Structural variation in genomics research

Fred Boehm

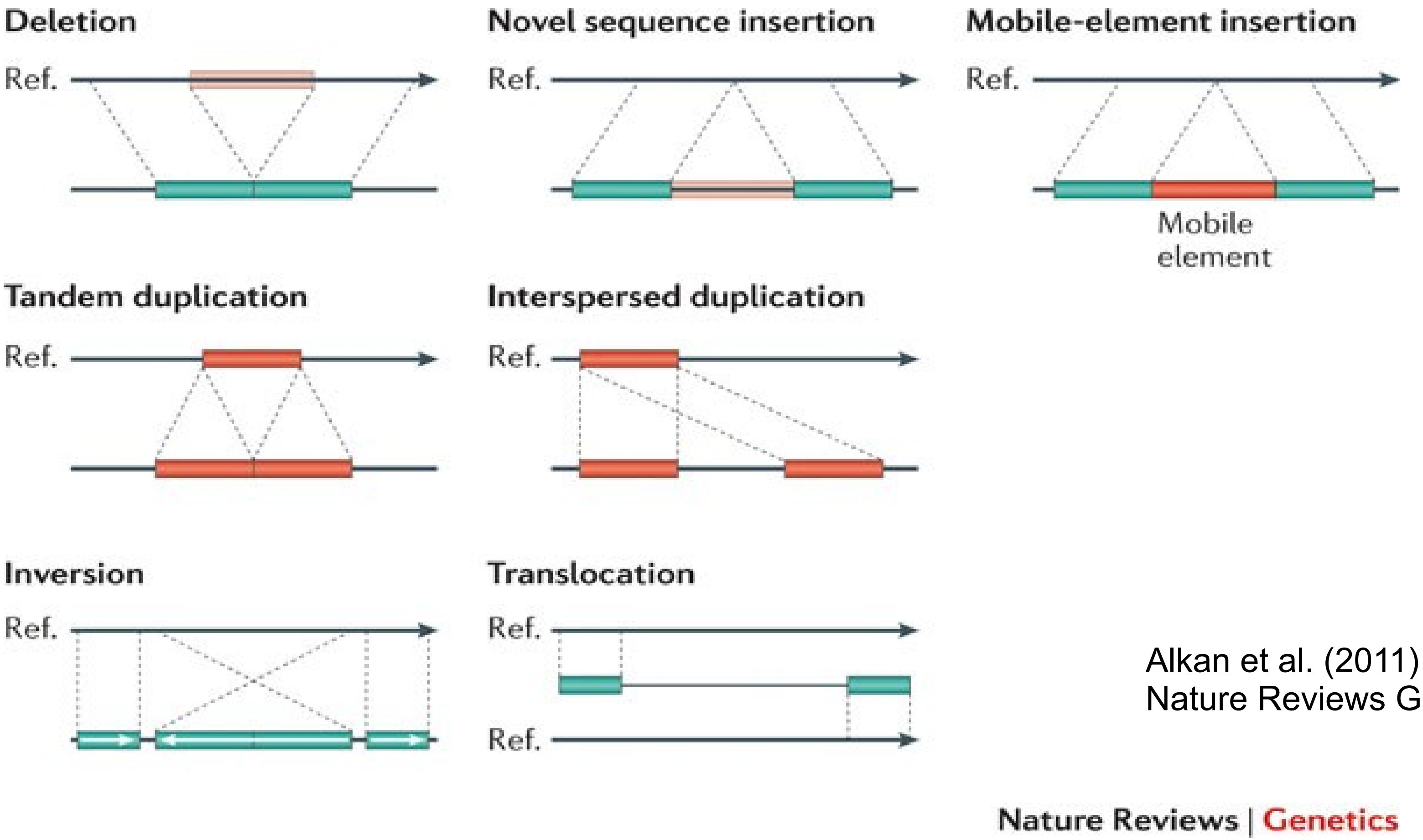
May 1, 2013

Kendziorski Research Group Meeting

Outline

- Definition
- Discovery methods
- Genotype calling methods
- Roles in complex traits

SV Defined by Examples



Alkan et al. (2011)
Nature Reviews Genetics

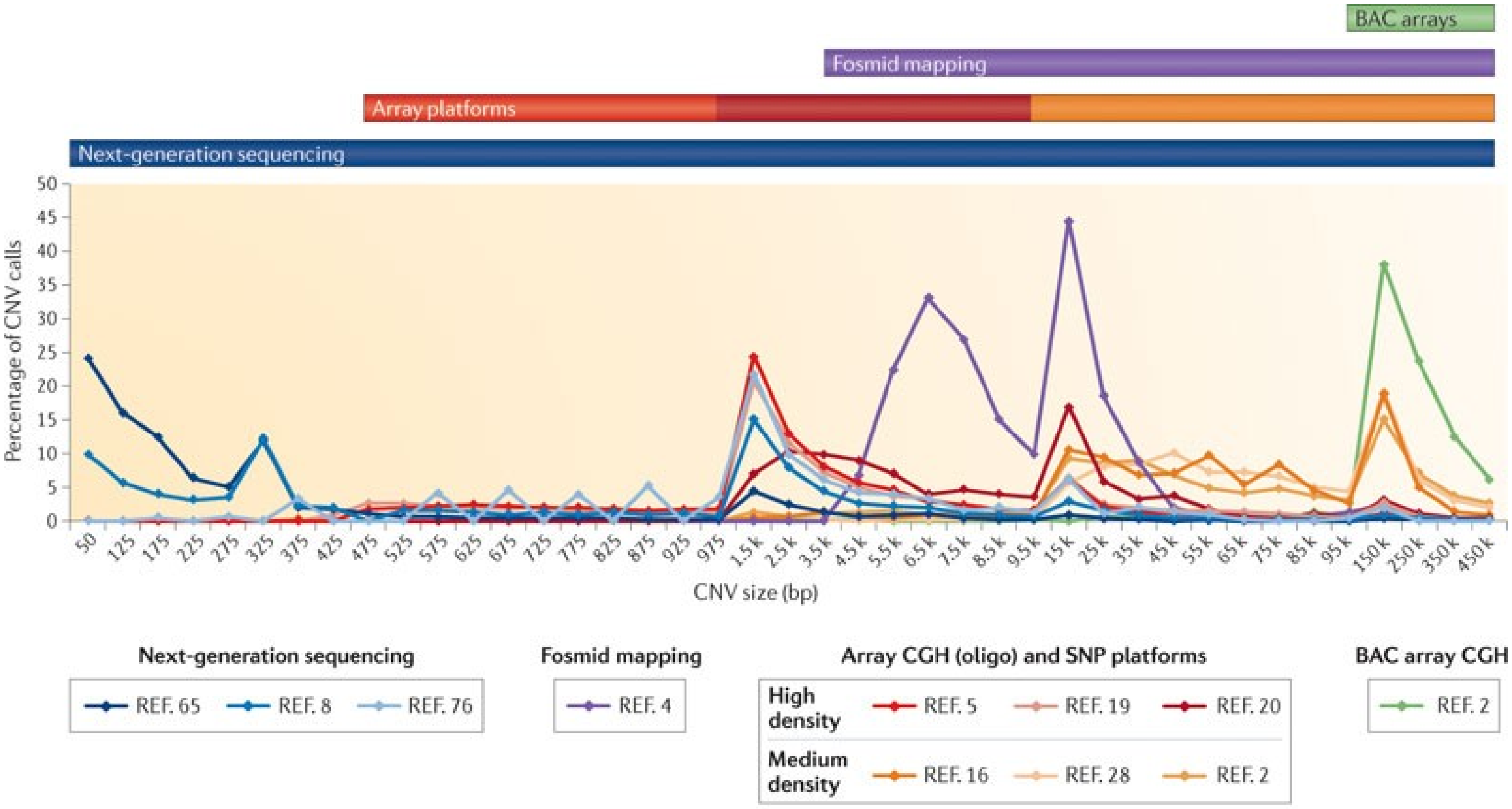
Goals of SV Studies

- Identify SV breakpoints
- Quantify copy number of SVs
- Interrogate possible roles in complex traits

SV Discovery Methods

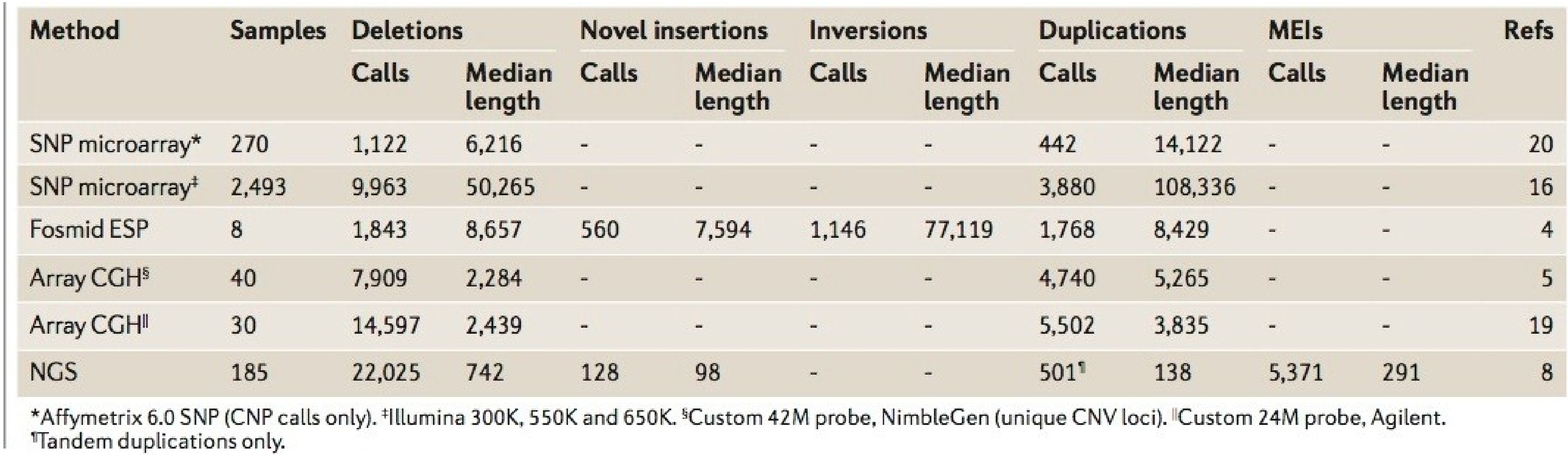
- Array CGH
- SNP Microarray
- Sequencing
  - Read-pair
  - Read-depth
  - Split-read
  - Sequence assembly

Discovery method & SV size



Nature Reviews | Genetics

Discovery method & SV class

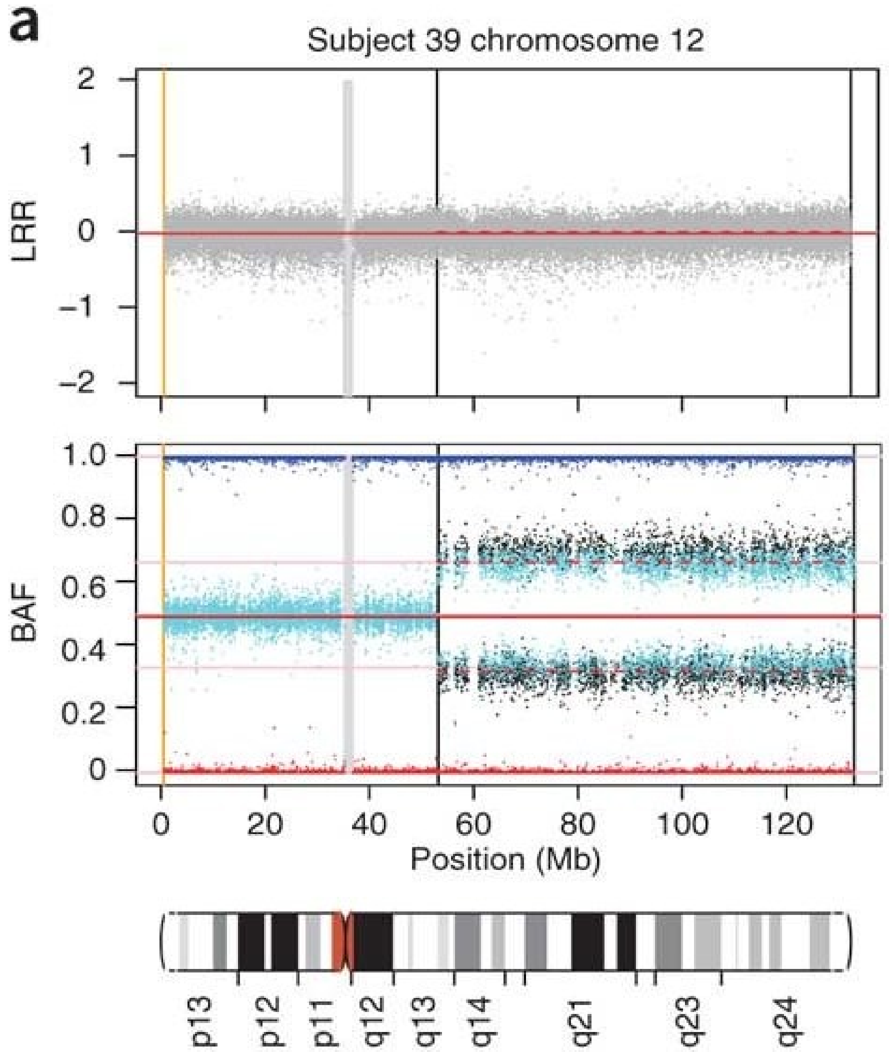


Method	Samples	Deletions		Novel insertions		Inversions		Duplications		MEIs		Refs
		Calls	Median length	Calls	Median length	Calls	Median length	Calls	Median length	Calls	Median length	
SNP microarray*	270	1,122	6,216	-	-	-	-	442	14,122	-	-	20
SNP microarray‡	2,493	9,963	50,265	-	-	-	-	3,880	108,336	-	-	16
Fosmid ESP	8	1,843	8,657	560	7,594	1,146	77,119	1,768	8,429	-	-	4
Array CGH§	40	7,909	2,284	-	-	-	-	4,740	5,265	-	-	5
Array CGH‖	30	14,597	2,439	-	-	-	-	5,502	3,835	-	-	19
NGS	185	22,025	742	128	98	-	-	501¶	138	5,371	291	8

*Affymetrix 6.0 SNP (CNP calls only). ‡Illumina 300K, 550K and 650K. §Custom 42M probe, NimbleGen (unique CNV loci). ‖Custom 24M probe, Agilent. ¶Tandem duplications only.

SNP Microarrays: BAF & LRR

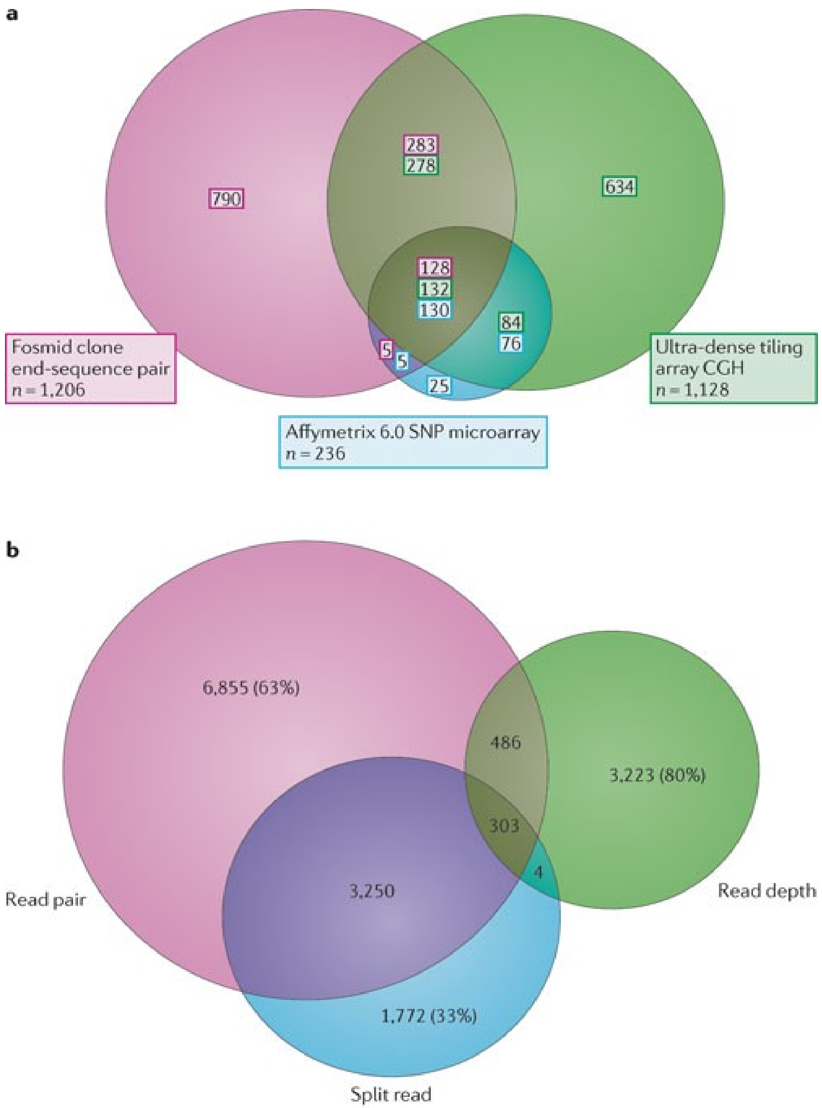
Laurie et al. (2012)
Nature Genetics



Comparing sequencing-based methods

Alkan et al. (2011)
Nature Reviews
Genetics

SV discovery biases



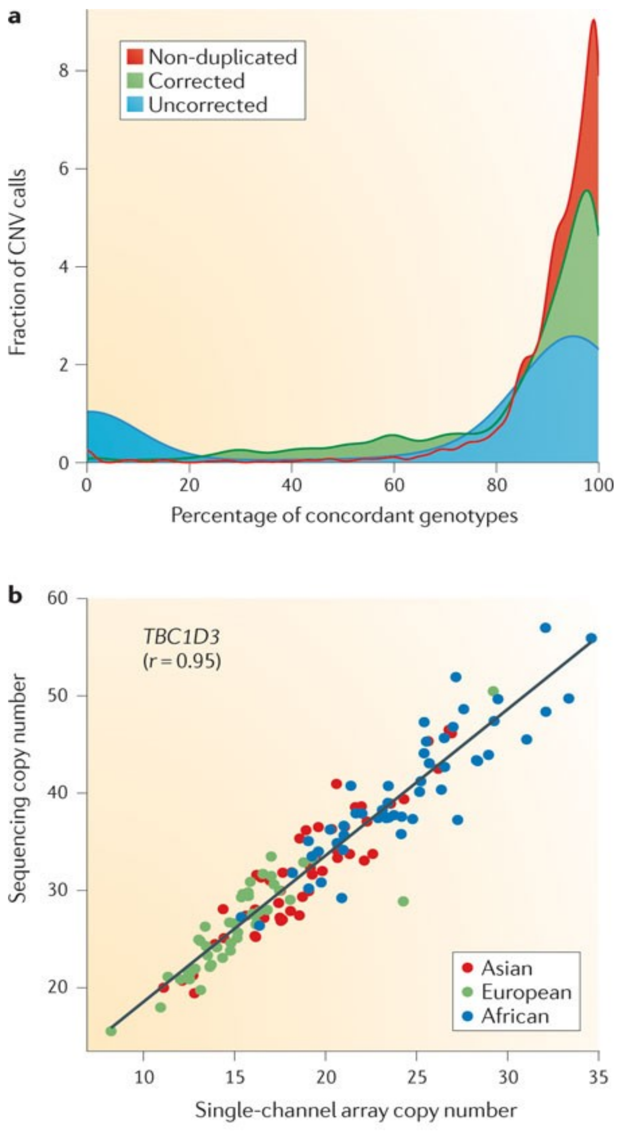
Nature Reviews | Genetics

- Many discoveries are unique to method
- Read depth accurately predicts absolute copy number
- Other sequencing-based methods fail to predict absolute copy number

Alkan et al. (2011)
Nature Reviews Genetics

Genotyping SVs

- PCR-based
  - PCR across known breakpoints
- SNP array-based
- Array CGH-based
  - WTCCC
- Sequencing-based



Nature Reviews | **Genetics**

- 114 subjects
- Affymetrix 6.0 SNP Chip
- Sequence read depth

- Highly duplicated TBC1D3 gene family
- Array CGH
- Sequence read depth

SV roles in complex traits

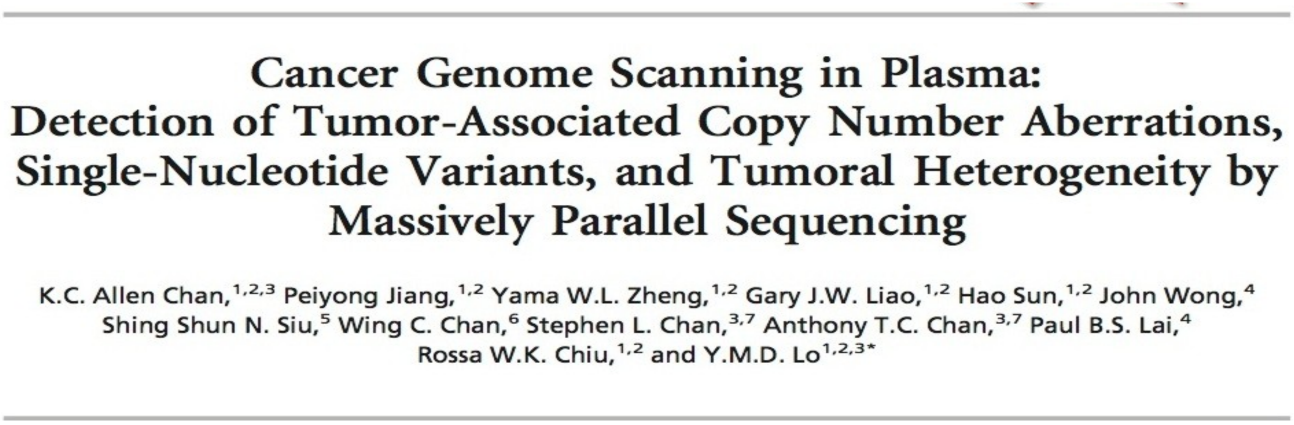
- Association studies
- Psychiatric phenotypes
  - Autism spectrum disorders
  - Schizophrenia
  - ADHD
- Cancer genomics

Vol 463|18 February 2010|**doi:10.1038/nature08822** nature

ARTICLES

The landscape of somatic copy-number alteration across human cancers

Clinical Chemistry 59:1
211–224 (2013)



Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing

K.C. Allen Chan,[1,2,3] Peiyong Jiang,[1,2] Yama W.L. Zheng,[1,2] Gary J.W. Liao,[1,2] Hao Sun,[1,2] John Wong,[4]
Shing Shun N. Siu,[5] Wing C. Chan,[6] Stephen L. Chan,[3,7] Anthony T.C. Chan,[3,7] Paul B.S. Lai,[4]
Rossa W.K. Chiu,[1,2] and Y.M.D. Lo[1,2,3]*

References

1. Alkan et al. (2011) Nature Reviews Genetics 12(5): 363-375.
2. Laurie et al. (2012) Nature Genetics 44(6):642-650.