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OMICS Group is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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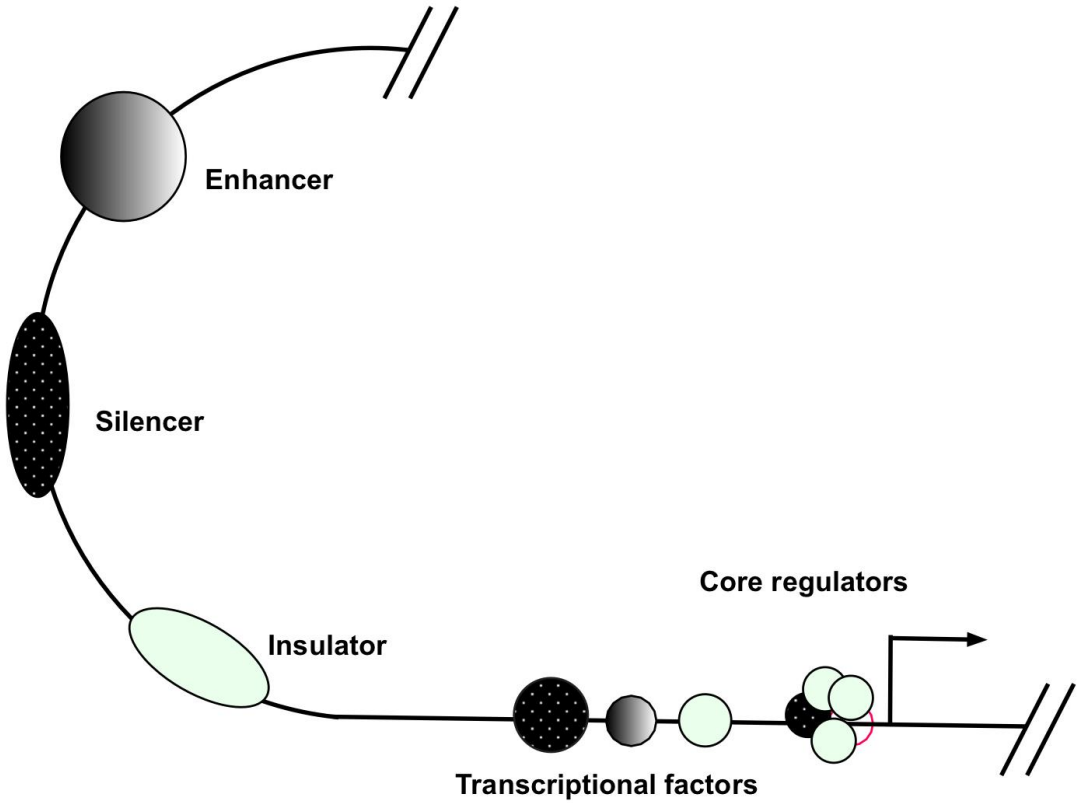
Genome-scale Promoter analysis using Exome Sequences (GPES)

San Ming Wang

Regulation of gene expression



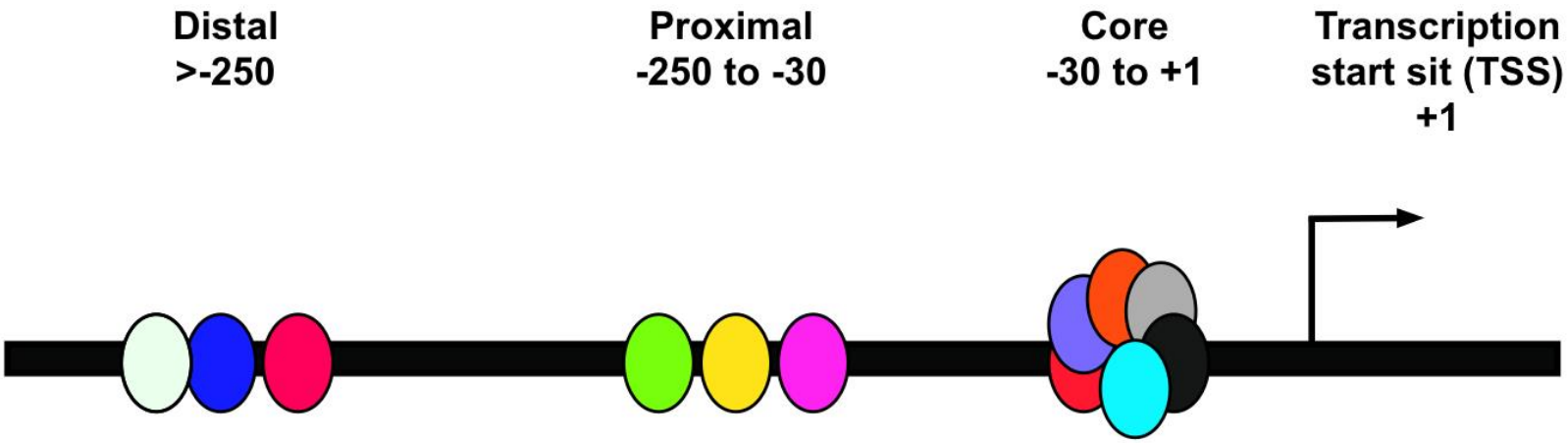
- Distal elements

– enhancer, silencer, insulator

- Promoter elements

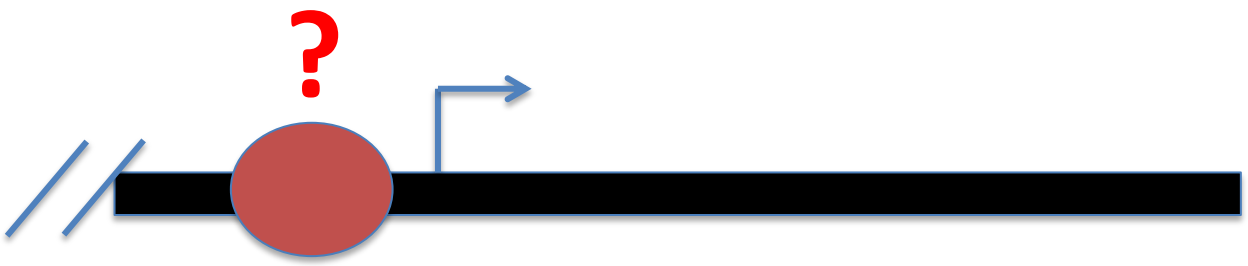
– transcriptional factors, basal transcriptional machinery

Promoter structure



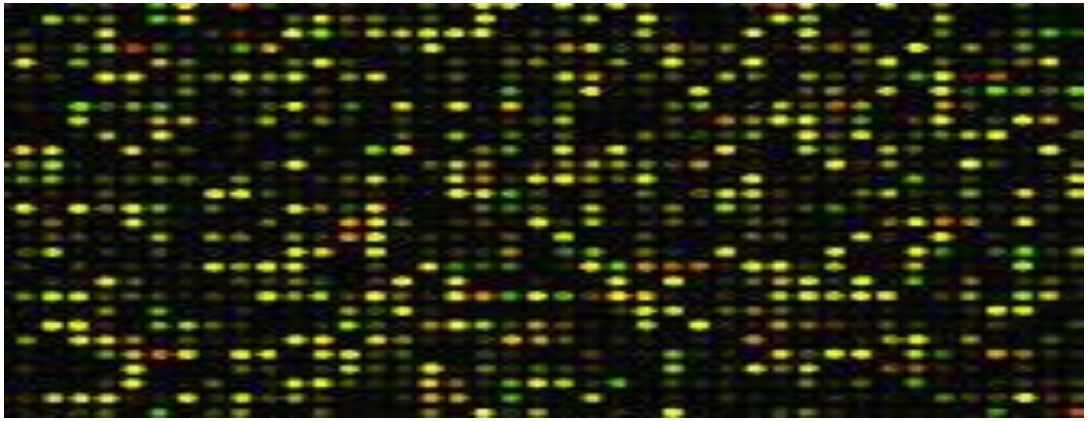
Promoter remains as a less-explored territory in disease study

- Promoter directly controls gene expression
- Mutation in promoter can have profound impact on biology and diseases
- Lack of systematic tools for *de novo* promoter analysis



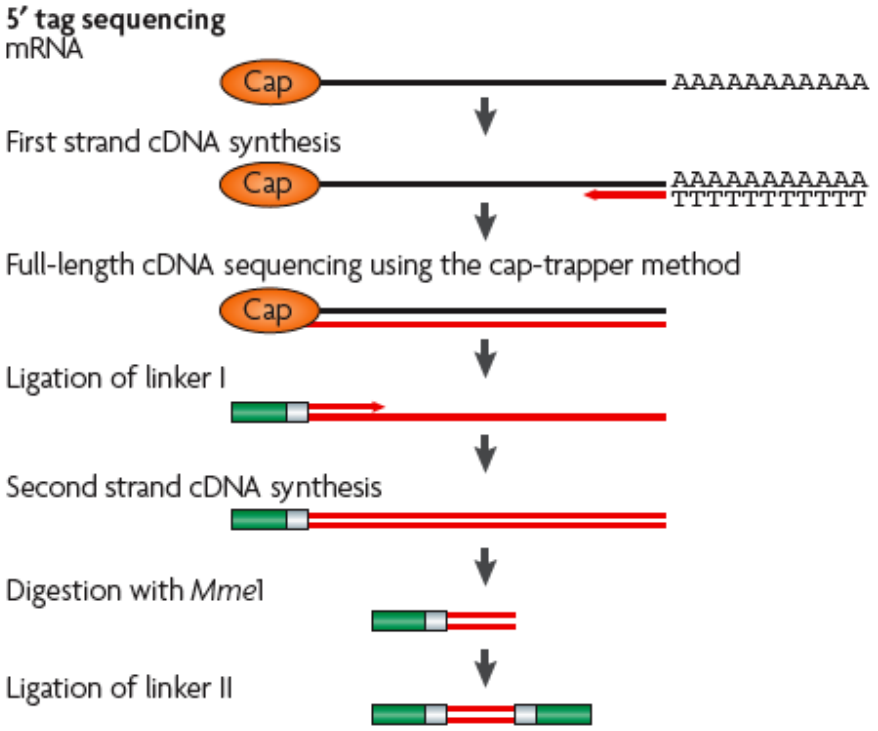
Existing method - Microarray

- Promoter probes are based on human genome reference sequences
- Human genome reference sequences were from “normal” individual genomes, not from disease genomes
- Array is lack of the power for *de novo* promoter analysis



Existing method
- Cap Analysis Gene Expression (CAGE)

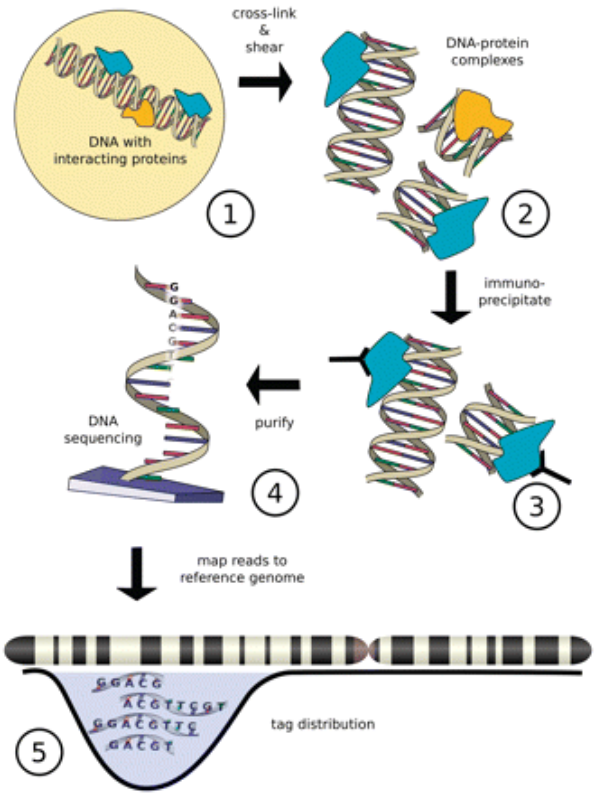
- Determine transcriptional start site
- Do not analyze promoter



(Nature genetics **38,** 626–35, 2006)

Existing method
- ChIP-seq

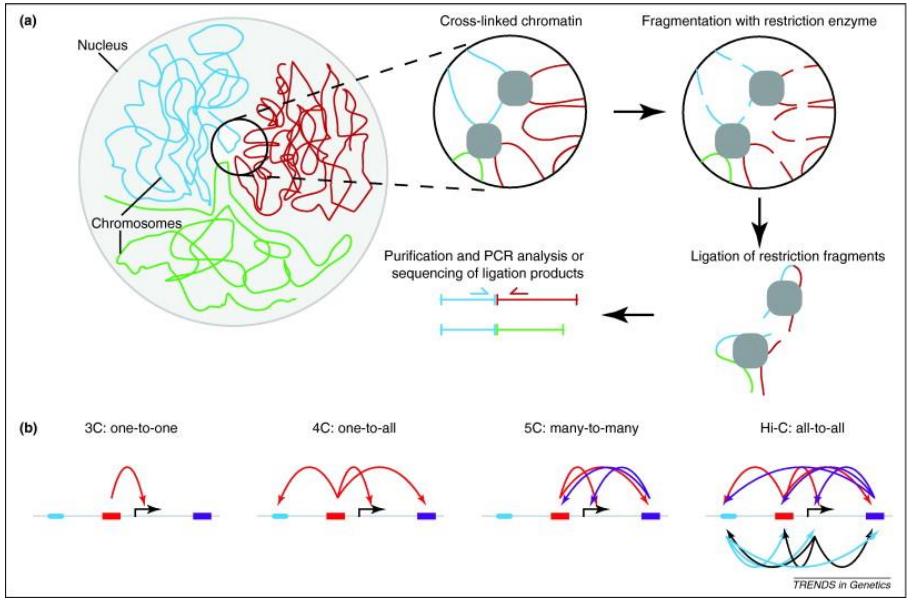
- Only analyze a given type of transcriptional factor-binding sites by immuno-precipitation



Brief Bioinform. 2011 Nov;12(6):626-33

Existing method – Hi-C

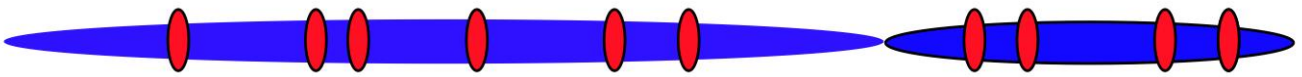
- Detect interaction between distal and promoter
- Not focus on *de novo* promoter mapping



Trends Genet. 2011;27:63-71

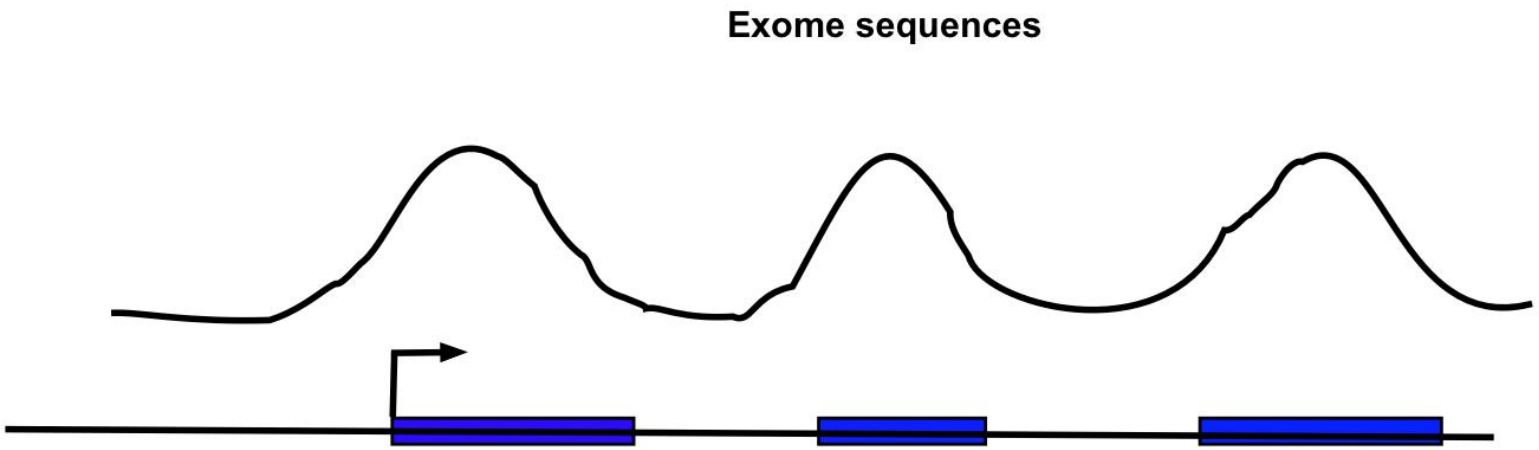
Existing method – Whole-genome sequencing

- It is not cost-effective to analyze promoters by sequencing the entire genome, as promoters account for only a small portion of the genome - using a canon to hit ants



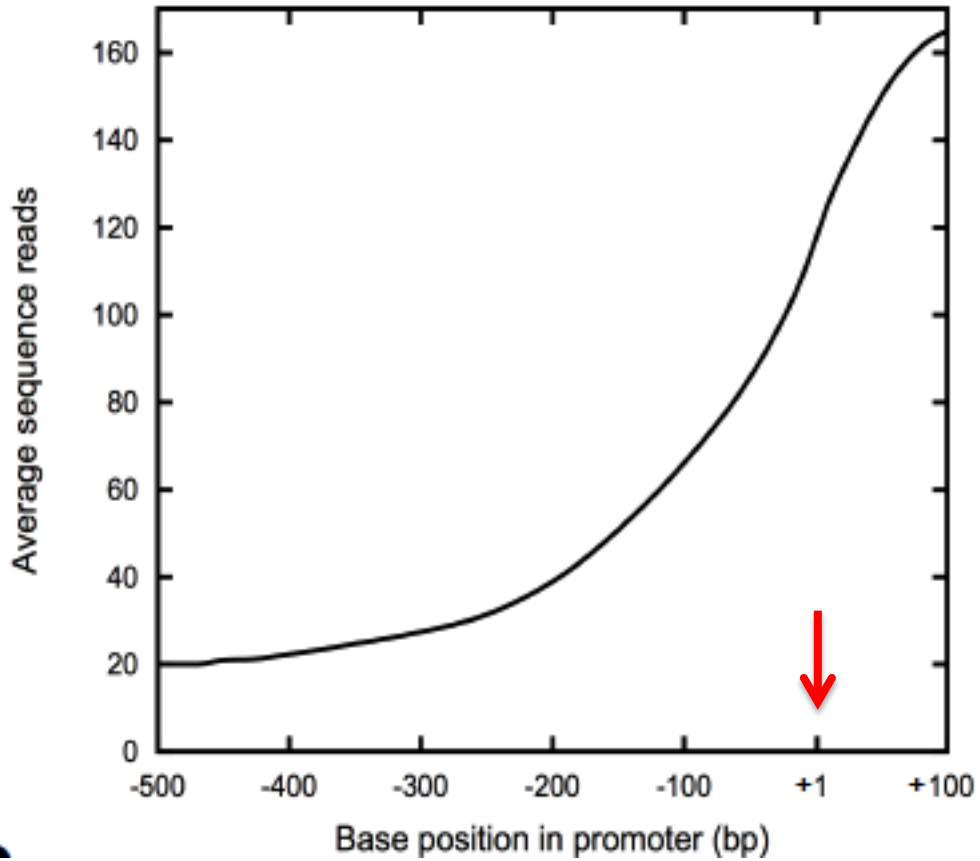
Can exome sequences be used for genome-scale, *de novo* promoter analysis?

Distribution of actual exome sequences

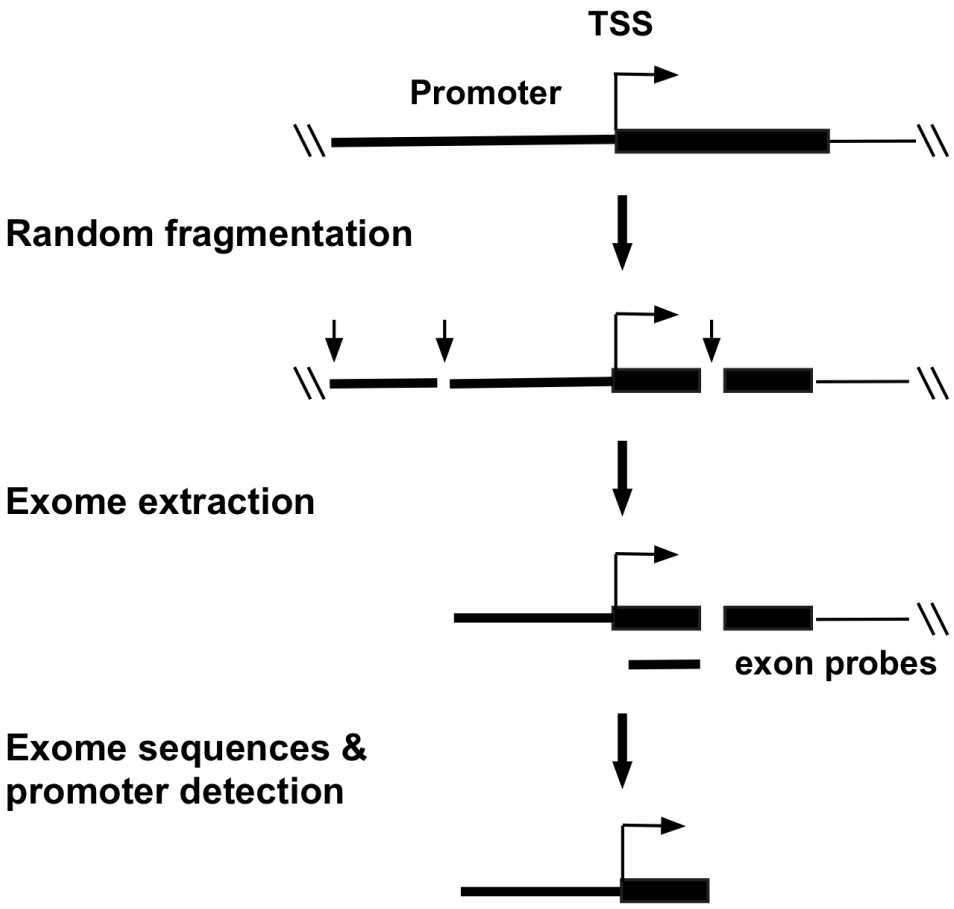


(BMC Genomics. 13:194, 2012)

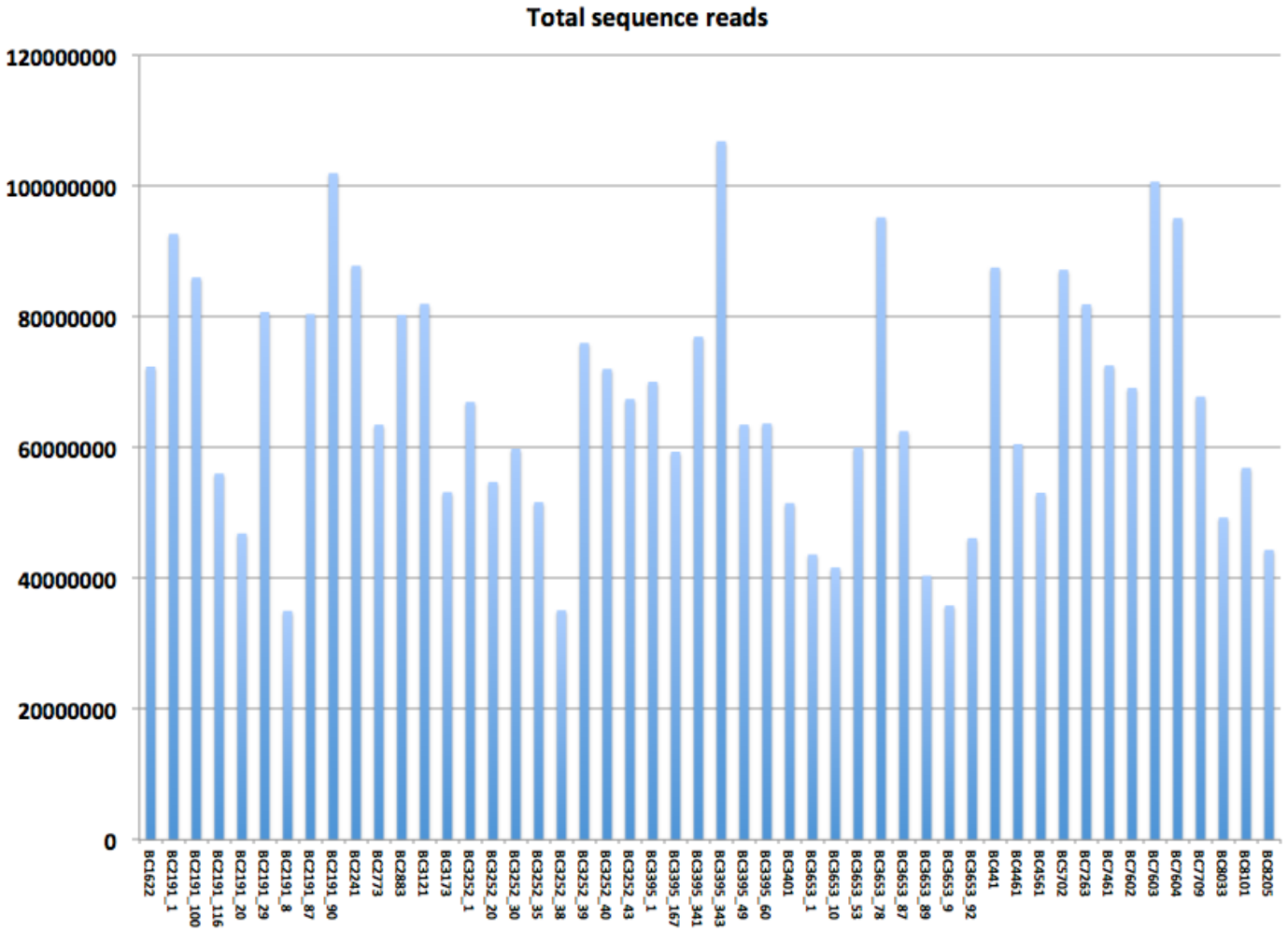
Distribution of exome data in promoter region (-500 to +100) from 50 exome data sets



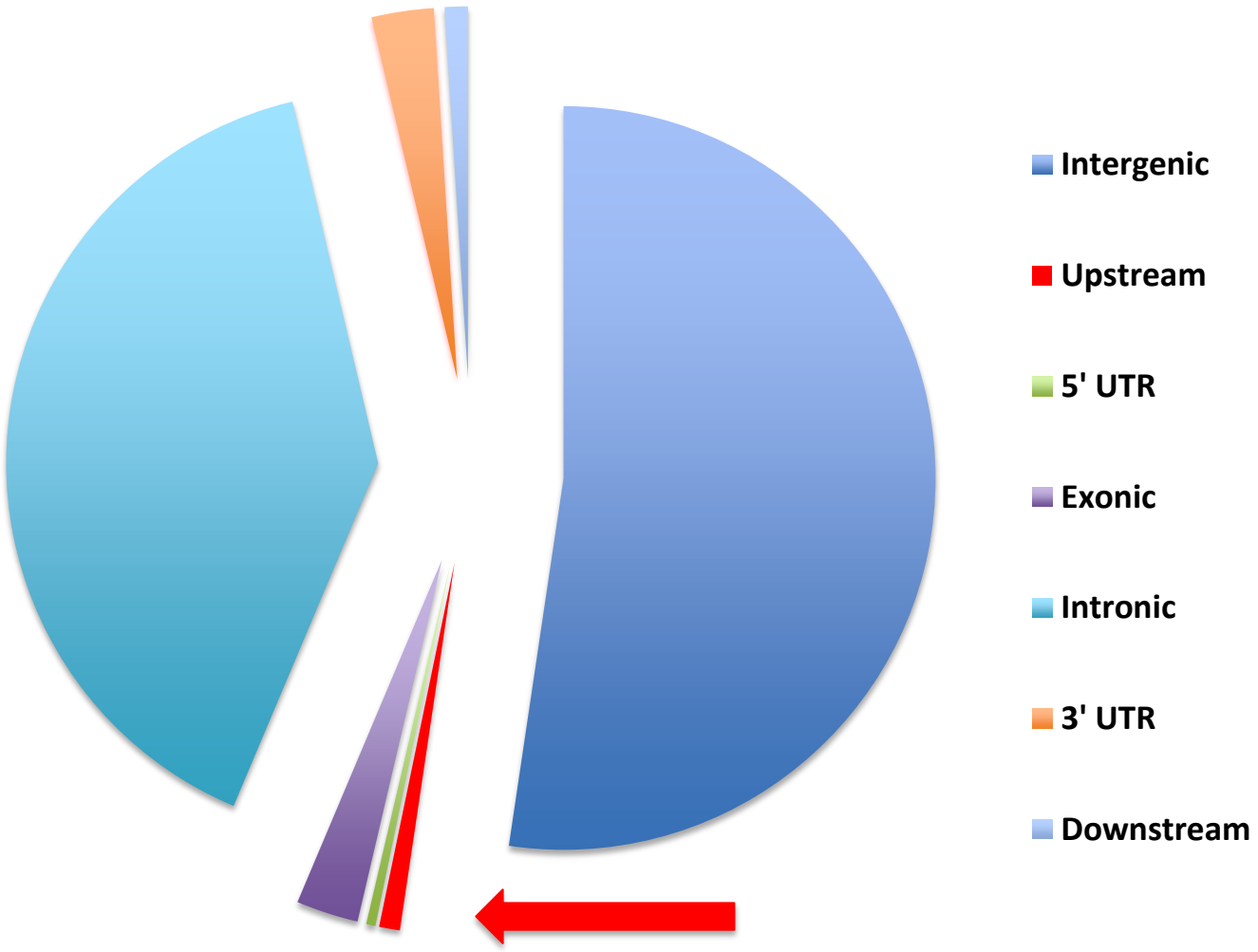
How does exome collect promoter sequences



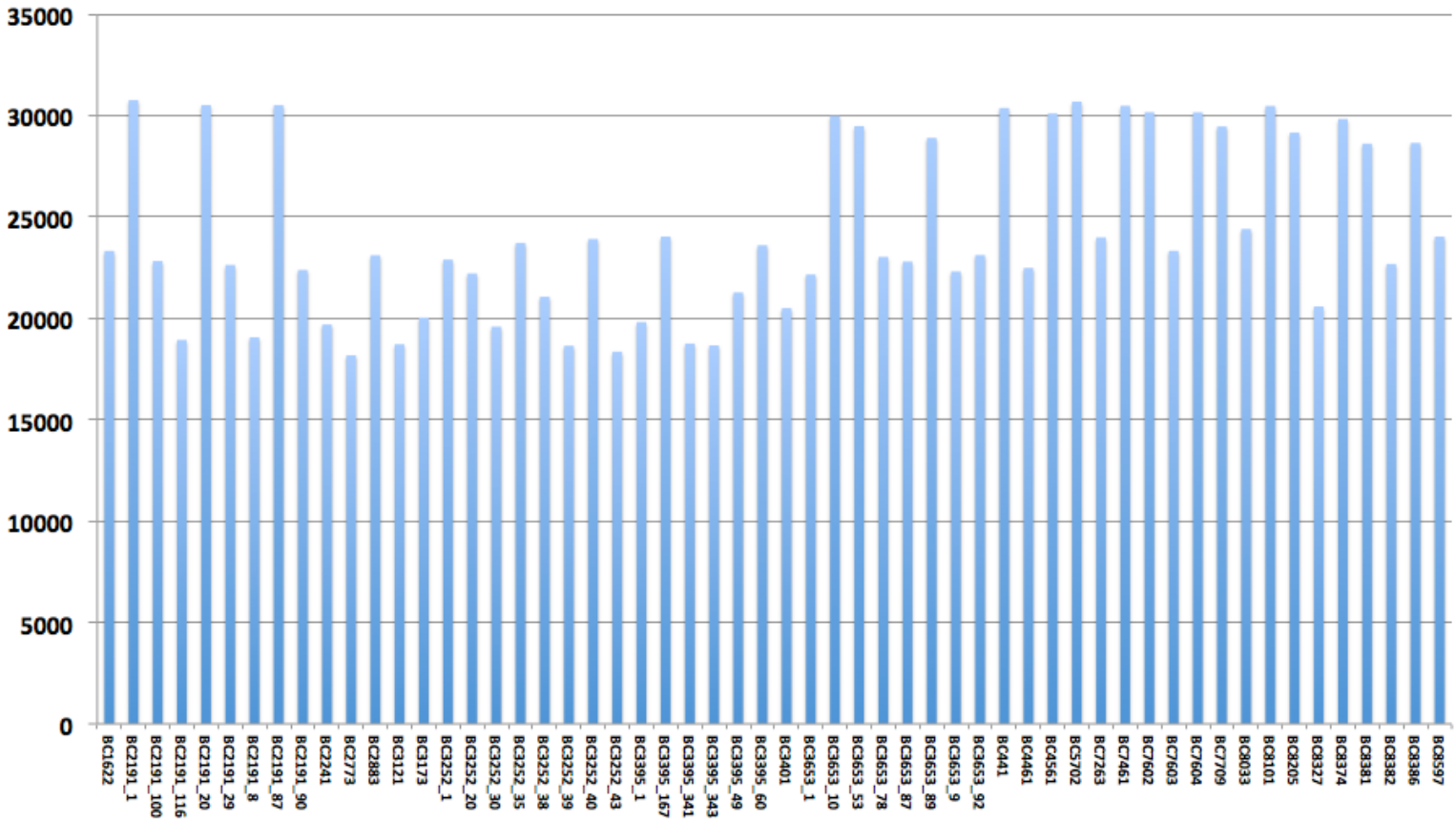
50 exome data from breast cancer



Distribution of variants from the 50 exomes



Variants detected in promoters



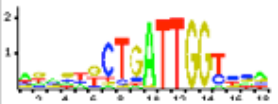
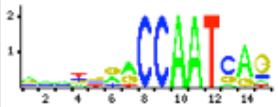
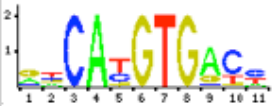
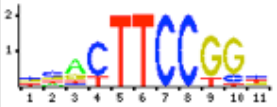
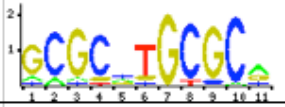
Types of promoter variants identified

Class	Promoter	SNV	Indel	Total
Known motif	601	521	57	578
TFBS motif	238	251	37	288
TATA box	179	195	30	225
Total	**1,018**	967	124	**1,091**

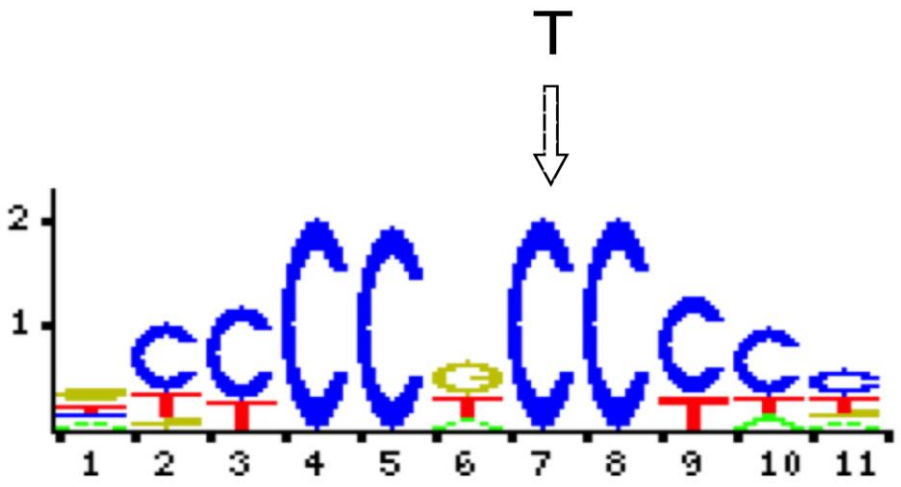
Examples - variants in TATA-boxes

Gene	Chromosome	Position	Reference	Variant	Strand	TATA-box	Changed
SUCLG1	chr2	84686610	A	G	-	TTATAAT	TTACAATT
UGT2B10	chr4	69886144	-	TC	-	TATATAA	TGAATATAA
CMA1	chr14	24977501	A	T	-	TTATAAA	ATATAAA
UFM1	chr13	38923863	T	C	+	TAATTTA	TAACTTA
IL22RA1	chr1	24469814	T	C	-	TACTATTG	TGCTATTG

Examples - variants in TFBS motifs

Gene	Chromosome	Position	Reference	Variant	dbSNP	Strand	Motif start	Motif end	Sequence logo	Name	Class	Family	ID
CHECK2	chr22	29137870	C	T	rs2236141	-	29137869	29137887		NFYA	Other Alpha-Helix	NFY CCAAT-binding	MA0060.2
GID4	chr17	17942708	G	A	Novel	+	17942694	17942709		NFYB	Other Alpha-Helix	NF-Y CCAAT-binding	MA0502.1
MED2B	chr4	17616214	G	T	rs2286773	+	17616212	17616223		USF2	Zipper-Type	Helix-Loop-Helix	MA0526.1
PALB2	chr16	23652769	C	G	Novel	-	23652765	23652776		ELK4	Winged Helix-Turn-Helix	Ets	MA0076.2
SMARCB1	chr22	24129129	G	T	rs11704810	+	24129126	24129137		NRF1	Other	NRF	MA0506.1

Example - a variant in Sp1 binding site

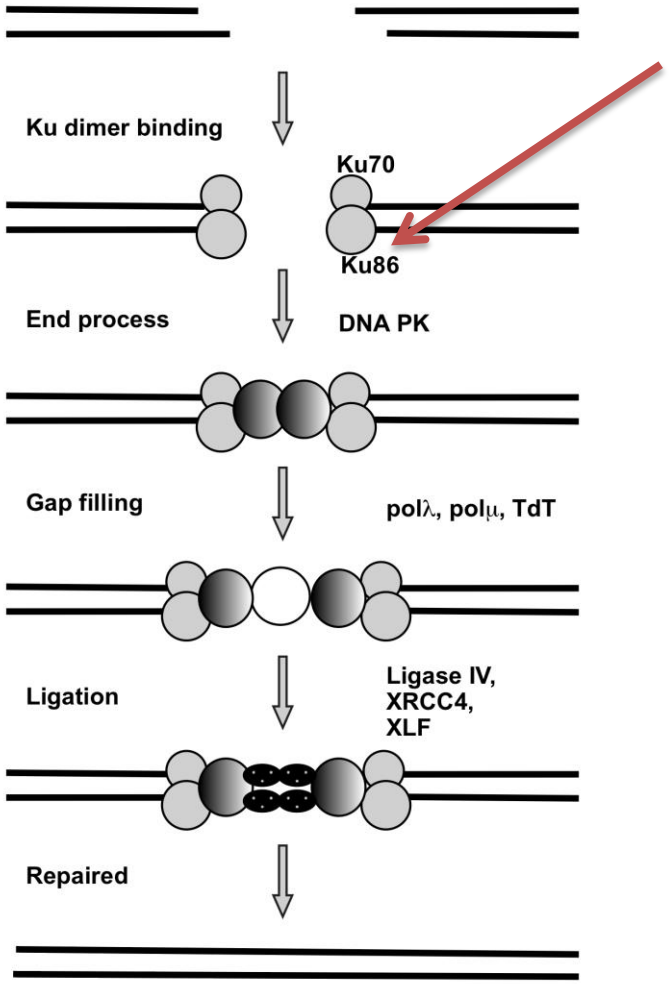


SP1 binding motif

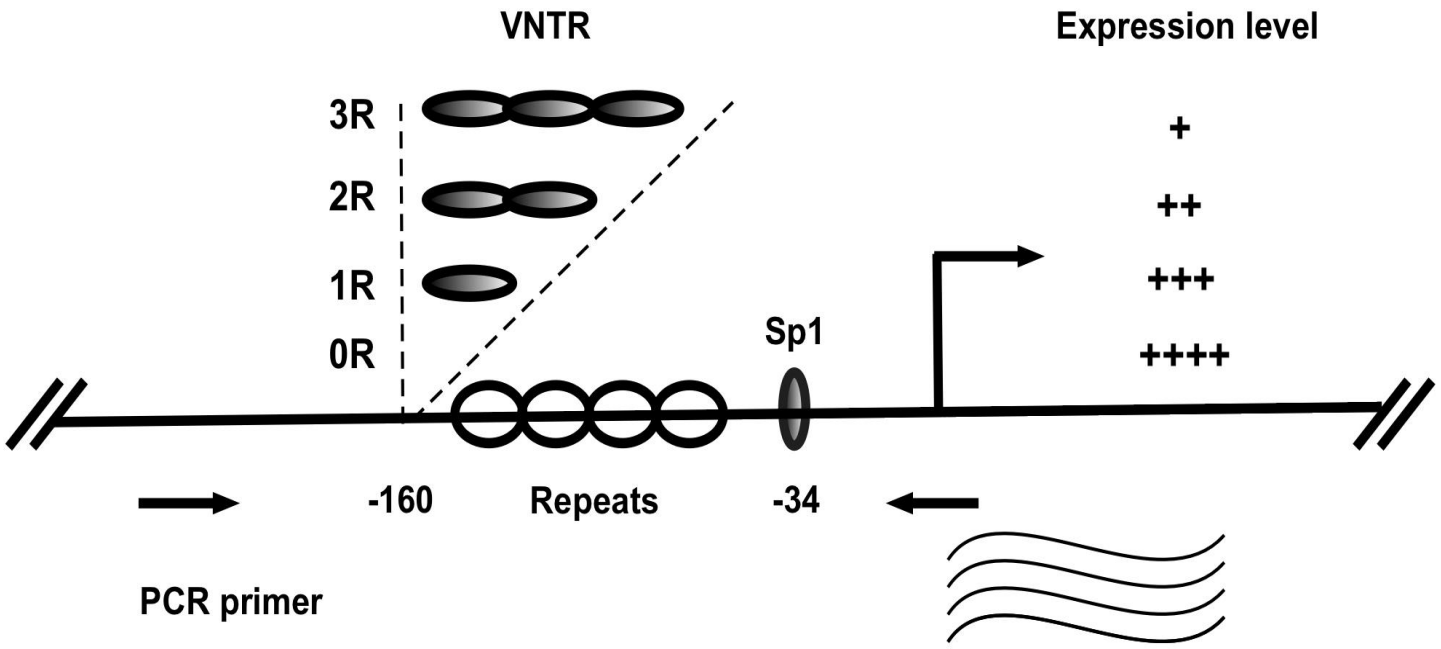
Example - Mapping variants in *XRCC5* promoter

XRCC5:

- Coding for Ku80
- Involve in non-homologous, double-strand break repair (NHEJ) pathway



XRCC5 promoter structure, variable number tandem repeat (VNTR) polymorphism, and expression regulation.

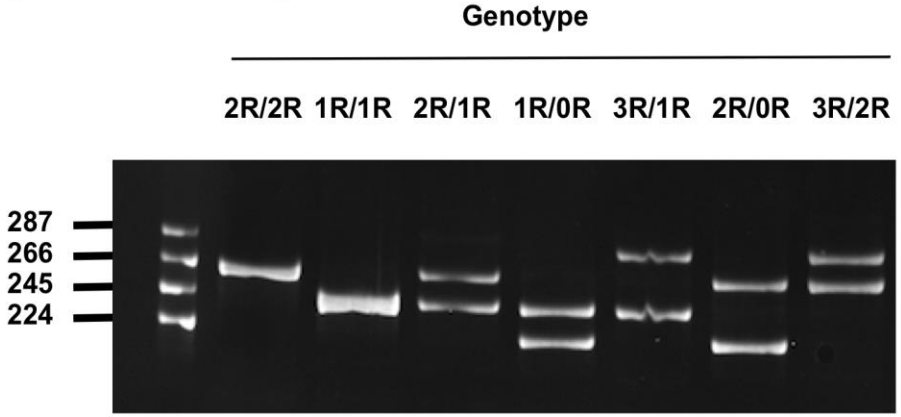


XRCC5 promoter VNTR in breast cancer

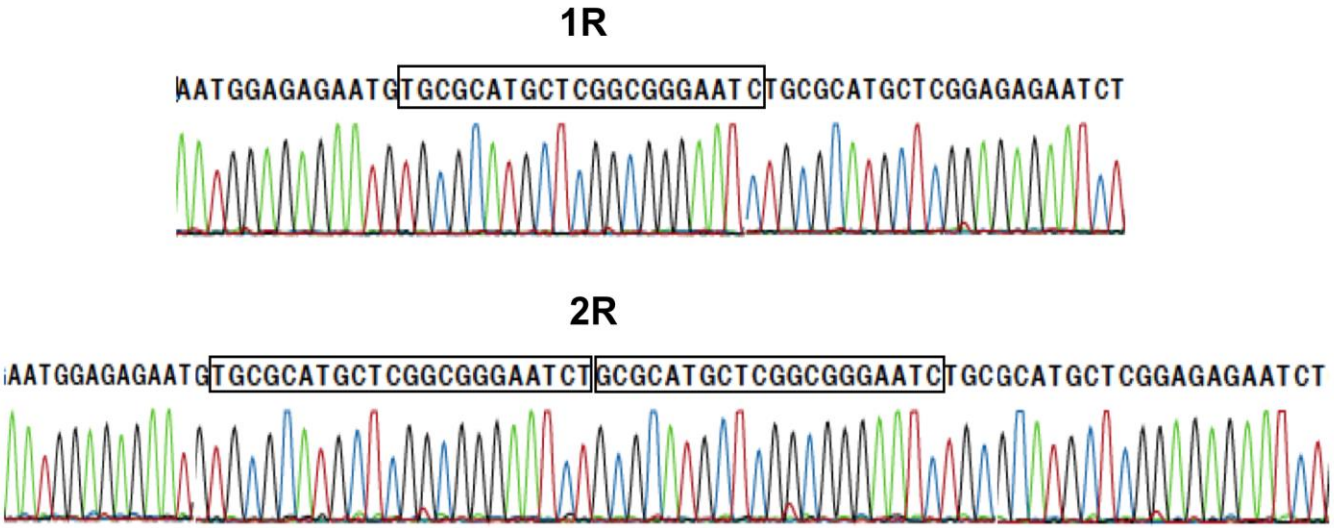
Genotype	Case number (%)*	
	Normal	BRCA1+
2R/2R	4 (7)	12 (28)
1R/2R	42 (72)	25 (58)
1R/1R	11 (19)	5 (12)
0R/2R	1 (2)	1 (2)
0R/1R	0 (0)	0 (0)
Total	58 (100)	43 (100)

* Fisher test: $p<0.03$

A. VNTR genotype shown in PAGE gel



B. VNTR shown by Sanger sequencing



Abundant exome data publically available

- Exome Aggregation Consortium (ExAC): 60,706
- NHLBI GO Exome Sequencing Project (EVS6500): >6500
- 1000 genomes: 2,551
- TCGA breast cancer: 1,081
- GEO: 130
- dbGaP: ?
- …?
- …?

Summary

- GPES method provides a powerful tool for *de novo* promoter analysis, especially in the core-proximal region
- Explore existing exome data using GPES should provide extensive knowledge for promoter architecture in biology and medicine
- Genetic variation in promoter is likely far more complicated than currently consideration

Contribution

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