Personal genome construction with SVs

M Gerstein (Yale)

What we have contributed to the SV Group

Deletion Calling
Breakpoint Assembly & Characterization
  Mechanism assignment
Functional Impact of SVs
Retroduplication Calling
SVs & personalized genome construction

...

Future directions

Personal Diploid Genome and Effects on SVs

Functional Impact of Various SVs

SV Formation Mechanism Annotation Using Long Reads

Loss-of-function Annotation

SVs and Disease Associated lncRNAs

Breakpoint Identification

Mobile Elements Using PacBio and 10x Data

CNVnator Calls on the Trios

Future directions

Personal Diploid Genome and Effects on SVs

-- one of the main purposes of having a good SV call set is to be able to build a genome for each person

-- can we move beyond a call-set-centric mindset to a personal-genome-centric mindset?

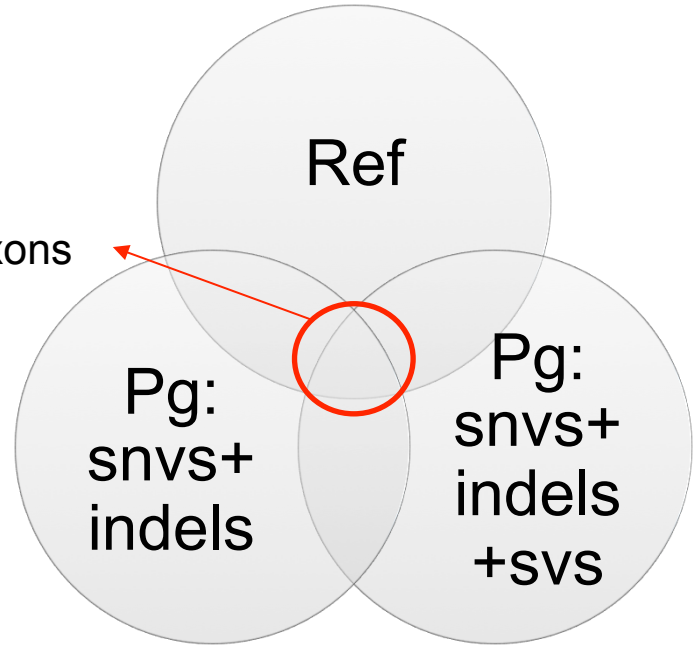
Personalized genomes analyses in Sudmant *et al., Nature* (2015)

Constructed 2 personal genomes of NA12878 based on GRCh37 reference genome

1. 1000 GP P3 **SNVs and indels** integrated call set (low coverage)
2. 1000 GP P3 **SNVs, indels and SVs** with breakpoint information from SVG

Personalized genomes analyses in Sudmant *et al.*, *Nature* (2015)

Number of exons



280,123 GENCODE consensus exons

-- this is a conservative set
-- we are also interested in SVs that completely knock genes out in the personal genomes (these would not have been included)

Oliver Stegle

Utility of SVs:
Exons with direct SV overlap

Comparing between Pgenome-SVs and Pgenome-snpsIndels

-- 18 exons with a direct SV overlap

-- 6/18 exons were expressed (>10 reads)

-- 4/6 showed substantial changes in expression (≥ 2-fold change)

[Sudmant *et al., Nature* (2015)]

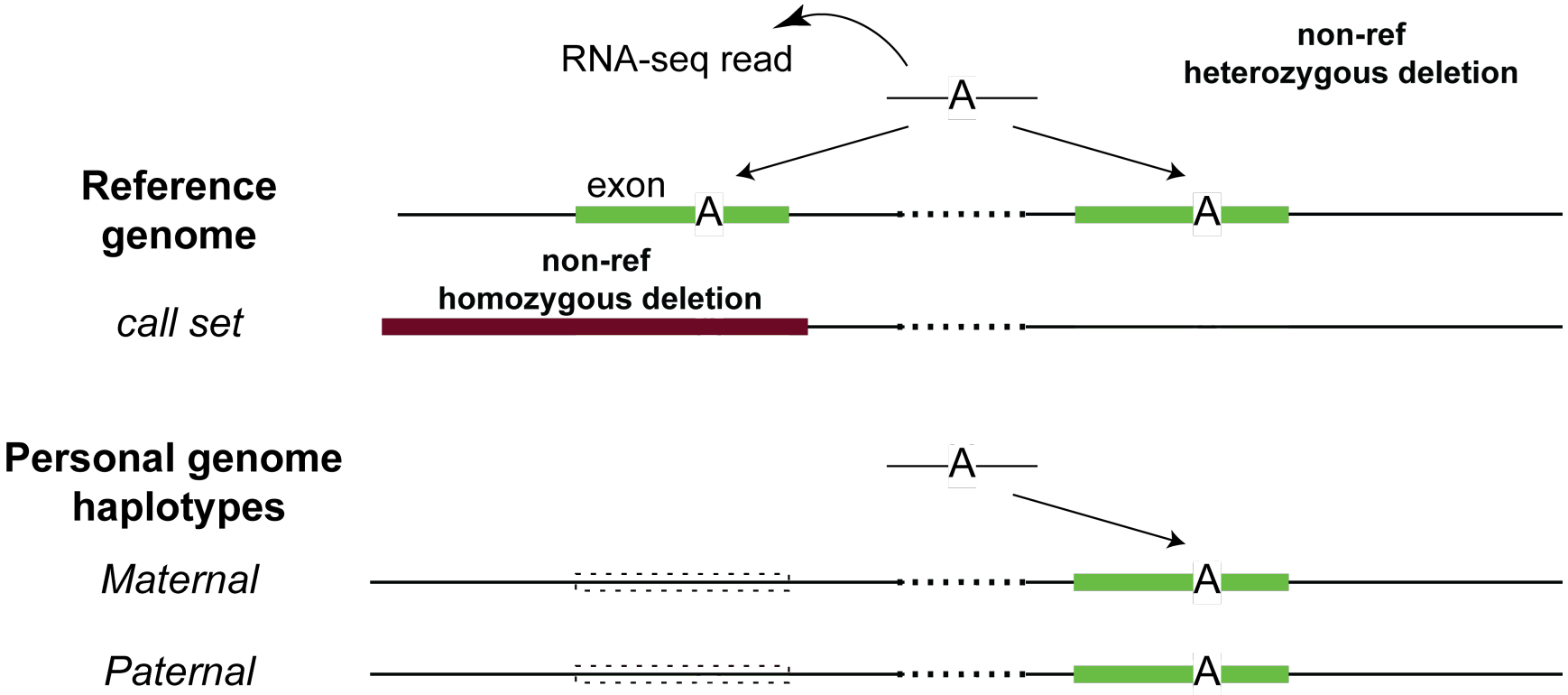
Metrics for Success

How can see how much better a personal genome is than the reference?

How can we compare one personal genome to another?

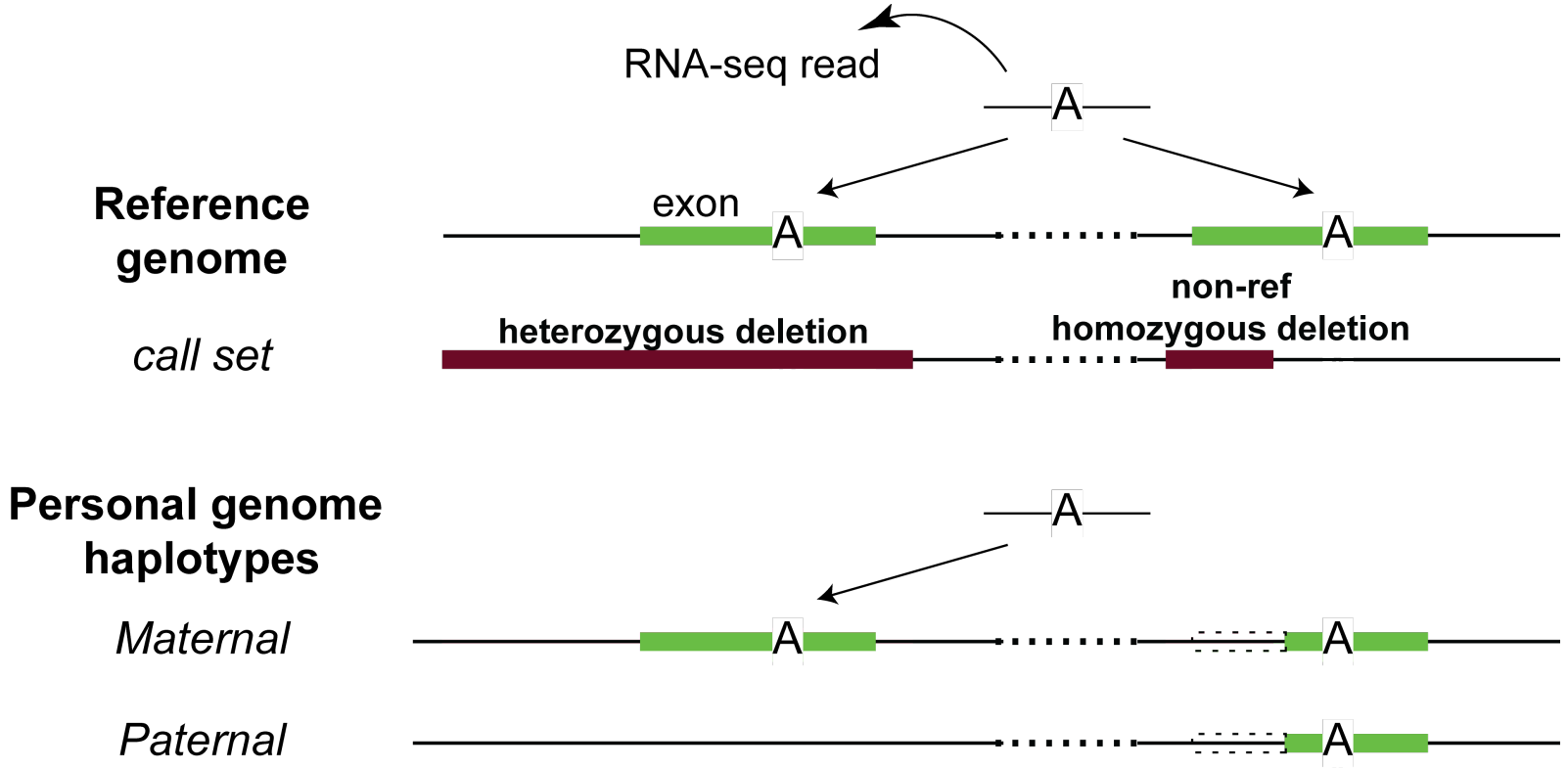
Formal Arguments
Quantities like N50, Ts/Tv

Personal genome is a better reference for alignment: a simple example



[Chen et al. *Nat. Comm.* (in rev.)]

Personal genome is a better reference for alignment : more complex



[Chen et al. *Nat. Comm.* (in rev.)]

Alignment gets better as variant sets are more complete: NA12878 Pol2 ChIP-seq

	Ref genome	Pgenome: snvs only	Pgenome: snvs + indels only	Pgenome: snvs + indels + SVs
Reads processed	208,051,087	208,051,087	208,051,087	208,051,087
# reads uniquely aligned	171,944,588 (82.65%)	172,591,380 (82.96%) M: 171,965,218 (82.66%) P: 171,969,566 (82.66%)	172,738,321 (83.03%) M: 171,982,014 (82.66%) P: 171,982,614 (82.66%)	172,743,175 (83.03%) M: 171,977,765 (82.66%) P: 171,978,147 (82.66%)
# reads that failed to align	18,279,824 (8.79%)	M: 18,290,611 (8.79%) P: 18,276,409 (8.78%)	M: 18,286,906 (8.79%) P: 18,270,944 (8.78%)	M: 18,293,522 (8.79%) P: 18,277,990 (8.79%)
# reads that multimap	17,826,675 (8.57%)	M: 17,795,258 (8.55%) P: 17,805,112 (8.56%)	M: 17,782,167 (8.55%) P: 17,797,529 (8.55%)	M: 17,779,800 (8.55%) P: 17,794,950 (8.55%)

Almost 1M increase in reads

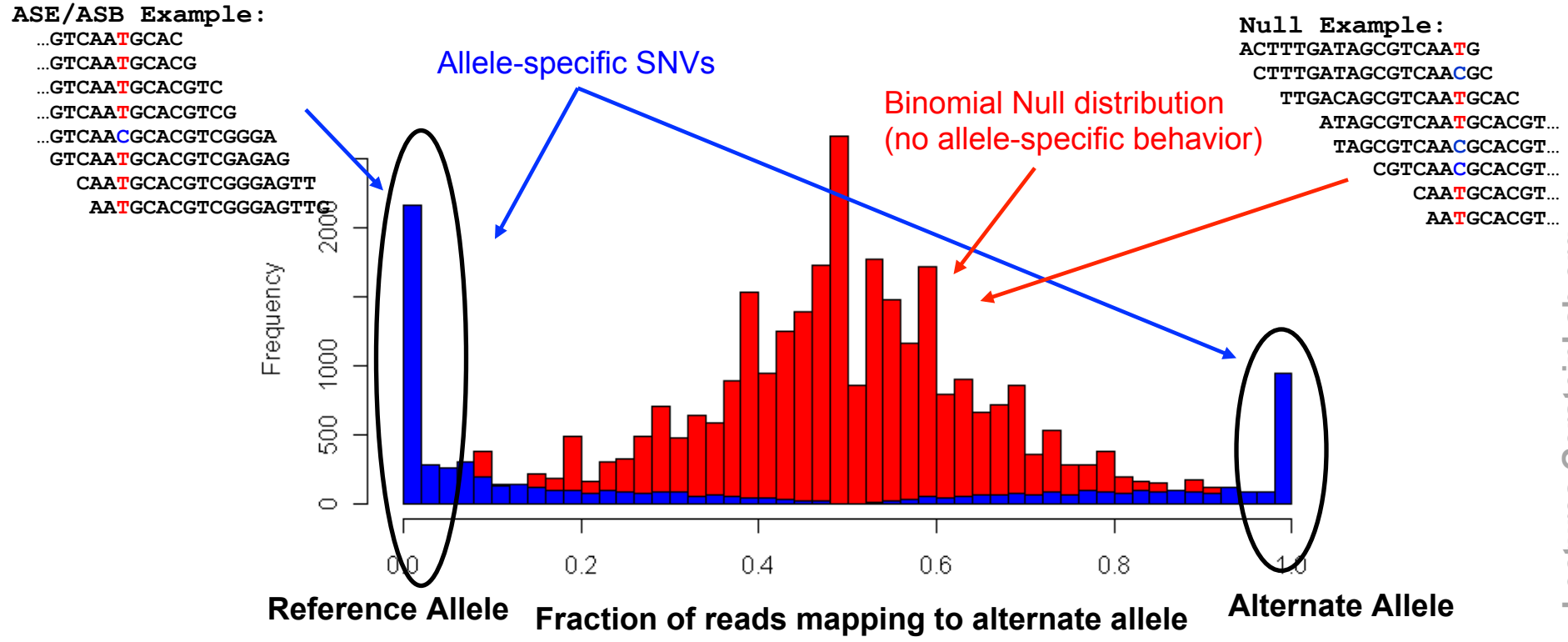
[Chen et al. *Nat. Comm.* (in rev.)]

Alignment gets better as variant sets are more complete: NA12878 RNA-seq (Kilpinen *et al.* 2013)

	Ref genome	Pgenome: snvs only	Pgenome: snvs + indels only	Pgenome: snvs + indels + SVs
Reads processed	37,558,398	37,558,398	37,558,398	37,558,398
# reads uniquely aligned	25,303,498 (67.37%)	25,486,837 (67.86%) M: 25,345,119 (67.48%) P: 25,352,964 (67.50%)	25,538,449 (68.00%) M: 25,371,892 (67.55%) P: 25,383,016 (67.58%)	25,568,042 (68.08%) M: 25,394,098 (67.61%) P: 25,412,184 (67.66%)
# reads that failed to align	8,213,405 (21.87%)	M: 8,195,227 (21.82%) P: 8,195,017 (21.82%)	M: 8,174,209 (21.76%) P: 8,172,957 (21.76%)	M: 8,181,317 (21.78%) P: 8,173,224 (21.76%)
# reads that multimap	4,041,495 (10.76%)	M: 4,018,052 (10.70%) P: 4,010,417 (10.68%)	M: 4,012,297 (10.68%) P: 4,002,425 (10.66%)	M: 3,982,983 (10.60%) P: 3,972,990 (10.58%)

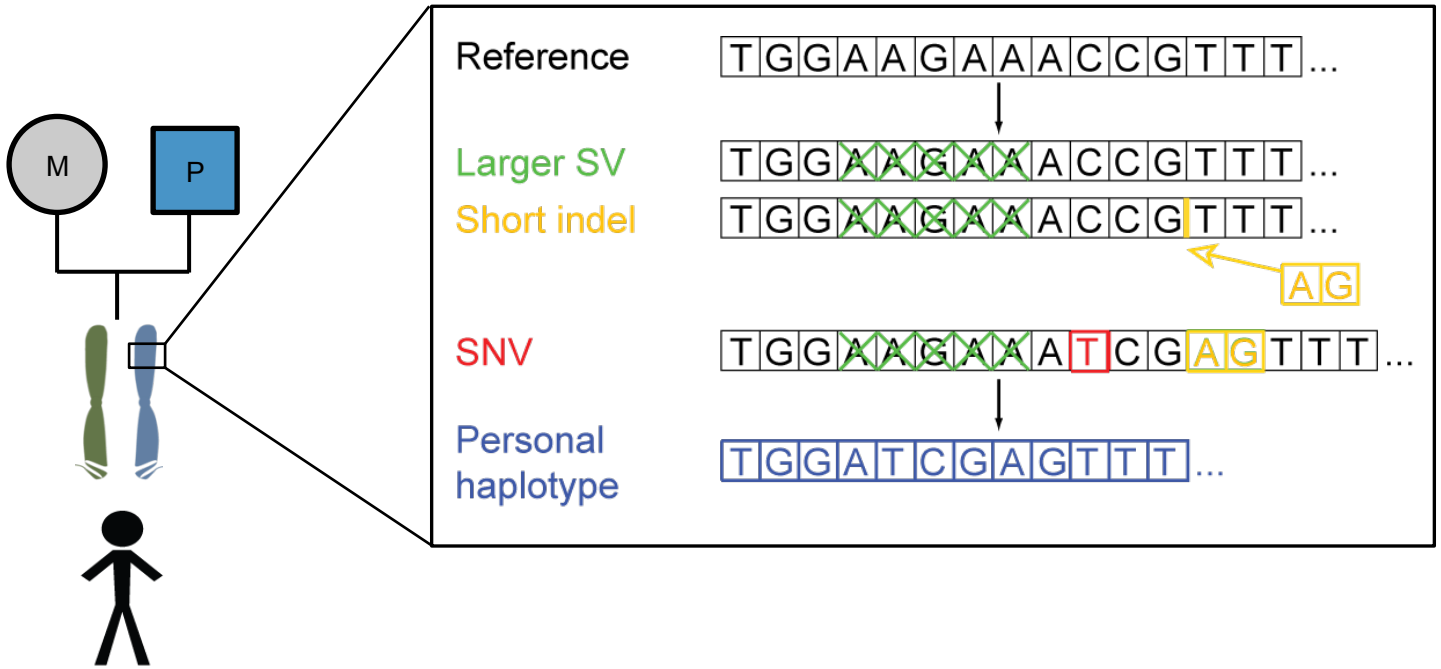
[Chen et al. *Nat. Comm.* (in rev.)]

Reference Bias in functional read mapping (naïve alignment against reference)



[Rozowsky *et al. MSB* ('11)]

Personal genome construction



[Rozowsky *et al. MSB* ('11)]

Construction considerations

1. **Choice of call set(s)**

-- e.g. different versions of 1000GP call sets

2. **Choice of reference**

-- choose the reference genome in which the call set is derived from

3. **Choice of variants**

-- e.g. SVs or indels or SNVs only

4. **Order of incorporation**

-- SVs > indels > SNVs

-- Increased SNV density around SV breakpoints (Abyzov *et al.* 2015)

Many choices of NA12878 call sets: Which one do we use?

1. Genome in a bottle
2. Complete Genomics
3. Illumina Platinum Genomes
4. Broad's GATK Best Practices bundles
5. 1000 Genomes Project
   -- low/high coverage
   -- long reads: PacBio, Moleculo

Assessing quality of call set: Mendelian inconsistency (e.g. GATK HC PCR-free CEU trio)

NA12891 Father	NA12892 Mother	NA12878			total	%Err
		RR	RA	AA		
RR	RR	0	6072	311	---	---
RR	RA	518631	505499	1215	1025345	0.12
RR	AA	1659	194589	1806	198054	1.75
RA	RR	507750	506699	1110	1015559	0.11
RA	RA	194409	397233	195245	786887	---
RA	AA	742	194722	206720	402184	0.18
AA	RR	1485	193636	1551	196672	1.54
AA	RA	653	198416	202366	401435	0.16
AA	AA	113	1316	816825	818254	0.17

*Autosomes only

Jieming Chen

Future development of personal genome construction

1. Iterative personal genome construction

iteration 1: construct pgenome per before

-- map DNA reads to pgenome

-- refine variants on pgenome

iteration 2: rebuild pgenome

2. What makes a personal genome ‘better’ than the other one

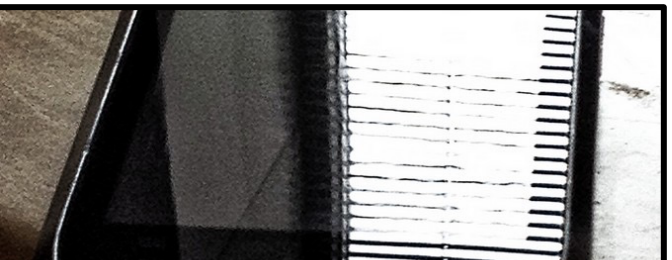
-- metrics to describe a ‘good’ personal genome

Current and future efforts in personal genome construction

- 382 personal genomes from 1000 Genomes Project with RNA-seq and/or ChIP-seq sets -- with only SNVs and indels
- Other high coverage trios in 1000GP and Svtrios

SV Group

Alexej Abyzov
Sushant Kumar
Shantao Li
Fabio Navarro
Yan Zhang



Acknowledgements

Personal genomes

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