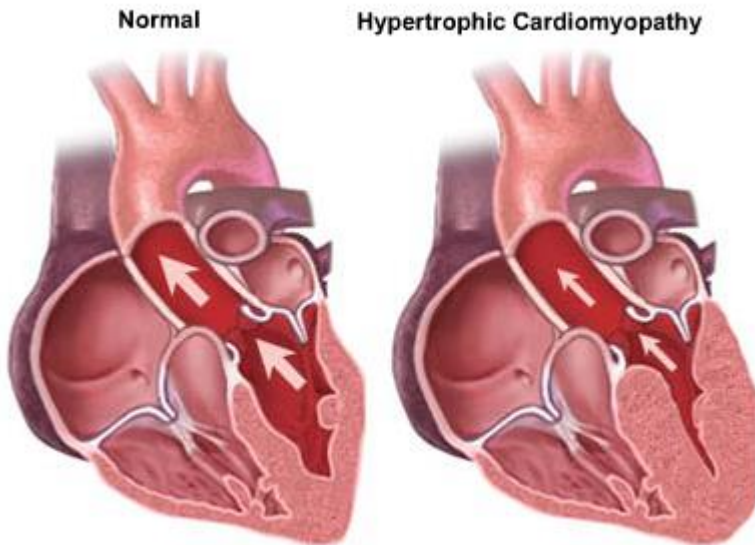


Natural selection against insufficiency in sarcomeric proteins reduces the risks of cardiomyopathy in humans versus chimpanzees as conventionally the nearest wild congeners, for whom it is the most common cause of spontaneous mortality

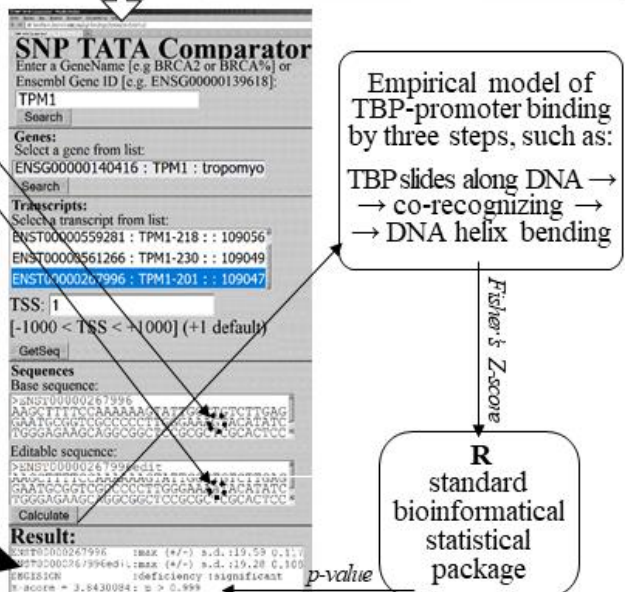
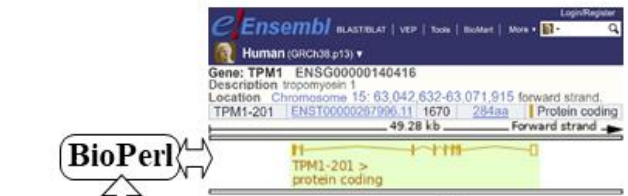
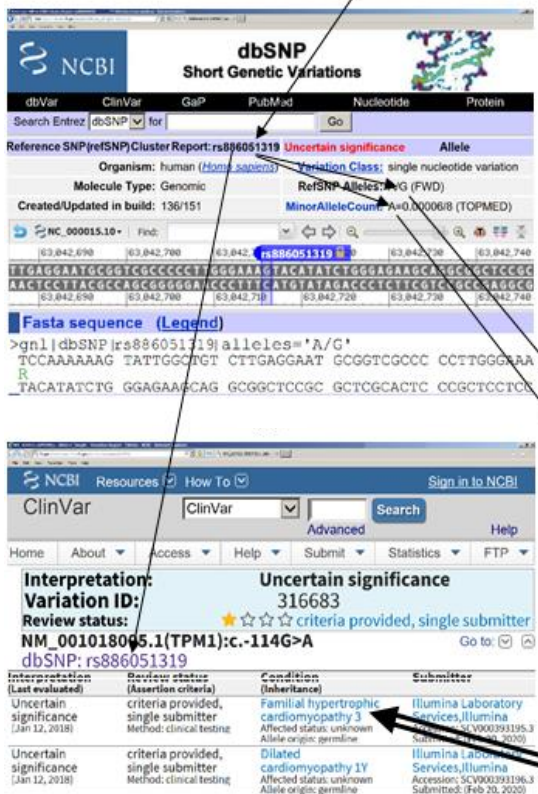
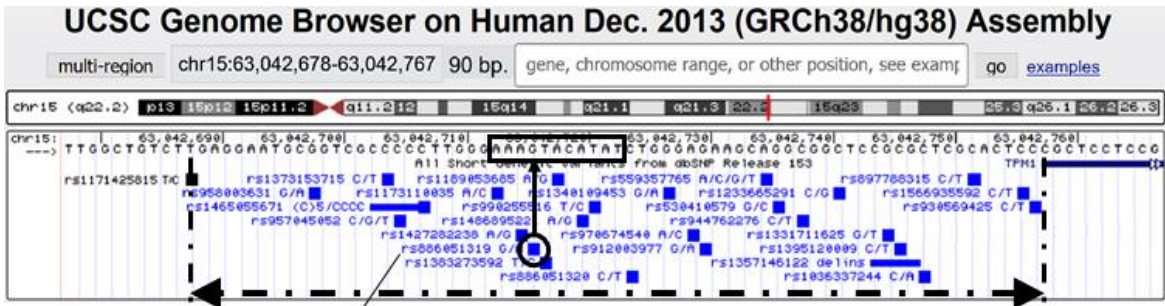


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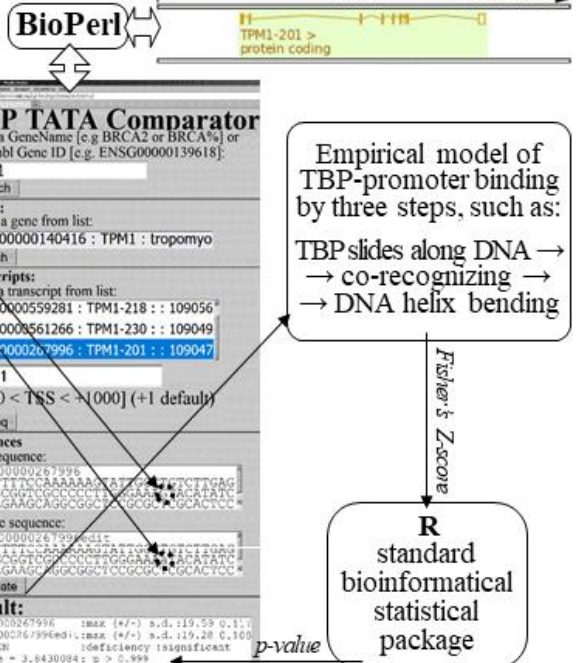
(1) Institute of Cytology & Genetics, SB RAS, Novosibirsk, Russia;
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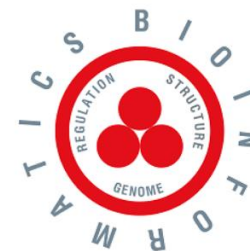
Motivation and Aim: Cardiomyopathy is the most common cause of spontaneous death in chimpanzees, who is our nearest wild congeners.

Methods and Algorithms: Using our previously published Web service SNP_TATA_Comparator, we analyzed single-nucleotide polymorphisms (SNPs) within 70 bp proximal promoters of eight human sarcomeric protein genes, as shown in Figure.



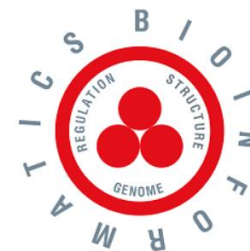
Results After analyzing 637 such SNPs, we identified 92 and 54 candidate SNP markers for worsened and relieved, respectively, hypertrophic cardiomyopathy (HC), as susceptibility to heart failure. Among them, 84 and 62 candidate SNP markers overexpressing and underexpressing, respectively, these genes as natural selection against the human sarcomeric protein deficit, being resistance to heart failure. This simultaneity of susceptibility and resistance to heart failure means disruptive natural selection of the considered human genes as if humans could exposed self-domestication that is debatable. We tested this using public 5591 differentially expressed gene (DEGs) of domestic versus wild animals. In the domestic animals, the overexpressed sarcomeric protein DEGs dominated the underexpressed ones (29 vs 15, respectively) just as natural selection against the human sarcomeric protein deficiency. Amounts of the domestic animal DEGs corresponding to relieved HC condition in humans surpassed those in wild animals (8 vs 1).





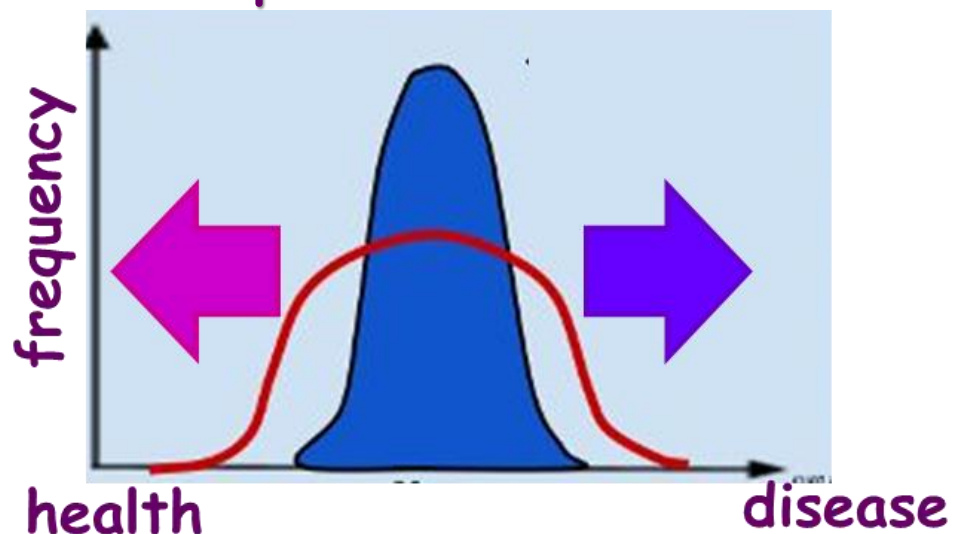
Natural selection against insufficiency in sarcomeric proteins reduces the risks of cardiomyopathy in humans versus chimpanzees as conventionally the nearest wild congeners, for whom it is the most common cause of spontaneous mortality

Human genome GRCh38 [Zerbino et al., <i>Genome Biol</i> , 2015]; dbSNP [Day, <i>Hum Mutat</i> , 2010]	Results			Neutral drift					
SNPs	N_{GENE}	N_{SNP}	N_{MARKER}	N_{DN}	N_{UP}	$P(N_{\text{DN}} > N_{\text{UP}})$	$N_{(-)}$	$N_{(+)}$	$P(N_{(-)} = N_{(+)})$
Genome-wide SNP norm of change in TBP affinity for the human gene promoters [1000 Genomes, <i>Nature</i> , 2012]	10^4	10^5	1000	800	200	>0,99	-	-	-
Hypertrophic cardiomyopathy-related candidate SNP markers at TBP-sites [this work]	8	637	146	62	84	<0,01	92	54	<0,01



Natural selection against insufficiency in sarcomeric proteins reduces the risks of cardiomyopathy in humans versus chimpanzees as conventionally the nearest wild congeners, for whom it is the most common cause of spontaneous mortality

Disruptive natural selection



Disruptive selection is an essential feature of the animal domestication [Belyaev, J Hered, 1979]

Hypothesis:
hypertrophic cardiomyopathy may be associated with the human evolutionary origin



Natural selection against insufficiency in sarcomeric proteins reduces the risks of cardiomyopathy in humans versus chimpanzees as conventionally the nearest wild congeners, for whom it is the most common cause of spontaneous mortality

RNA-Seq data that we could find within the PubMed database		Effect of expression changes of genes encoding the sarcomeric proteins under this study during divergence of both domestic animals and their wild congeners from their most recent common ancestor		Binomial distribution	x ² test	Fisher's exact test
ANIMALS		wild	domestic	P-value	P-value	P-value
Expression changes of the animal genes homologous to the human genes encoding sarcomeric proteins under this study	Deficit	29	15	0,05	0,01	0,01
	Excess	15	29	0,05		
Effect of expression changes of the human genes encoding sarcomeric proteins under this study on hypertrophic cardiomyopathy development	Worsening	43	36	0.25	0.05	0.05
	Relief	1	8	0.05		



Natural selection against insufficiency in sarcomeric proteins reduces the risks of cardiomyopathy in humans versus chimpanzees as conventionally the nearest wild congeners, for whom it is the most common cause of spontaneous mortality

Conclusion: Thus, natural selection against the sarcomeric proteins deficit reduces the risks of cardiomyopathy in humans versus chimpanzees as the nearest wild congeners, for whom it is the most common cause of spontaneous death.



The retrospective veterinary review
[Laurence et al., J Med Primatol. 2017]:
cardiomyopathies are the most common
cause of mortality for
the captive chimpanzees, who are the
nearest wild congeners of humans

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