

# Global Repeat Map algorithm as genomic technology for Higher Order Repeat identification (Case study Human Y Chromosome)

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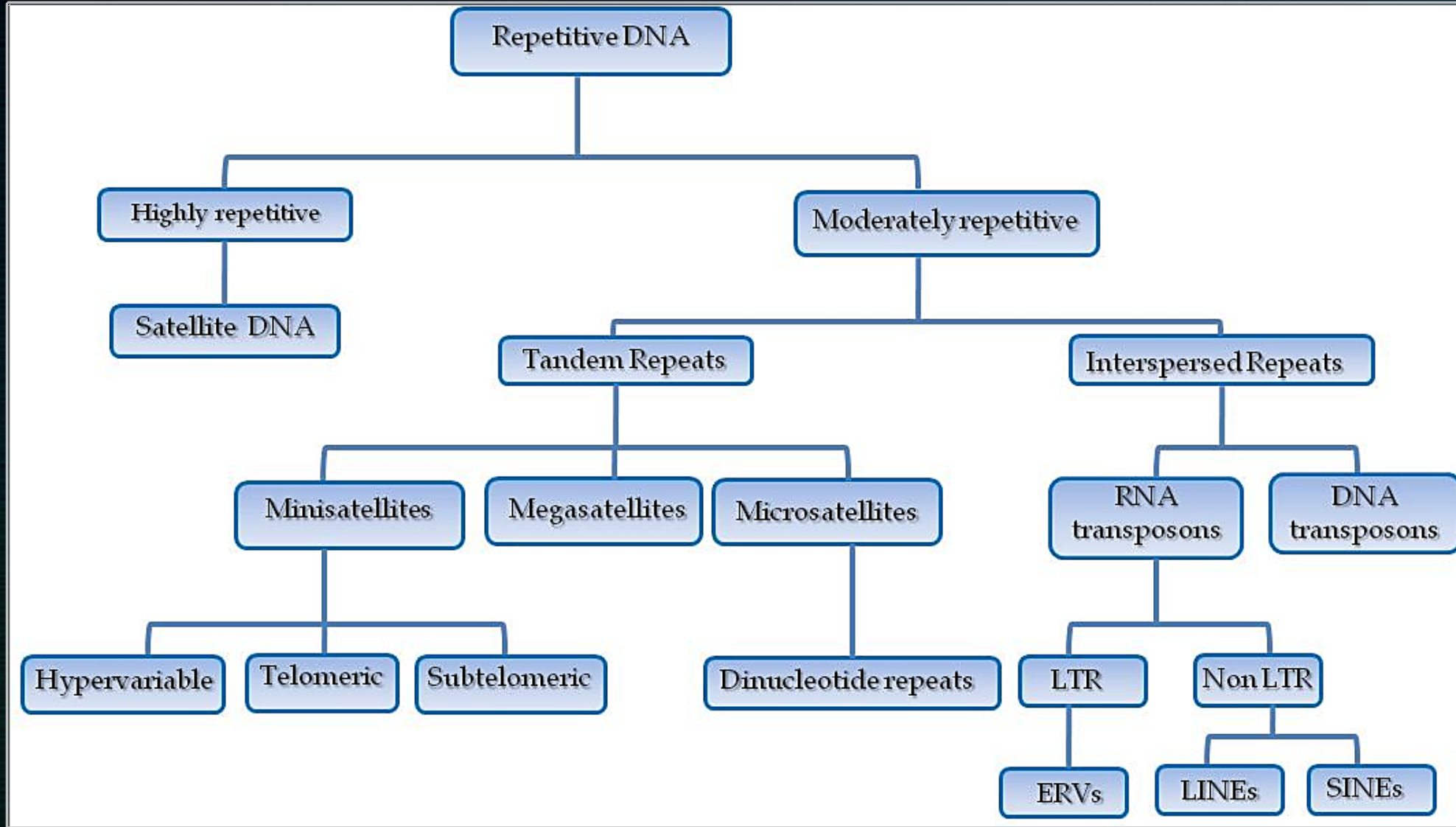
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d School of Medicine, University of Zagreb



# Introduction – types of repetitions

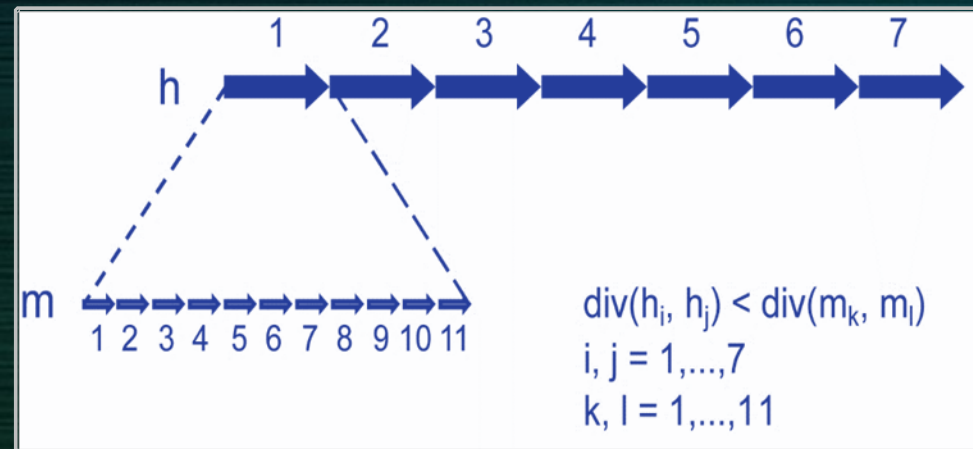


# Introduction - tandem repeats

- tandem repeats – *repeating pattern of nucleotide bases in DNA sequence*



- higher order repeats – HOR

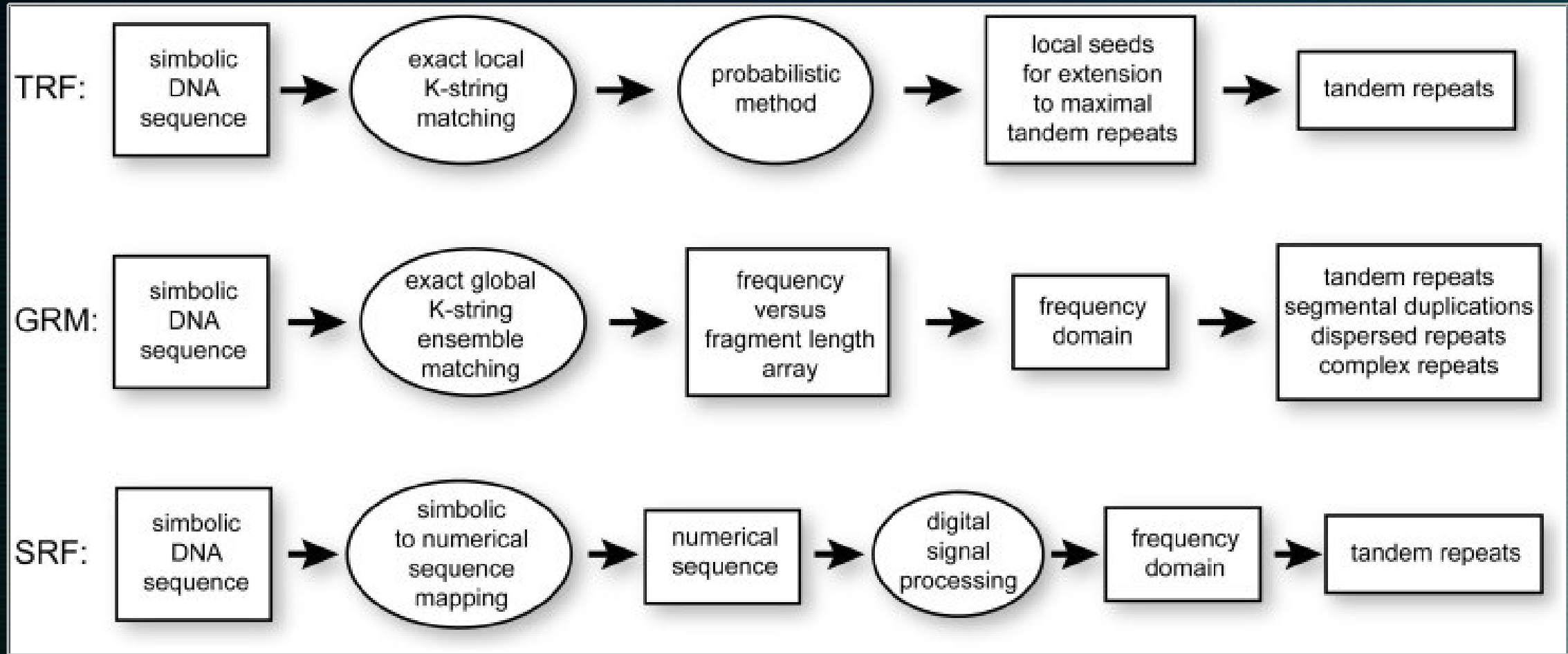


Glunčić M., Paar V. Direct mapping of symbolic DNA sequence into frequency domain in global repeat map algorithm. Nucleic Acids Research, 2012

# What are the roles of tandem repeats?

- **gene regulation**
- **changes in chromatin structure**
- **protein binding sites**
- **development** of the immune system of cells
- repeat **analysis** in closely related species
- **diseases** caused by copy number polymorphism

# Computational methods for tandem repeats detection



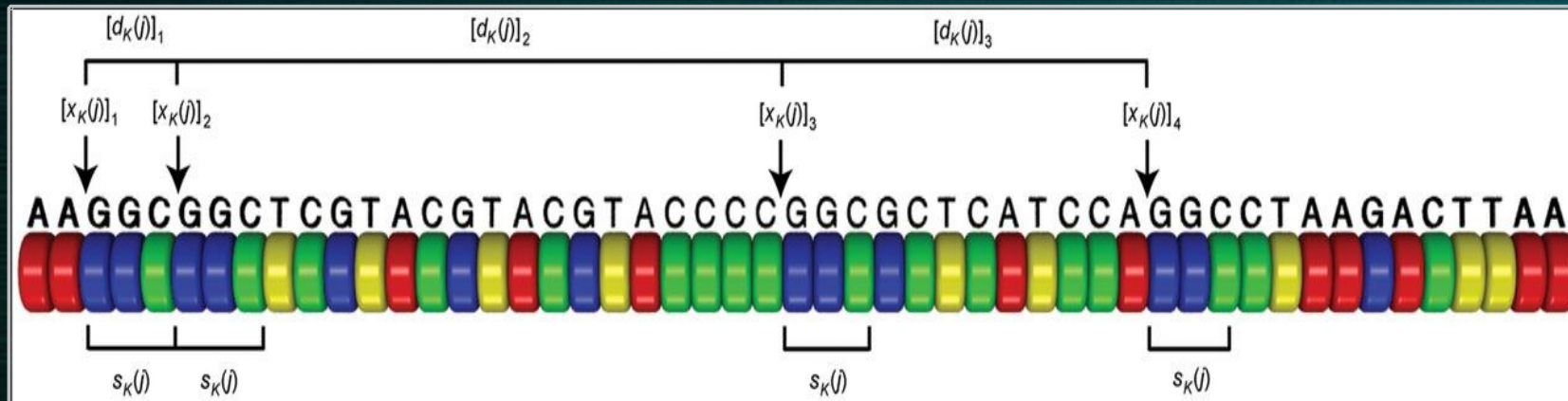
Glunčić M., Paar V. Direct mapping of symbolic DNA sequence into frequency domain in global repeat map algorithm. Nucleic Acids Research, 2012

# Global Repeat Map method

- directly maps the DNA symbolic sequence into the frequency domain- „**GLOBAL MAP**”
- uses a complete **k-word** ensemble (global - local)
- **parameter - free**
- identifies repetitions of **all lengths**
- **robust to copy deviations** from the perfect sample
- identifies higher order repeats (**HOR**)
- consensus lengths and sequences are **simply determined** from results obtained with GRM
- „good” in combination with **BLAST**

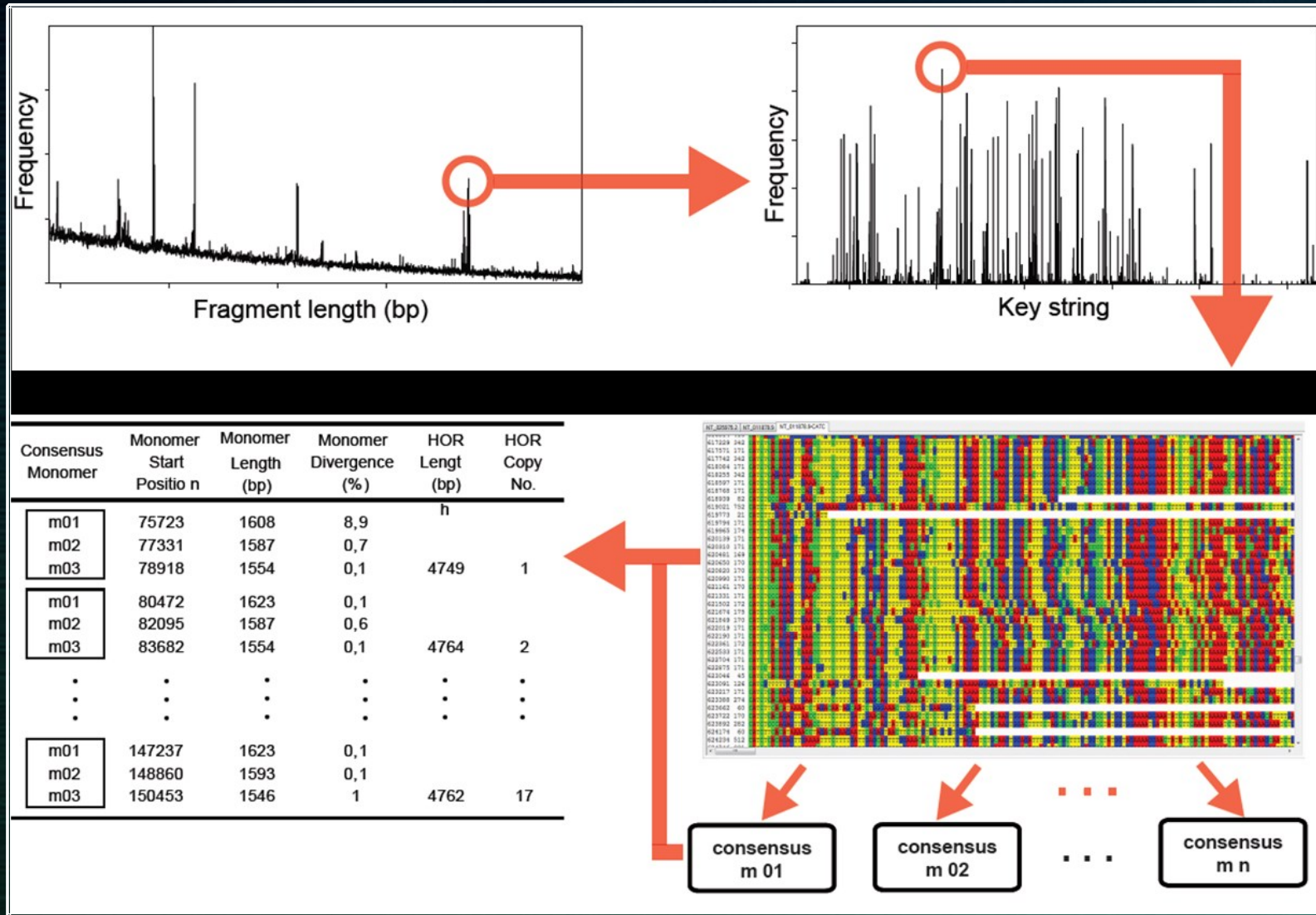
# Global Repeat Map method - GRM

- $S_K(j) = \alpha_1(K, j) \alpha_2(K, j) \alpha_3(K, j) \dots, j = 1, 2, \dots, 4^K$
- $\{X_K(j)\} = [X_K(j)]_1, [X_K(j)]_2, \dots, [X_K(j)]_n, [X_K(j)]_{n+1}$
- $[d_K(j)]_n = [X_K(j)]_{n+1} - [X_K(j)]_n \rightarrow \{d_K(j)\} = [d_K(j)]_1, [d_K(j)]_2, \dots$
- $\{f_K(j)\} = [f_K(j)]^1, [f_K(j)]^2, \dots, [f_K(j)]^V$   
 $\rightarrow \{f_{K(E)}\} = \sum_{j=1}^N [f_K(j)]^1, \sum_{j=1}^N [f_K(j)]^2, \dots, \sum_{j=1}^N [f_K(j)]^V, N = 4^K$



Glunčić M., Paar V. Direct mapping of symbolic DNA sequence into frequency domain in global repeat map algorithm. Nucleic Acids Research, 2012

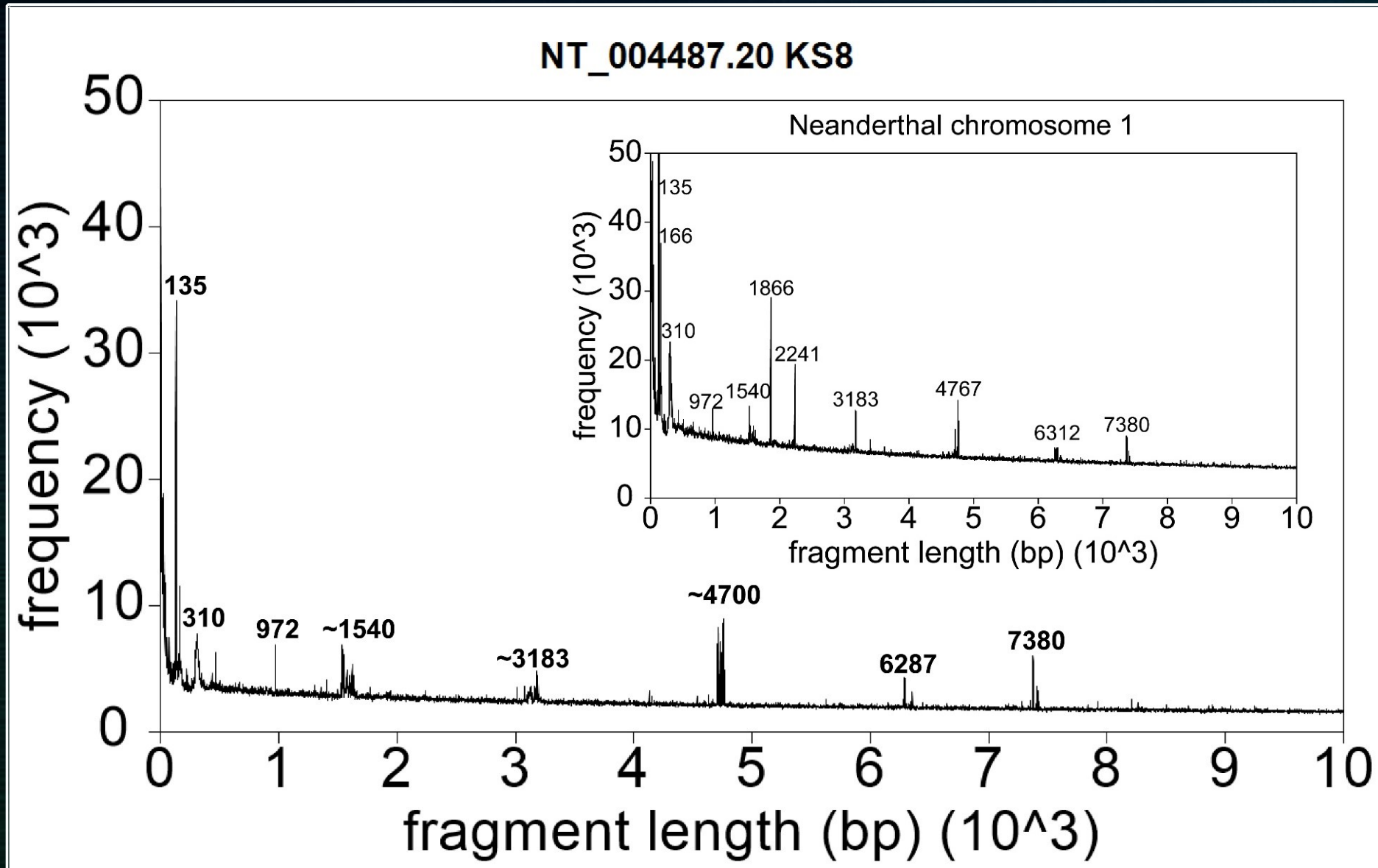
# GRM steps



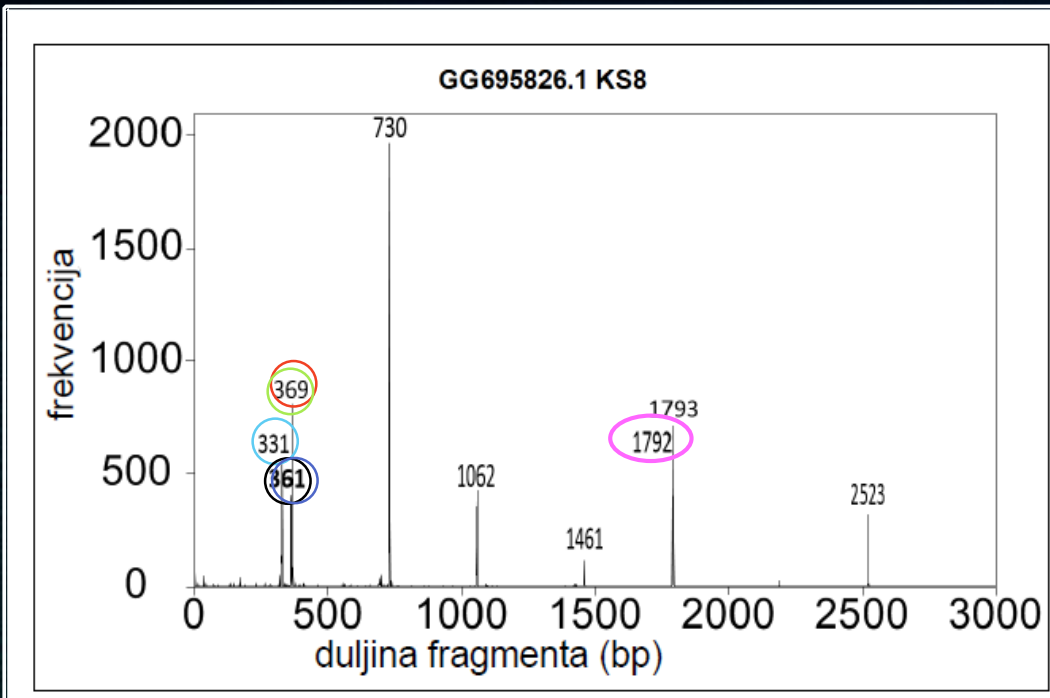
Glunčić M., Paar V. Direct mapping of symbolic DNA sequence into frequency domain in global repeat map algorithm. *Nucleic Acids Research*, 2012



# Examples - GRM diagrams for human and Neanderthal chromosome 1



# GRM steps *T.castenaum* example



Monomer type	length of consensus(bp)	range of copy length
m1	331	328-332
m2	362	362-363
m3	369	369
m4	361	361-362
m5	369	369

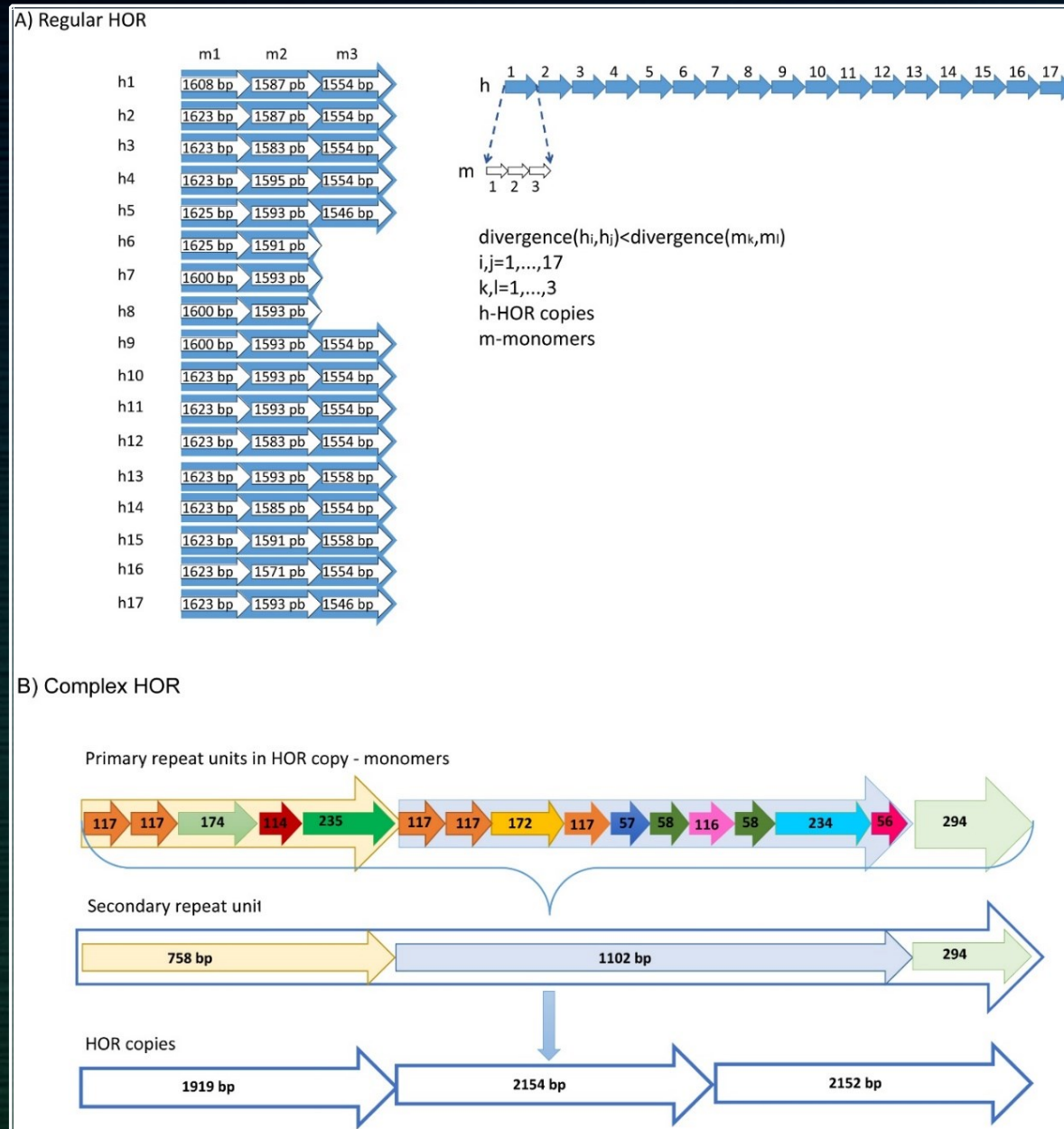
	m1	m2	m3	m4	m5	m6	m7	m8	m9	m10	m11	m12	m13	m14	m15	m16	m17	m18	m19	m20	m21	m22	m23	m24	m25	m26	m27	m28	m29	m30	m31	m32	m33	m34	m35	m36				
m1	1	0	27	9	26	19	8	26	4	27	4.1	27	19	8.6	27	4.1	27	19	8.3	27	3.6	27	19	7.7	26	3.6	27	19	8.3	27	4.4	28	19	8.5	27	4.1	27			
m2	361	0	27	9	26	5	25	26	2	26	2.2	25	26	5.1	25	1.6	24	26	4.9	26	1.4	25	25	4.3	26	2.2	25	26	5.1	26	2.2	25	26	5.1	26	1.6				
m3	731	0	0	26	18	2	26	9	26	9.4	26	18	2.8	26	9.1	26	18	2.5	27	8.8	26	18	2.5	26	8.8	26	19	2.5	27	9.6	27	18	2.5	27	9.4	26				
m4	1094	0	0	25	26	1	25	4	25	5.2	25	26	2.2	25	4.6	25	26	0.8	25	4.3	25	25	0.8	25	5.2	25	26	1.6	26	5.1	25	26	1.6	26	4.6	26				
m5	1463	0	0	17	25	17	25	17	26	1.5	18	25	17	26	2.7	17	25	17	25	2.1	17	25	17	26	3.3	17	25	18	26	0.9	18	25	18	26	26					
m6	1792	0	26	8	25	8.3	26	17	0.6	26	7.7	26	17	0.3	26	7.7	25	17	0.8	25	7.7	26	18	0.3	26	8.6	26	17	0.6	26	8.3	26	26	26	26					
m7	2154	0	0	25	4	25	5.7	25	26	1.1	25	5.2	25	26	0.3	25	4.9	25	25	0.8	25	5.7	25	26	0.5	26	5.7	25	26	0.5	26	5.2	26	5.2	26					
m8	2523	0	0	25	17	25	18	8.8	25	1.7	26	17	8.6	26	0.6	25	18	8	25	1.1	25	18	8.6	26	0.8	26	17	8.8	26	0.6	26	0.6	26	0.6	26					
m9	2884	0	0	0	25	2.4	25	26	3.5	25	1.9	25	26	4.1	25	1.6	25	25	3.5	25	2.4	25	26	4.1	26	2.4	25	26	4.1	26	2.4	25	26	1.9	26					
m10	3253	0	0	0	25	17	8.8	25	2.2	25	17	8.6	26	1.1	25	18	8	25	1.1	25	18	8.6	26	1.9	26	17	8.8	26	1.7	25	1.7	25	1.7	25						
m11	3614	0	26	26	5.7	25	1.1	25	26	6	25	0.8	26	25	5.4	25	1.6	26	26	6.2	26	1.6	26	26	6.2	26	1.6	26	6.2	26	1.1	26	1.1	26	1.1					
m12	3983	0	0	18	25	17	25	2.4	17	25	17	25	1.8	17	25	1.7	25	3	17	25	17	25	3	17	26	18	26	0.9	18	25	18	25	18	25						
m13	4315	0	0	26	8.3	26	18	0.3	26	8.3	26	18	1.4	26	8.3	26	19	0.3	27	9.1	27	17	0.6	26	8.8	26	17	8.8	26	8.8	26	8.8	26	8.8	26					
m14	4677	0	0	25	5.2	25	26	1.4	25	4.9	25	25	1.9	25	5.7	25	26	1.1	26	5.7	25	26	1.1	26	5.7	25	26	1.1	26	5.2	26	5.2	26	5.2	26					
m15	5046	0	25	17	8	25	1.1	25	18	7.5	25	1.7	25	18	8	25	1.9	26	18	8	25	1.9	26	18	8	25	1.9	26	17	8.3	25	1.7	25	1.7	25					
m16	5408	0	25	17	25	5.4	26	0.3	25	25	4.9	26	1.1	26	26	5.7	26	0.5	25	26	5.7	26	0.5	25	26	5.7	26	0.5	26	5.7	26	0.5	26	0.5	26					
m17	5777	0	17	25	17	25	1.2	17	24	17	25	2.4	17	25	18	26	2.1	18	25	18	26	2.1	18	25	18	26	2.1	18	25	18	25	18	25	18	25					
m18	6108	0	0	26	8	26	17	1.1	26	8	26	18	0	26	8.8	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	8.6	26	8.6	26					
m19	6470	0	0	26	5.2	25	25	1.1	26	6	26	0.8	26	6	25	26	0.8	26	6	25	26	0.8	26	6	25	26	0.8	26	6	25	26	0.8	26	6	25	26				
m20	6839	0	0	25	18	7.5	25	0.6	25	18	8	26	0.8	26	17	8.3	26	0.6	26	17	8.3	26	0.6	26	17	8.3	26	0.6	26	17	8.3	26	0.6	26	0.6	26				
m21	7200	0	25	25	4.6	25	0.8	26	26	5.4	26	0.8	25	26	0.8	25	26	0.8	25	26	5.4	26	0.8	25	26	0.8	25	26	5.4	26	0.3	26	0.3	26	0.3	26				
m22	7569	0	0	17	25	18	25	1.8	17	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25			
m23	7900	0	25	7.5	25	18	1.1	26	8.3	26	17	1.4	26	8	25	1.9	26	18	8	25	1.9	26	18	8	25	1.9	26	18	8	25	1.9	26	18	8	25	1.9	26			
m24	8262	0	25	5.4	25	26	1.4	26	5.4	25	26	1.4	26	5.4	25	26	1.4	26	5.4	25	26	1.4	26	5.4	25	26	1.4	26	5.4	25	26	1.4	26	5.4	25	26	1.4	26		
m25	8631	0	25	18	8	26	1.4	26	17	8.3	26	1.1	26	18	8	26	1.4	26	17	8.3	26	1.1	26	18	8	26	1.4	26	17	8.3	26	1.1	26	1.1	26	1.1	26			
m26	8992	0	26	26	6.2	26	1.6	25	26	6.2	26	1.6	25	26	6.2	26	1.6	25	26	6.2	26	1.6	25	26	6.2	26	1.6	25	26	6.2	26	1.6	25	26	6.2	26	1.6	25	26	
m27	9361	0	0	18	26	19	26	2.7	18	25	18	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26			
m28	9689	0	26	8.8	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26		
m29	10051	0	26	6.2	25	27	0.5	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26	5.7	26		
m30	10420	0	27	18	9.1	26	0.8	26	9	26	0.8	26	9	26	0.8	26	9	26	0.8	26	9	26	0.8	26	9	26	0.8	26	9	26	0.8	26	9	26	0.8	26	9	26		
m31	10781	0	0	26	27	6.2	27	0.5	26	27	6.2	27	0.5	26	27	6.2	27	0.5	26	27	6.2	27	0.5	26	27	6.2	27	0.5	26	27	6.2	27	0.5	26	27	6.2	27	0.5	26	
m32	11150	0	0	17	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	25	18	25	1.5	18	
m33	11481	0	0	26	8.8	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	8.6	26	17	0.3	26	
m34	11844	0	0	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26
m35	12213	0	0	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26
m36	12574	0	0	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26	5.7	26	1.4	26

	0	500	1000	1500
h1				360 370
h2		363	369	
h3	329	362	369	361 369
h4				361 369
h5	332	362	369	362 369
h6	331	362	369	361 369
h7	331	362	369	361 369
h8	328	362	369	361 369
h9	331	363	369	361 368



Consensus length

# Types of HOR structures



Vlahović I., Glunčić M., Rosandić M., Ugarković Đ., Paar V.. Regular Higher Order Repeat Structures in Beetle *Tribolium castaneum* Genome. Genome Biol.Evol., 2016. A.) Regular HOR. B) complex HOR.

# Results

## Intragenic Higher Order Repeats in Neuroblastoma BreakPoint Family Genes Distinguish Humans from Chimpanzees

Vladimir Paar,\*†<sup>1</sup> Matko Glunčić,†<sup>1</sup> Marija Rosandić,<sup>2</sup> Ivan Basar,<sup>1</sup> and Ines Vlahović<sup>1</sup>

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†These authors contributed equally to this work.

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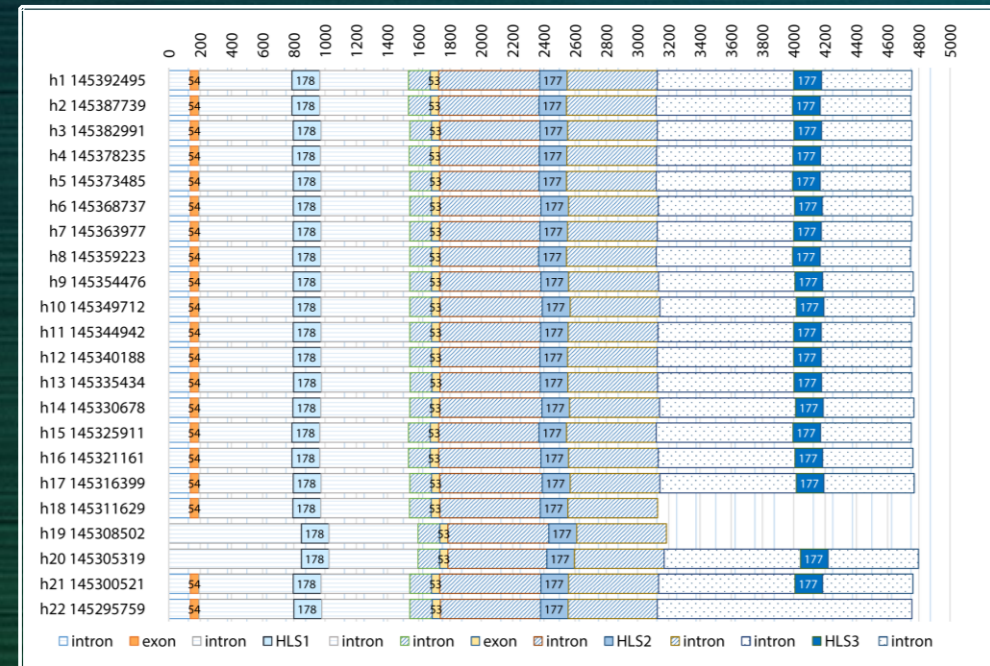
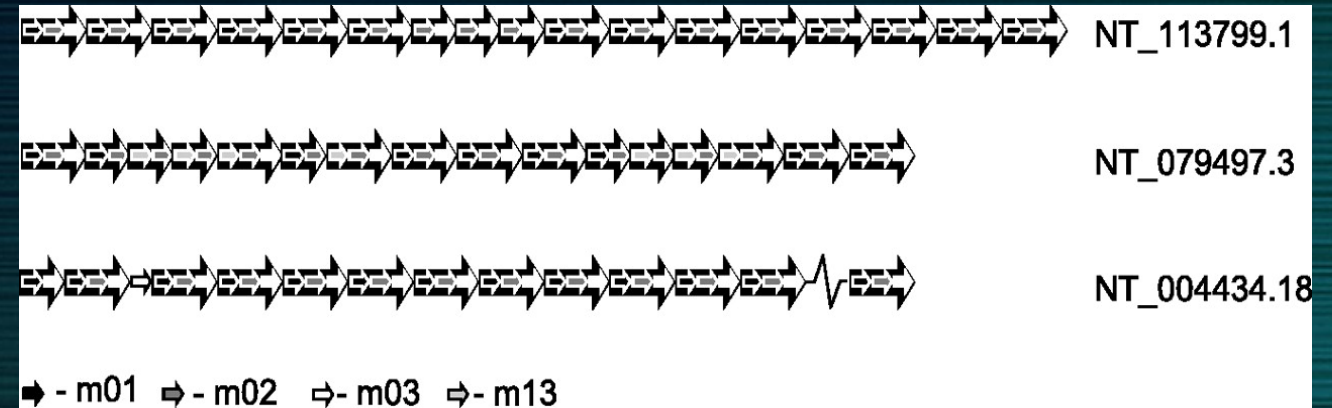
### Abstract

Much attention has been devoted to identifying genomic patterns underlying the evolution of the human brain and its emergent advanced cognitive capabilities, which lie at the heart of differences distinguishing humans from chimpanzees, our closest living relatives. Here, we identify two particular intragenic repeat structures of noncoding human DNA, spanning as much as a hundred kilobases, that are present in human genome but are absent from the chimpanzee genome and other nonhuman primates. Using our novel computational method Global Repeat Map, we examine tandem repeat structure in human and chimpanzee chromosome 1. In human chromosome 1, we find three higher order repeats (HORs), two of them novel, not reported previously, whereas in chimpanzee chromosome 1, we find only one HOR, a 2mer alphoid HOR instead of human alphoid 11mer HOR. In human chromosome 1, we identify an HOR based on 39-bp primary repeat unit, with secondary, tertiary, and quartic repeat units, fully embedded in human hornerin gene, related to regenerating and psoriatic skin. Such an HOR is not found in chimpanzee chromosome 1. We find a remarkable human 3mer HOR organization based on the ~1.6-kb primary repeat unit, fully embedded within the neuroblastoma breakpoint family genes, which is related to the function of the human brain. Such HORs are not present in chimpanzees. In general, we find that human–chimpanzee differences are much larger for tandem repeats, in particularly for HORs, than for gene sequences. This may be of great significance in light of recent studies that are beginning to reveal the large-scale regulatory architecture of the human genome, in particular the role of noncoding sequences. We hypothesize about the possible importance of human accelerated HOR patterns as components in the gene expression multilayered regulatory network.

**Key words:** human brain evolution, chromosome 1, higher order repeats, NBPF genes, human hornerin gene, global repeat map.

Research article  
doi:10.1371/journal.pcbi.1001911

Schematic illustrating three NBPF 3mer HOR copies based on the ~1.6-bp monomers in human chromosome 1. (Results from 2011 -Build 36.3 assembly)



Schematic illustrating three NBPF 3mer HOR copies based on the ~1.6-bp monomers in human chromosome 1. (Results from 2019, Build hg38 assembly)

V. Paar, M. Glunčić, M. Rosandić, I. Basar, I. Vlahović, **Intragenic Higher Order Repeats in Neuroblastoma BreakPoint Family Genes Distinguish Humans from Chimpanzees**, *Molecular Biology and Evolution*, Volume 28, Issue 6, June 2011, Pages 1877–1892

# Results

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†These authors contributed equally to this work.

\*Corresponding author: E-mail: paar@hazu.hr.

Associate editor: James McInerney

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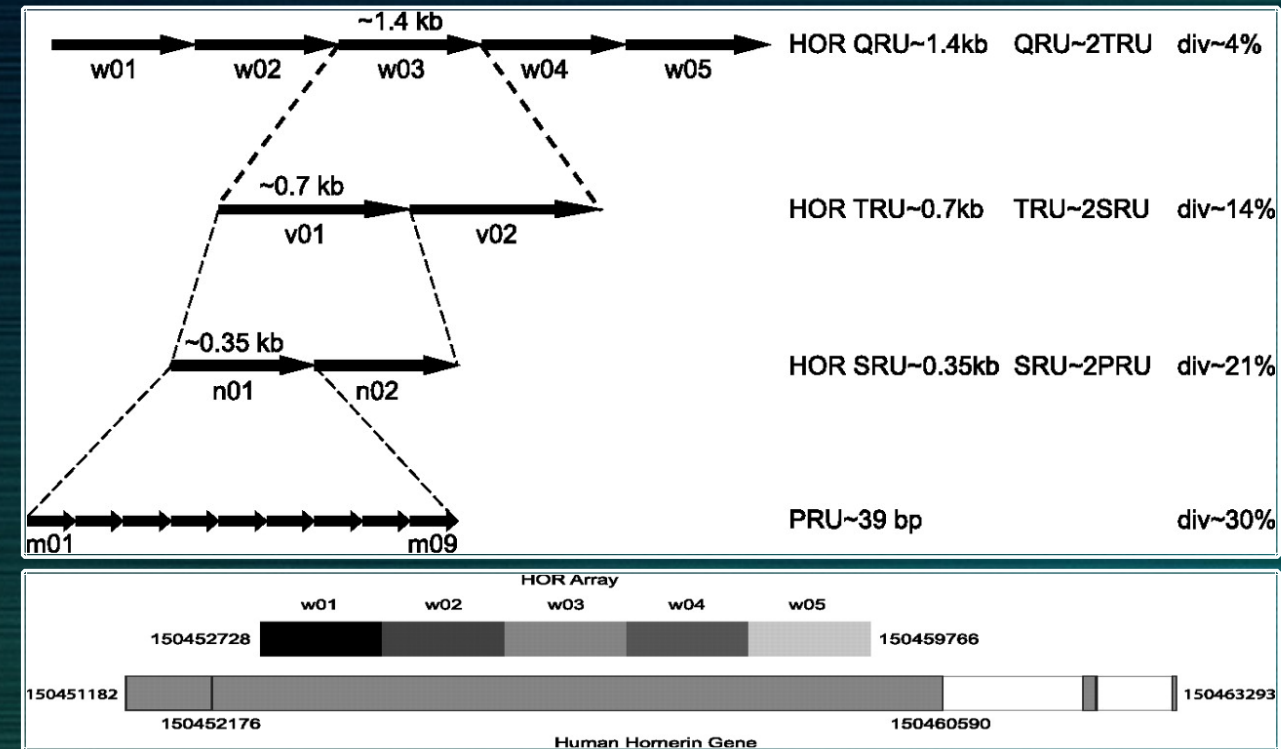
**Key words:** human brain evolution, chromosome 1, higher order repeats, NBPF genes, human hornerin gene, global repeat map.

Research article

10.1093/molbev/article-abstract/29/6/1182

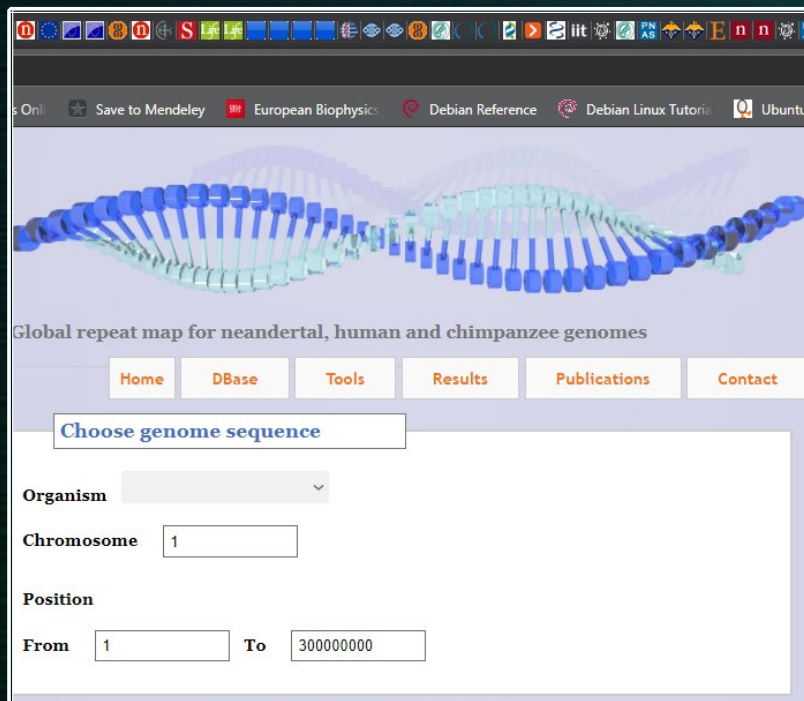
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Schematic illustrating hierarchical structure of 1,410-bp quartic HOR.



Confirmed by V. Romero et al. **High Order Formation and Evolution of Hornerin in Primates**. *Genome Biology and Evolution*, Volume 10, Issue 12, December 2018, Pages 3167–3175.

# HRZZ project – Human-Neanderthal – Chimpanzee -Results



- Goal of the project:
  - Creation of the repetition database for human, Neanderthal and chimpanzee genomes (<http://genom.hazu.hr>)
  - Over 2000 records
  - **ALPHAsub** algorithm -extension

# Results chromosome 21

www.nature.com/scientificreports

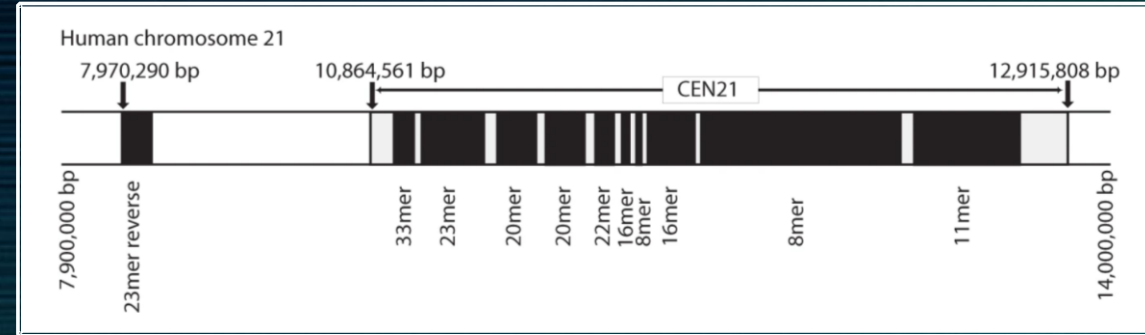
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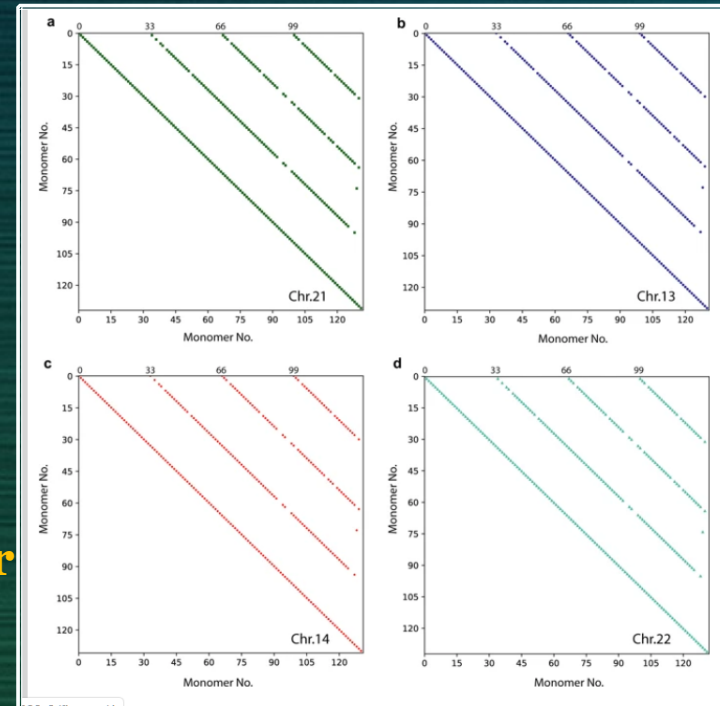
## Discovery of 33mer in chromosome 21 – the largest alpha satellite higher order repeat unit among all human somatic chromosomes

Matko Glunčić<sup>1</sup>, Ines Vlahović<sup>1,2</sup> & Vladimir Paar<sup>1,3</sup>

The centromere is important for segregation of chromosomes during cell division in eukaryotes. Its destabilization results in chromosomal missegregation, aneuploidy, hallmarks of cancers and birth defects. In primate genomes centromeres contain tandem repeats of ~171 bp alpha satellite DNA, commonly organized into higher order repeats (HORs). In spite of crucial importance, satellites have been understudied because of gaps in sequencing - genomic "black holes". Bioinformatical studies of genomic sequences open possibilities to revolutionize understanding of repetitive DNA datasets. Here, using robust (Global Repeat Map) algorithm we identified in hg38 sequence of human chromosome 21 complete ensemble of alpha satellite HORs with six long repeat units ( $\geq 20$  mers), five of them novel. Novel 33mer HOR has the longest HOR unit identified so far among all somatic chromosomes and novel 23mer reverse HOR is distant far from the centromere. Also, we discovered that for hg38 assembly the 33mer sequences in chromosomes 21, 13, 14, and 22 are 100% identical but nearby gaps are present; that seems to require an additional more precise sequencing. Chromosome 21 is of significant interest for deciphering the molecular base of Down syndrome and of aneuploidies in general. Since the chromosome identifier probes are largely based on the detection of higher order alpha satellite repeats, distinctions between alpha satellite HORs in chromosomes 21 and 13 here identified might lead to



Alpha satellite HOR ideogram for linear positioning of alpha satellite HOR arrays with long repeat units ( $n \geq 8$ ).



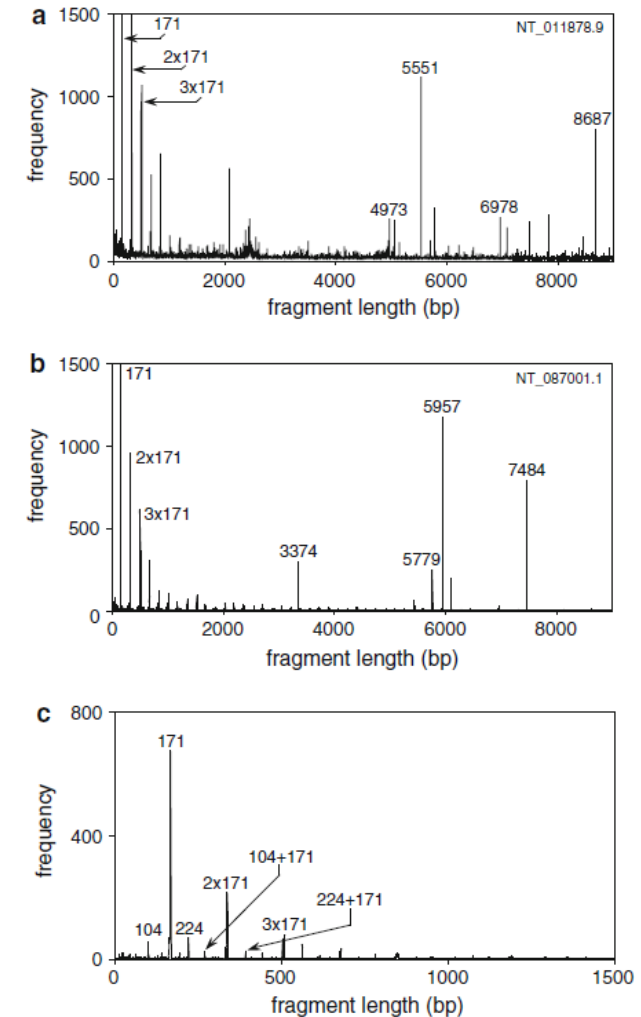
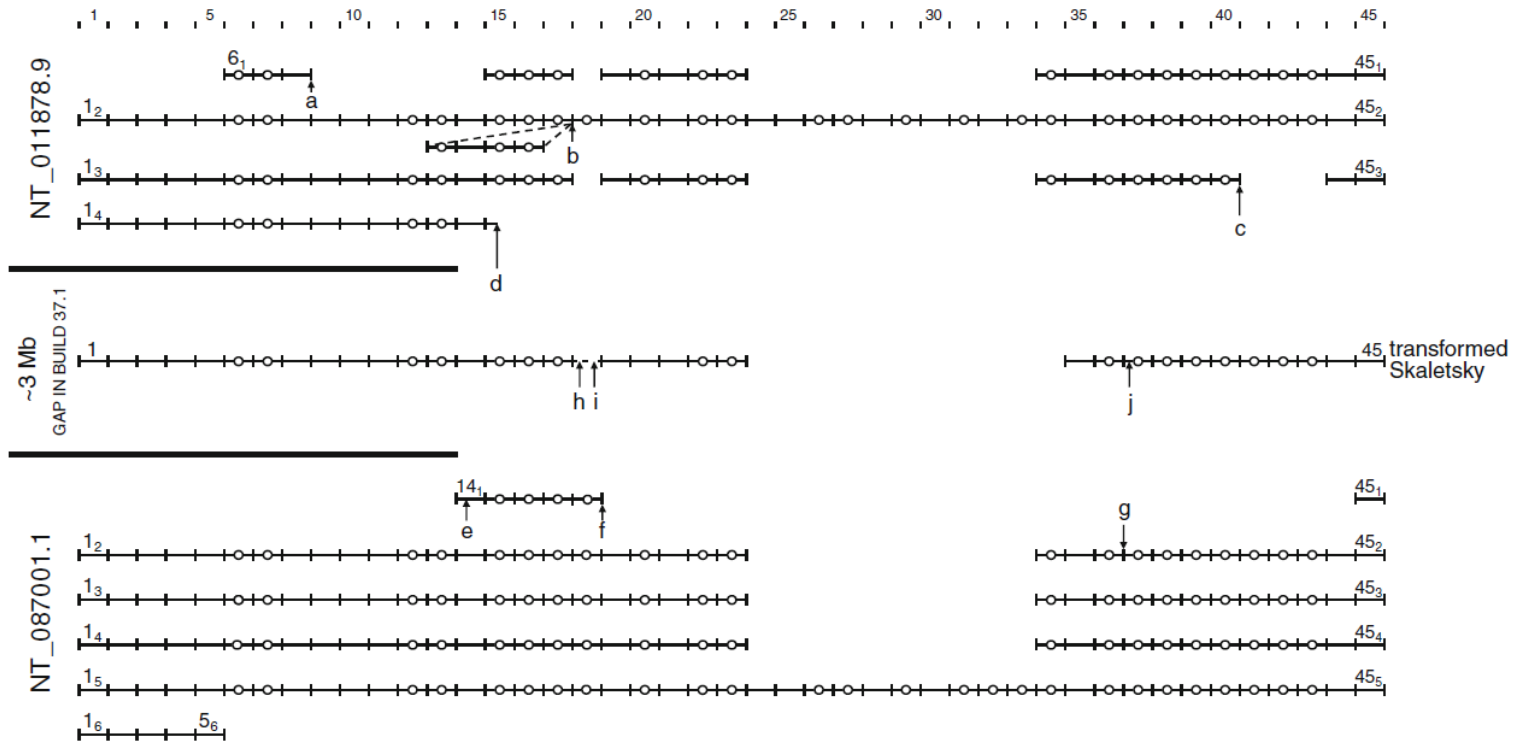
Dot-matrix plots of 33mer HORs in four acrocentric chromosomes. (a) chromosome 21; (b) chromosome 13; (c) chromosome 14; (d) chromosome 22.

M. Glunčić, I. Vlahović, V. Paar . **Discovery of 33mer in chromosome 21 – the largest alpha satellite higher order repeat unit among all human somatic chromosomes.** Scientific Reports volume 9, Article number: 12629 (2019)

# Results chromosome Y

J Mol Evol (2011) 72:34–55

41

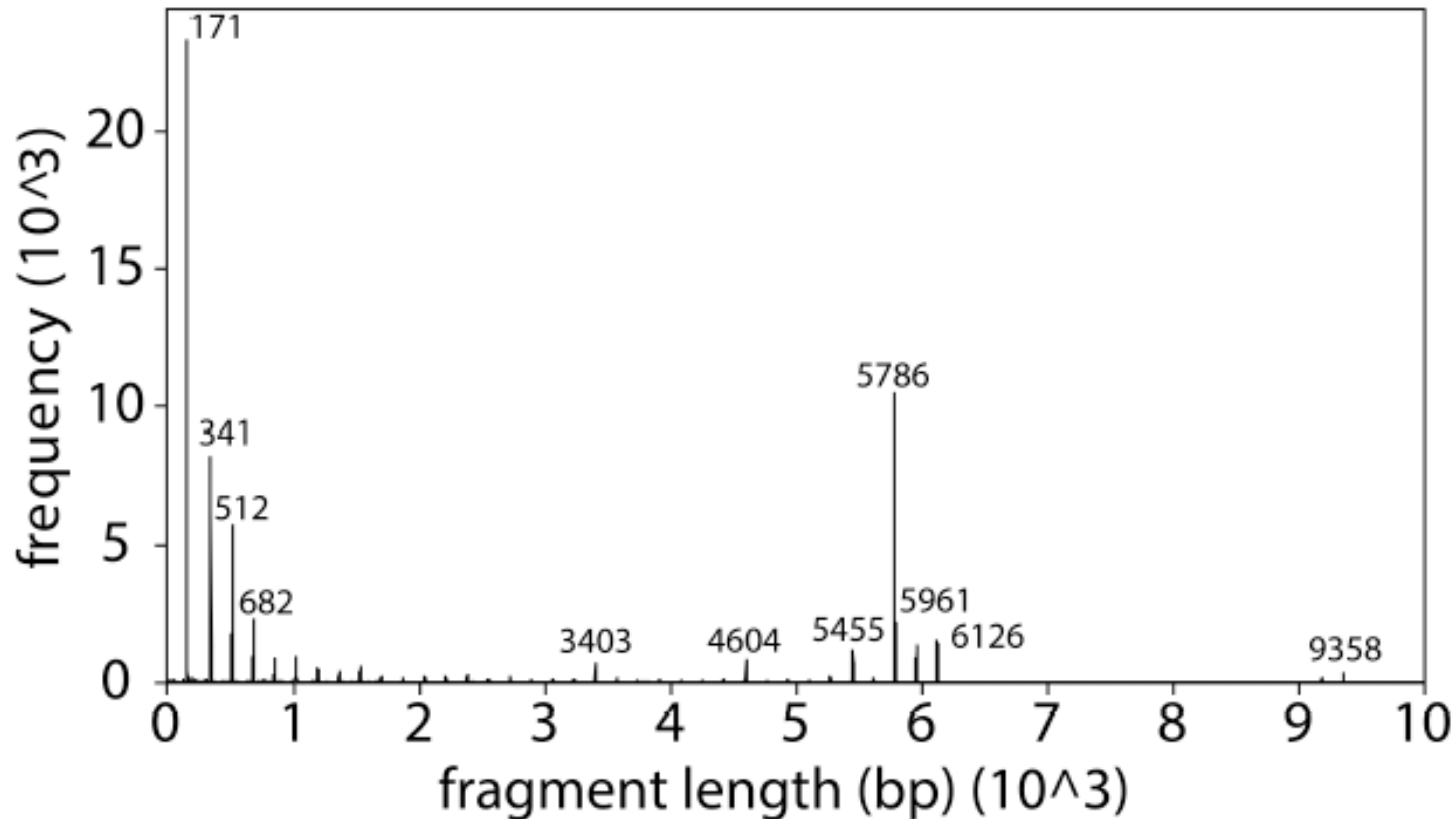


Schematic presentation of aligned monomer structure of 45mer alphoid HOR (consensus length 7662 bp) in human chromosome Y (Build 37.1). V. Paar, M. Glunčić, I. Basar, M. Rosandic, P. Paar, M. Cvitković. **Large Tandem, Higher Order Repeats and Regularly Dispersed Repeat Units Contribute Substantially to Divergence Between Human and Chimpanzee Y Chromosomes.** 2011, Journal of Molecular Evolution 72(1):34-55

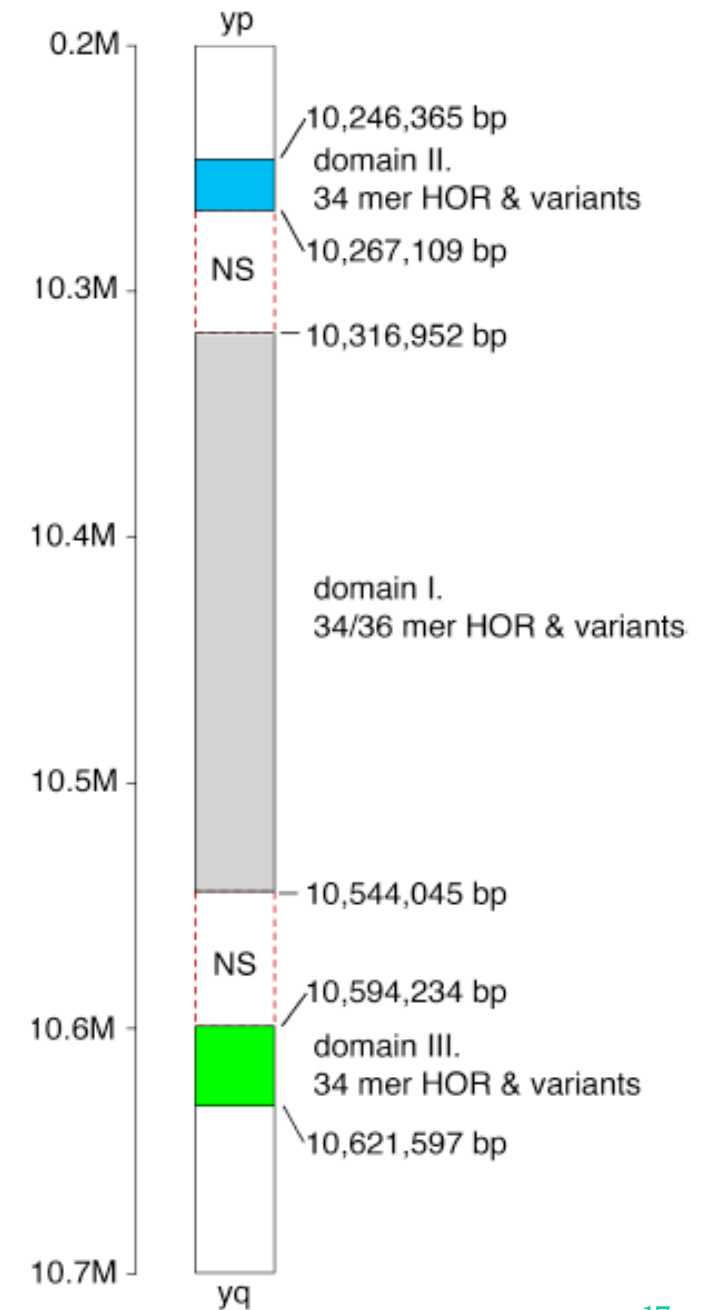


# Results chromosome Y

GRM diagram and ideogram for human chromosome Y (Build hg38).

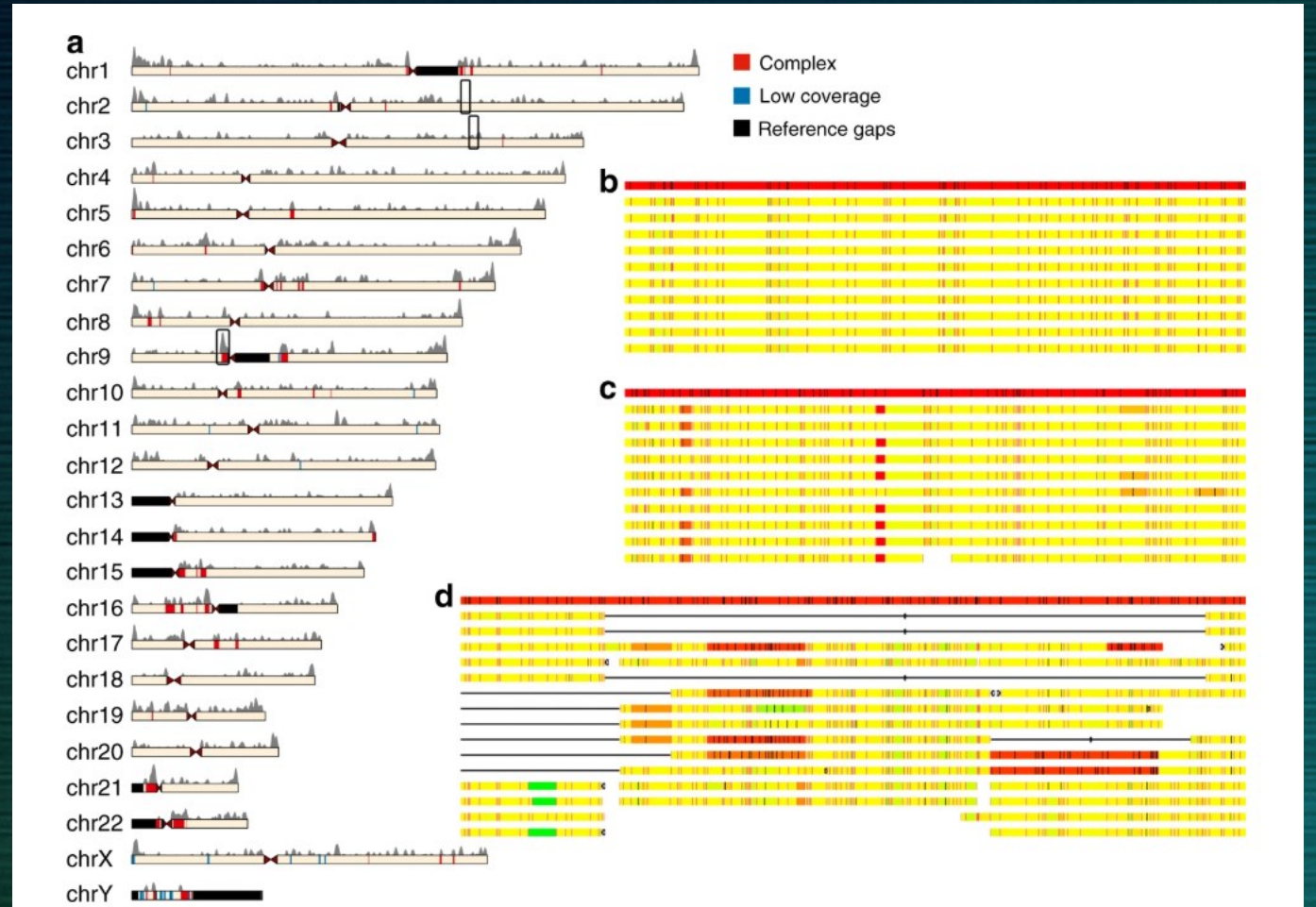


I. Vlahović, M. Glunčić, V. Paar. **Rich polymorphic variants of alpha satellite 34mer higher order repeats in hg38 assembly of human chromosome Y.** (submitted paper)



# What are disadvantages of GRM algorithm?

- main: it depends only on DNA sequences, so variation in schemas are **due to different assemblies of genomes** because of tandem repeats which are very hard to assemble
- solution → **new sequencing technologies** able to sequence complex region of genomes



Michal Levy-Sakin et al. **Genome maps across 26 human populations reveal population-specific patterns of structural variation.** Nature Communications volume 10, Article number: 1025 (2019). <sup>18</sup>

# Future work

## DNA analysis of some diseases:



- autism genomes  
<https://research.mss.ng/>

- cancer genomes  
<https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga>


- **population genomics/genetics:**

- structural variants in tandem and HOR repeats

- **differences** in repeats between close related species (in animals and plants)



Review  
**Repetitive Fragile Sites: Centromere Satellite DNA as a Source of Genome Instability in Human Diseases**  
Elizabeth M. Black and Simona Giunta \*  
Laboratory of Chromosome and Cell Biology, The Rockefeller University, 1230 York Avenue, New York, NY 10065, USA;  
\* Correspondence:




Received: 5 Nov 2019  
Abstract: Mair...  
The centromer...  
each round of c...  
alpha-satellite l...

ARTICLE  
<https://doi.org/10.1038/s41467-019-08992-7> OPEN

**Genome maps across 26 human populations reveal population-specific patterns of structural variation**

Michal Levy-Sakin<sup>1</sup>, Steven Pastor<sup>2</sup>, Eleanor Young<sup>2</sup>, Ernest T. Lam<sup>5</sup>, A Justin Sibert<sup>2</sup>, Ramakrishnan Rajag Chin Lin<sup>1</sup>, Ahmed Naguib<sup>5</sup>, Wei-Pin Pui-Yan Kwok<sup>1,8,9</sup>

Large structural variants (SVs) in the h...  
conventional sequencing technologies. V...  
optical mapping, one can identify large...  
Analyzing optical genome maps of 154 i...  
1000 Genomes Project, we find that phyl...  
to those of single nucleotide variations...  
genome has high structural complexity...



natureresearch


OPEN **The Genomic Landscape of Centromeres in Cancers**

Anjan K. Saha<sup>1,2,3</sup>, Mohamad Mourad<sup>3</sup>, Mark H. Kaplan<sup>3</sup>, Ilana Chefetz<sup>4</sup>, Sami N. Malek<sup>3</sup>, Ronald Buckanovich<sup>5</sup>, David M. Markovitz<sup>2,3,6,7</sup> & Rafael Contreras-Galindo<sup>3,4</sup>

Centromere genomics remain poorly characterized in cancer, due to technologic limitations in sequencing and bioinformatics methodologies that make high-resolution delineation of centromeric

2019  
2019  
02 August 2019

Garbus et al. *BMC Genomics* (2015) 16:375  
DOI 10.1186/s12864-015-1579-0



RESEARCH ARTICLE Open Access

**Characterization of repetitive DNA landscape in wheat homeologous group 4 chromosomes**

Ingrid Garbus<sup>1†</sup>, José R Romero<sup>1†</sup>, Miroslav Valarik<sup>2</sup>, Hana Vanžurová<sup>2</sup>, Miroslava Karafiátová<sup>2</sup>, Mario Cáccamo<sup>3</sup>, Jaroslav Doležel<sup>2</sup>, Gabriela Tranquilli<sup>4</sup>, Marcelo Helguera<sup>5</sup> and Viviana Echenique<sup>1\*</sup>

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