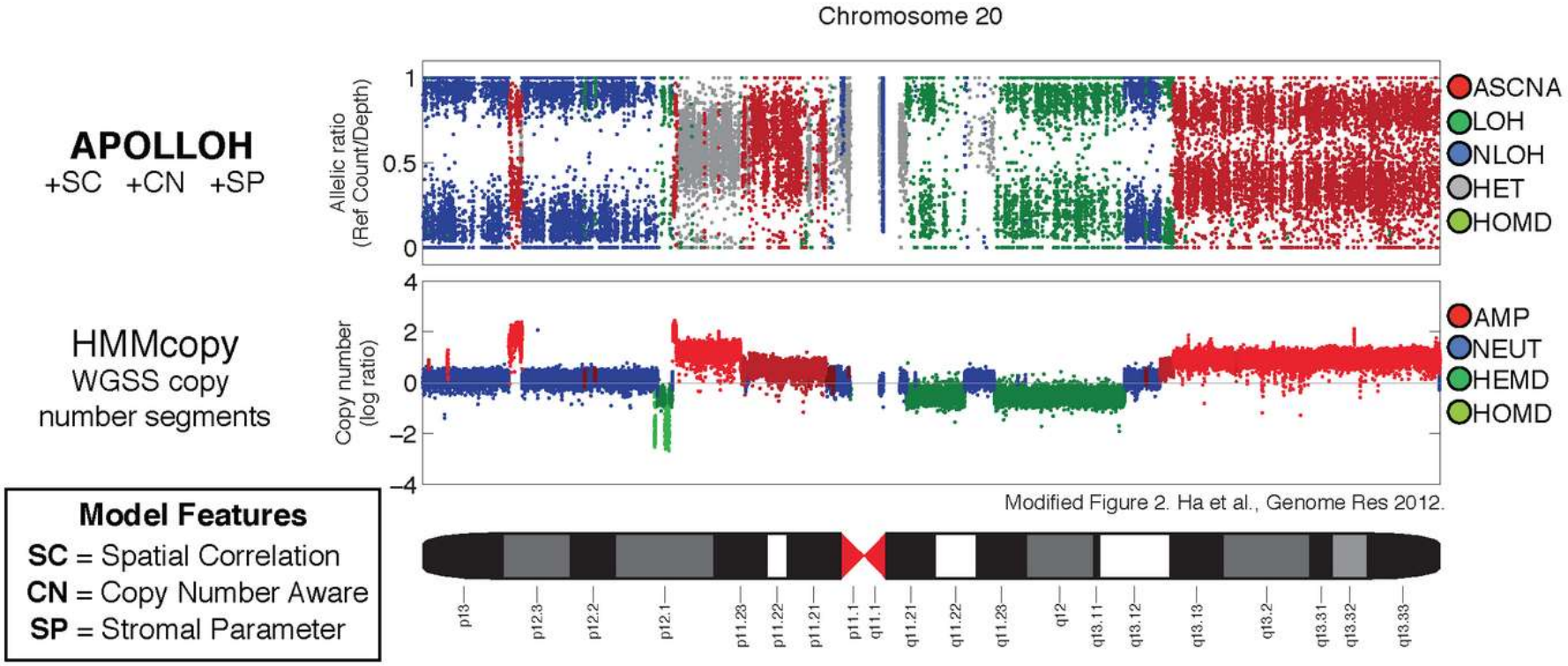
Somatic SNVs in matched T/N pairs

Sample ID	# non-synonymous variants in coding region (>0.8)	INDELS	
DG1021	35	243	WGSS
DG1010	21	278	WGSS
DAH466	4		Exome
DAH471	97		Exome
DAH472	1		Exome
DAH891	30		Exome

*Classifier Probability score >0.8

APOLLOH

APOLLOH is a hidden Markov model (HMM) for predicting somatic loss of heterozygosity and allelic imbalance in whole tumour genome sequencing data.



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PLoS COMPUTATIONAL BIOLOGY

deFuse: An Algorithm for Gene Fusion Discovery in Tumor RNA-Seq Data

Andrew McPherson[1,2], Fereydoun Hormozdiari[2], Abdalnasser Zayed[1], Ryan Giuliany[1], Gavin Ha[1], Mark G. F. Sun[1], Malachi Griffith[3], Alireza Heravi Moussavi[1], Janine Senz[1], Nataliya Melnyk[1], Marina Pacheco[4], Marco A. Marra[3], Martin Hirst[3], Torsten O. Nielsen[4], S. Cenk Sahinalp[2], David Huntsman[1,4], Sohrab P. Shah[1,4,5]*

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BIOINFORMATICS ORIGINAL PAPER

Vol. 28 no. 2 2012, pages 167–175
doi:10.1093/bioinformatics/btr629

Sequence analysis

Advance Access publication November 13, 2011

Feature-based classifiers for somatic mutation detection in tumour–normal paired sequencing data

Jiarui Ding[1,2], Ali Bashashati[1], Andrew Roth[1], Arusha Oloumi[1], Kane Tse[3], Thomas Zeng[3], Gholamreza Haffari[1], Martin Hirst[3], Marco A. Marra[3], Anne Condon[2], Samuel Aparicio[1,4] and Sohrab P. Shah[1,2,4,*]

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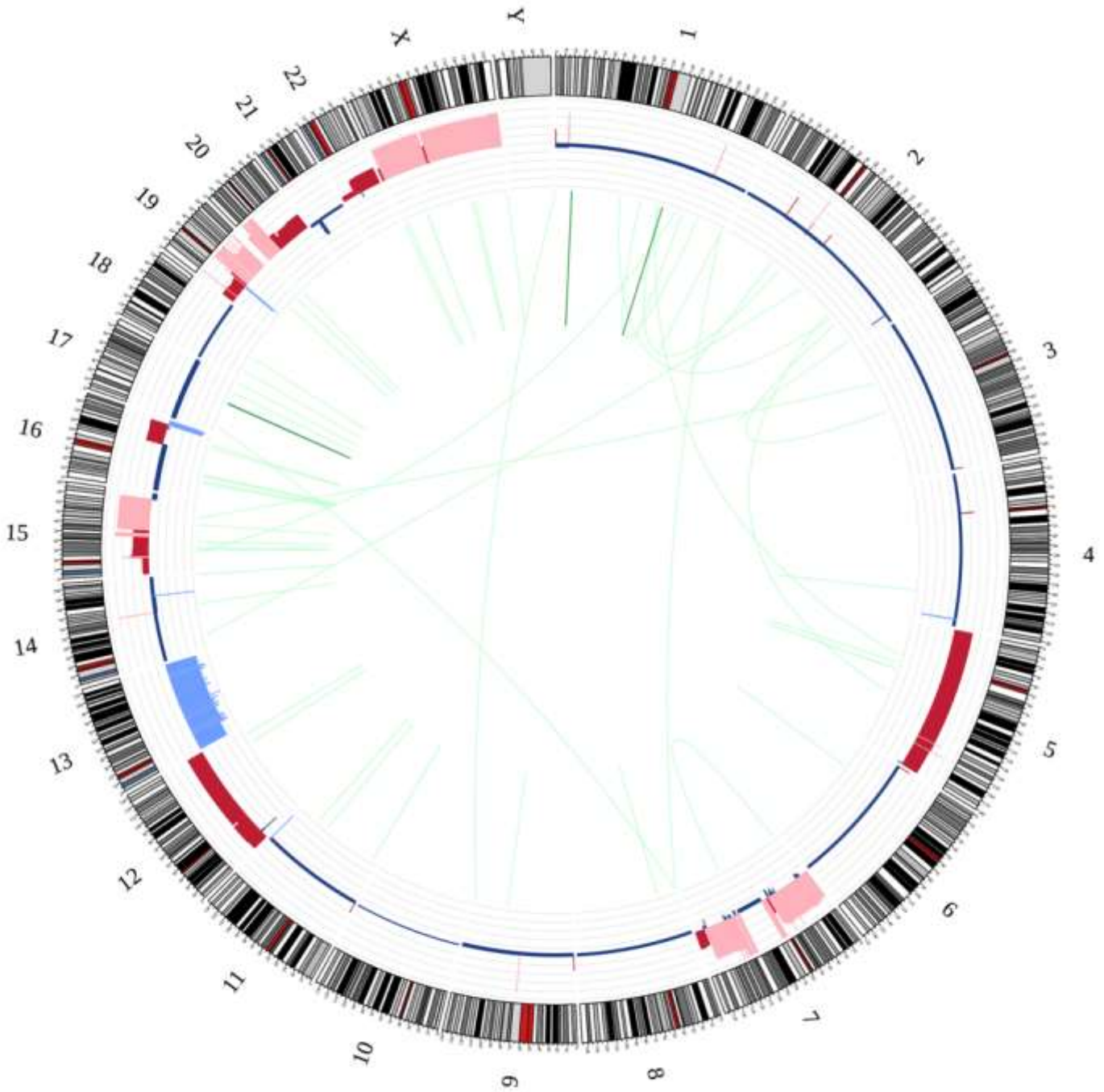
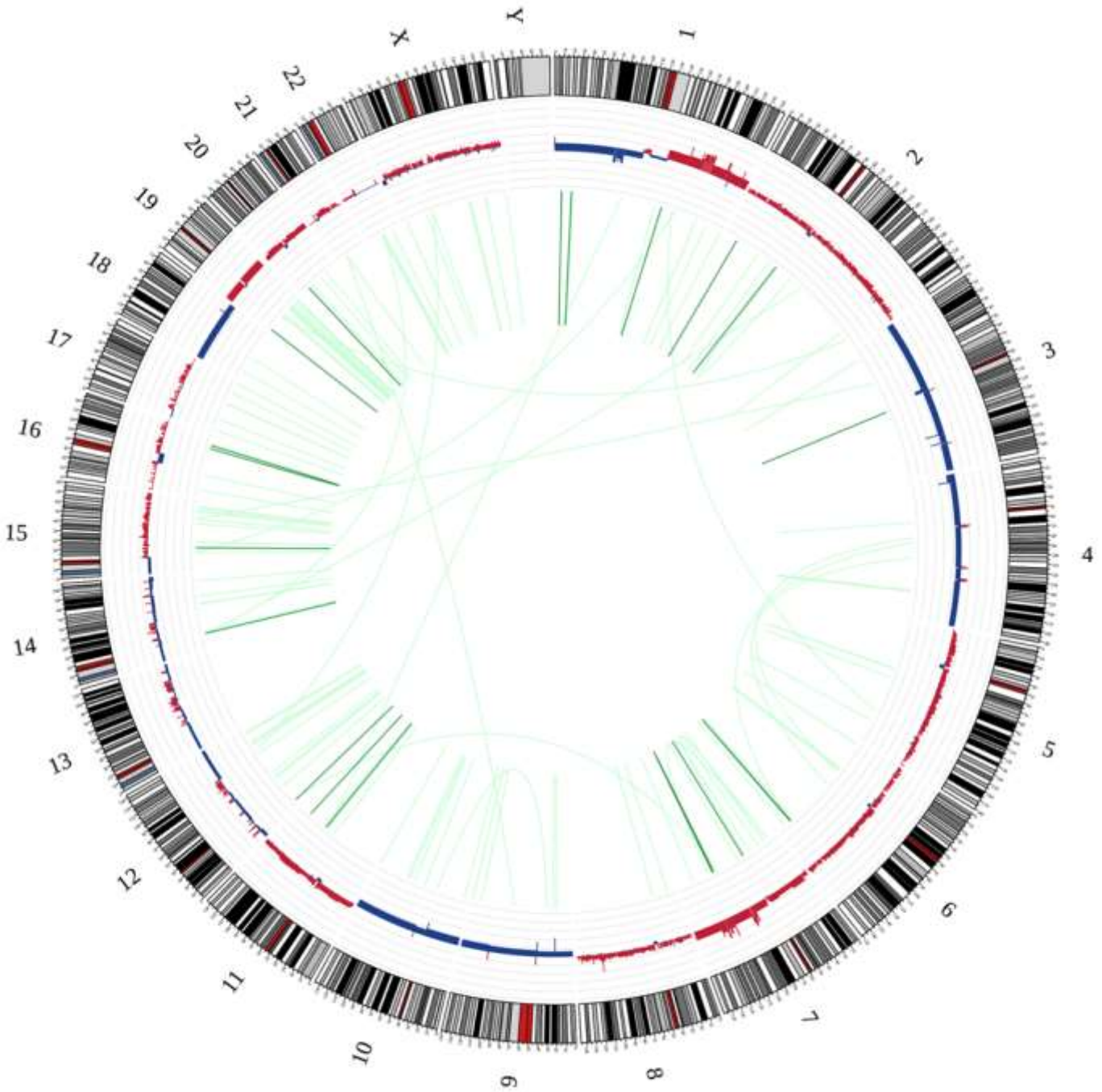
Associate Editor: Alex Bateman



Karey Shumansky



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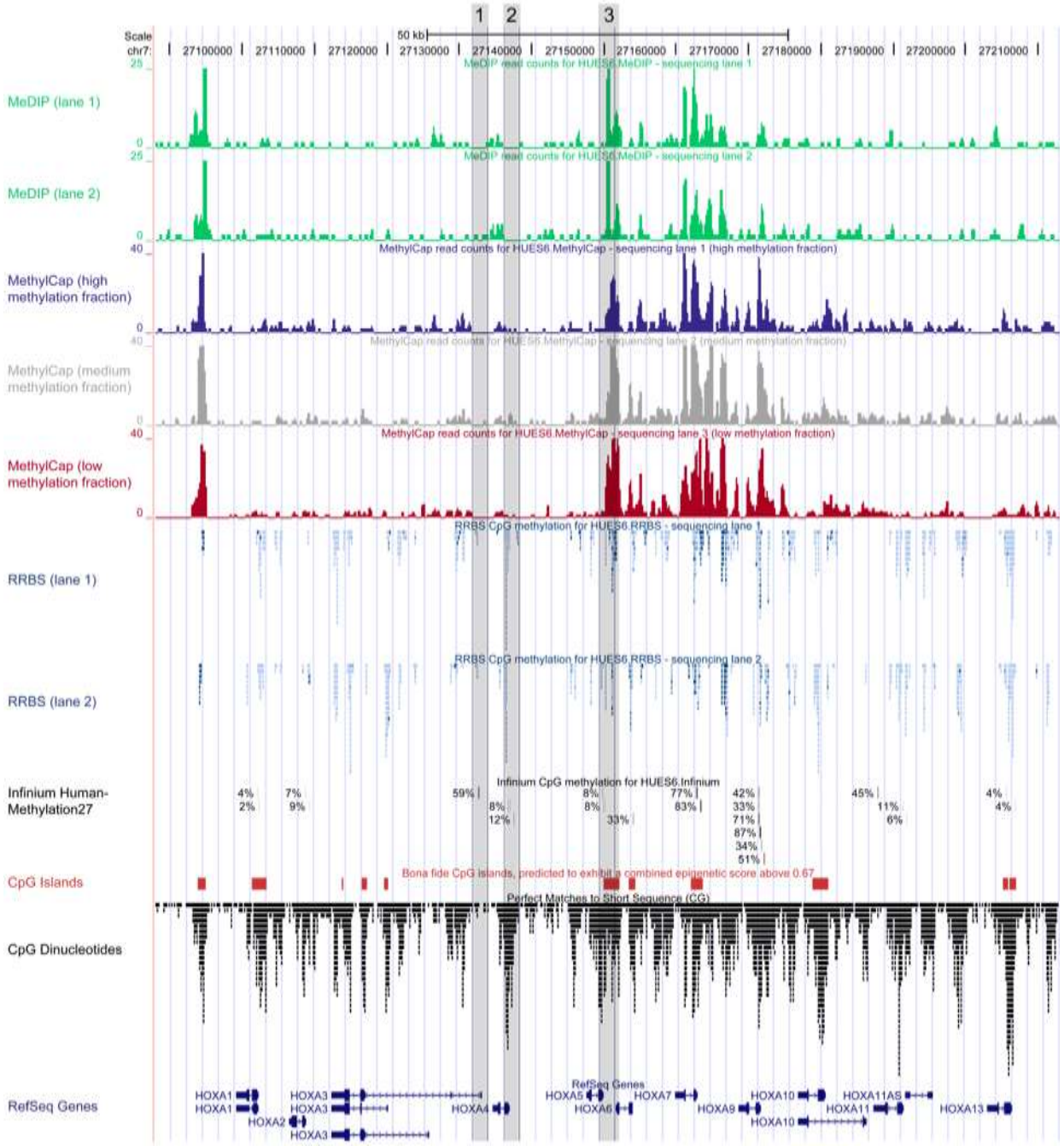
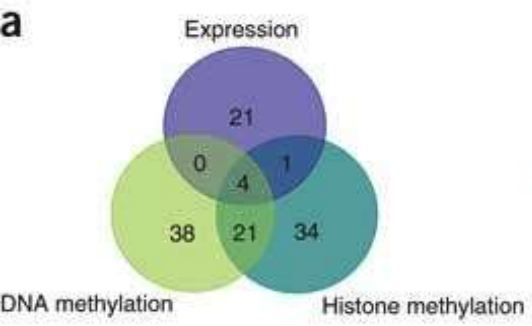
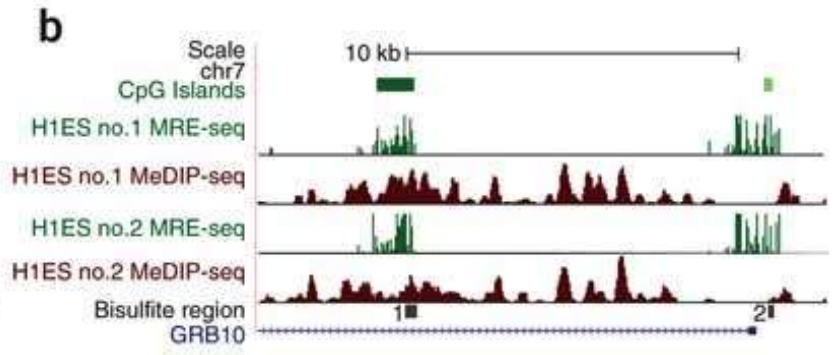
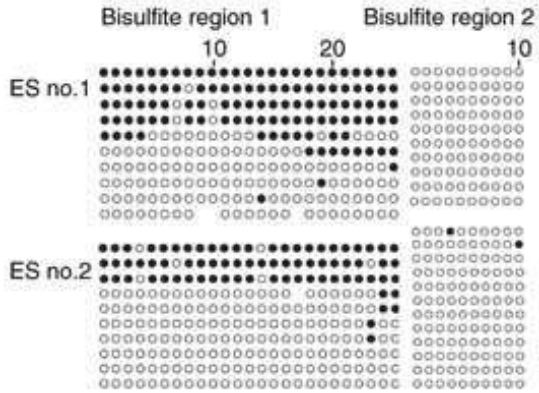


Harris RA, Wang T, Coarfa C, et al: Comparison of sequencing-based methods to profile DNA methylation and identification of monoallelic epigenetic modifications. Nat Biotechnol 28:1097-105, 2010

MeDIP/MRE- Sequencing







40440 – WTSS/Exome/MeDIP/MRE

Profiling of chordoma methylome and correlation with gene expression

Martin Hirst

Harris RA, Wang T, Coarfa C, et al: Comparison of sequencing-based methods to profile DNA methylation and identification of monoallelic epigenetic modifications. Nat Biotechnol 28:1097-105, 2010

Summary

- Tumours with homogenous histology/clinical behaviour may be driven by limited number of genetic events
- Completion of 5 matched pairs of chordoma exomes
- Completion of 2 sets of chordoma “holy trinities”
- Ongoing methylome analysis
  - Relatively small number of somatic mutations
  - No recurrent mutations identified in 5 matched exomes
  - WGSS revealed numerous fusion events