Evolutionary elongation of purine stretches in the genome and their possible role in resonance signaling

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Abstract

The concept of electromagnetic signaling in biological tissues has been around almost since Hertz's experiment proving the existence of electromagnetic waves. Although electromagnetic signaling would better explain the speed and precision of the work of the genome and coordination between the cells than chemical signaling, molecular mechanisms and experimental evidence for it are insufficient. Recently, we proposed that DNA, being the central program of life and a very stable substance, is directly involved in electromagnetic signaling and that its sequences harbor sequence-dependent electromagnetic oscillators. We also proposed two types for sequence-dependent electromagnetic oscillation - the ones that include delocalized negative and positive charges. The first type is proposed to occur in purine stretches in DNA, i.e. stacks of purine bases (A and G) with electron clouds delocalized within stacked aromatic rings. Here, we utilized the public data on genetic variations in genomes of several biological species to test the evolutionary pressure on the length of purine stretches. The single nucleotide polymorphism (SNP) replacing a

purine with pyrimidine would disrupt the purine stack and the corresponding delocalized electron cloud and thus impact its oscillation frequency. As a result, it was demonstrated that there is a consistent evolutionary pressure towards the elongation of purine stretches in the genomes of the human and all other tested species. Additional analysis demonstrated that this pressure is independent of the bias caused by unequal chemical nucleotide lability and is therefore genuinely caused by the functional evolutionary advantage of longer purine stretches. This offers additional support for the proposed mechanisms of electromagnetic signaling in the genome.

In 1912 a prominent embryologist A.G. Gurwitsch put forward a hypothesis of a morphogenetic field, that is the field determining the shape of a multicellular organism during its development (Gurwitsch, 1912). A decade later A.G. Gurwitsch showed that an onion root was able to stimulate a cell division in the other root and showed that it was mediated by an ultraweak photon emission in the middle ultraviolet (UV) range (Gurwitsch, 1923, 1924a, 1924b). Both the effect and emission were called mitogenetic (later, A.G. Gurwitsch accepted that the term was too narrow (Gurwitsch, 1999). During the first fifteen years after the discovery, the mitogenetic effect was successfully demonstrated by more than a hundred researchers in different countries (Gurwitsch, 1934; Rahn, 1936; Reiter, 1928), see also recent reviews (Elena Valerievna Naumova, 2021; EV Naumova, 2018; Ilya Vladimirovich Volodyaev, 2021; IV Volodyaev, 2015). It was observed with a large number of various inducer-recipient pairs from yeast and bacteria to tissues of animals. It should be noted that an inducer and a recipient often were taken even from different kingdoms that implied that the mechanism of mitogenetic effect was formed at the very early stages of evolution. The concept of morphogenetic field and experimental data prompted A.G. Gurwitsch to suggest that it was chromatin that was responsible for the morphogenetic field, and developing this hypothesis further, he envisioned “the existence of some sort of the equivalent of chromosomes after their complete optical fading during interkinesis” (Gurwitsch, 1944) it was as early as in 1944, that is a decade before the Watson and Crick’s discovery.

All experiments related to mitogenetic effect can be divided into three groups:

1. both an inducer and a recipient are biological objects;
2. a recipient is a biological object, while an inducer is replaced with an artificial source of radiation, and a similar biological effect is observed;
3. radiation of a biological inducer was studied with an artificial device.

Later, a number of other effects of non-chemical distant cell interactions were shown (Burlakov, 1999; Kaznacheev, 1981). These experiments clearly demonstrate that biological objects emit electromagnetic radiation and this radiation can exert an influence on the other biological objects (particularly it can change mitotic rate in them

locally). However, having no model of the process mechanism it is still difficult to design experiments validating that observed effects are used in the biological mechanism of morphogenesis or in the broader sense have some signaling or regulatory function in biological systems.

In 1972 one of the coauthors of this paper (R.A. Miller) put forward an idea that it was DNAs of the whole body that served both as sources and detectors of the morphogenetic field (Miller, 1972, 2002). It is well known that DNA is the most stable and conservative biomolecular structure ever known, it determines all the basic processes in the cell, it is reproduced with incredible precision, and comprises a substantial amount of the body. Moreover, recently it was shown both theoretically and experimentally that DNA design possesses unique electromagnetic properties

(Semchenko, 2010). Under resonance conditions DNA-like double helices have equal dielectric, magnetic and chiral susceptibilities, which means they are geometrically optimal in terms of classical electrodynamics, i.e. equally activated by magnetic and electric fields of the wave, that results in the extreme selectivity in the interaction with circular electromagnetic waves. A right-handed DNA-like antenna radiates only left-hand polarized waves and interacts only with left-hand waves. A number of promising technical applications of DNA-like artificial resonators were demonstrated (antennas, polarization transformers, nonreflective metamaterials, and metamaterials with negative index of refraction) (Mikhalka, 2019). It prompts one to suggest that such unique efficient electromagnetic design invented by nature is not random and has some function in biological systems. We think that DNA is the best candidate for the harboring oscillators needed in the electromagnetic signaling of cells, it would make the signaling path rather simple and straight. Intercellular and intracellular communication with DNA serving as an emitter and a detector of an electromagnetic signal is a very attractive model for explaining not only morphogenesis but a number of other biological phenomena, for instance, a huge processing capacity of the brain or its amazingly high efficiency.

Our research is motivated by yet unproven hypotheses that DNA works as a biological quantum computer (Myakishev-Rempel, 2020) and that nucleotide sequences within the genome communicate to each other via electromagnetic and electroacoustic waves that propagate through the basestack of DNA and the nucleoplasm (Savelev, 2020a, 2020b). Motivated this, we specifically were seeking sequence-dependent oscillations of positive and negative charges in DNA sequences.

Specifically, we predicted the existence of proton wires in DNA which could support oscillations of positive charges in a sequence-dependent manner (Savelev, 2020a). It is also commonly believed that pi-electrons of aromatic rings of purines in the base stack are overlapped and form a shared cloud. Therefore, we also suggested the existence of oscillations of electron

clouds in stretches of purines. Next, we suggested that an interplay between positively and negatively charged oscillations serves as a basis for quantum computing by the genome. This would suggest that certain patterns of proton wires and electron clouds in the DNA would be evolutionarily beneficial. Therefore, we utilized computational genomics to determine repetitive patterns of proton wires and electron clouds in the DNA sequences of various species. We demonstrated the 20-fold enrichment of patterns of proton wires in DNA compared to a randomized sequence. A similar, although smaller, enrichment was observed for patterns of electron clouds. All these repetitive patterns were found in non-repetitive primary sequences. In other words, the DNA repeats were masked first and then we used non-repetitive DNA to seek repetitive patterns of proton wires and electron clouds. We also observed colocalization of the above patterns with conserved sequences and transcription start sites. In summary, our previous computational studies suggested that patterns of proton wires and electron clouds predicted by us are enriched in evolution and conserved and located in promoter regions, thus suggesting biological function, yet more evidence (especially experimental evidence) would be needed to further substantiate this finding.

In this work, we focus on the investigation of the evolutionary pressure to elongate electron clouds harbored by purine stretches as verified by genetic data. For that, we utilized the GWAS data from a human, a bird, a fish, and a plant. Genome-wide association studies (GWAS) are widely used in the human population since they provide valuable evidence for the approximate location of genes of mutations responsible for human disease and nonpathological traits such as IQ, longevity, and metabolic traits. GWAS studies utilize high throughput genomic analysis. A typical GWAS study encompasses over 1,000 individuals and over 11 million SNPs (single nucleotide polymorphisms). By now over 4000 GWAS studies are published (Loos, 2020). Additionally, there are hundreds of studies of nonhuman species. In addition to humans, we analyzed salmon, big tit, and cacao. This unusual choice of species resulted from easier availability of the data of these species. While human studies are well standardized, the GWAS studies of nonhuman biological species are done largely independently by different groups and the data is not centralized and not formatted in the same way. So, we were lucky to obtain the data of non-human species which were easily interpretable and were easy to analyze using our method. The analyzed species represent different branches of life such as a mammal, a human, a bird, a fish, and a plant. In our analysis, we ignored the phenotypic data and only used the frequency data for the alleles (sequence variants). Among all SNPs, we chose only those where purine is substituted for a pyrimidine or vice versa. This comprised only about half of the SNPs. This means that from 11 million SNPs, we used only about 5.5 million SNPs containing substitutions of a purine to a pyrimidine or the other way around. For each SNP, we calculated the length of purine stretch as shown in Fig. 1. For example, a SNP is a substitution of G for T. We obtained the frequencies of alleles G and T from GWAS data and these frequencies characterize a specific pool of individuals used in the genetic study. While single individuals can have combinations of alleles G+G, G+T, and T+T in homologous chromosomes, the frequencies reflect the proportions of chromosomes containing G and T variants in the studied group of individuals, which may be over 1000 individuals in a GWAS study.

The primary sequences of A1s and A2s alleles are converted to the purine code, sequences A1p and A2p. The length of purine stretch in the A1p sequence is 10 nucleotides and it is marked

blue. The G>T substitution interrupts this stretch of purines breaking it apart into two shorter stretches in A2p.

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A1s     actgagaaGggaattcc    90%  continuous
A2s     actgagaaTggaattcc    10%  interrupted

A1p     ryyrrrrrRrrrryyyy    90%  continuous
A2p     ryyrrrrrYrrrryyyy    10%  interrupted
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Fig. 1. Example of interruption of a purine stretch by a SNP. *A1s and A2s - allele sequences in the primary code. A1p and A2p - Same alleles recoded to the purine code. R-purine, Y-pyrimidine.*

Using genomic sequence, we counted the lengths of all purine stretches interrupted by approximately 5 million genotyped SNPs. The data was split into bins by minor (less frequent) allele frequency and purine stretch length was averaged for major and minor alleles, Fig. 2. The figure shows that in general, major alleles have longer purine stretches and that at lower frequencies this difference is larger.

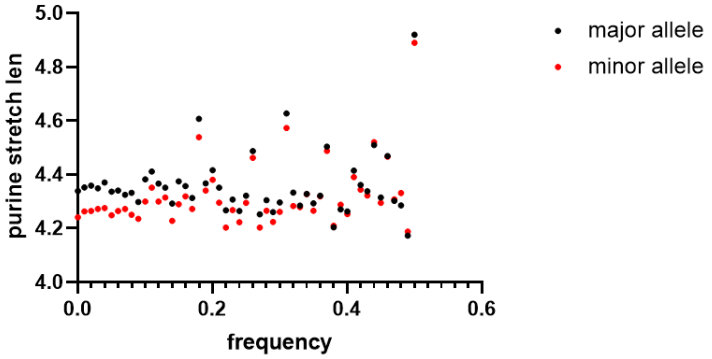

Fig. 2. Major alleles on average have longer purine stretches than minor alleles
Axis X - frequency of the minor (Less frequent) allele. Axis Y - Average length of purine stretches interrupted by SNPs.

Next, to exclude the effects of aminoacid code, we selected only the SNPs located in non-coding DNA, that is the genomic sequence that doesn't code for proteins. The data was split into bins by purine stretch length in such a way that each bin contained an equal number of SNPs. An average frequency of the continuous allele was plotted for each bin, Fig. 3.

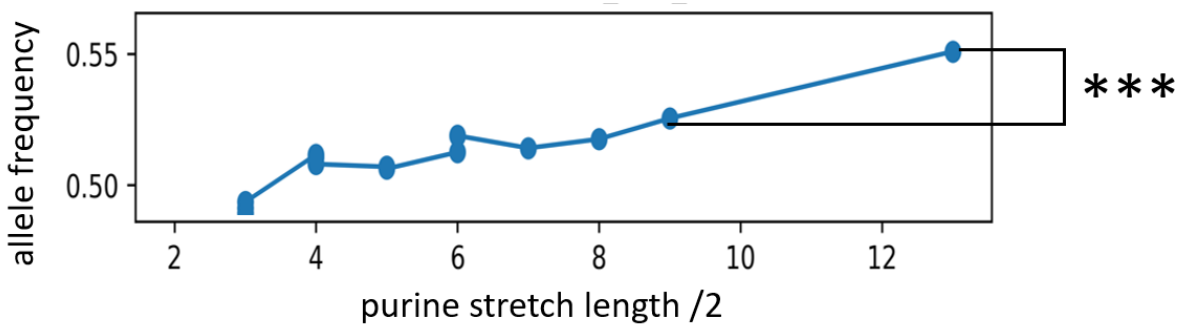

Fig.3. Proximity sensing, shoulder signal, and the dependence of allele frequency on the length of purine stretch length*. Axis X, Purine stretch length/2: the average length of purine stretch in nucleotides affected by a SNP divided by 2. Axis Y - The average frequency of a longer allele.*

Fig. 3 shows that purine stretches of 2 and 3 nucleotides are depleted in the studied population ($p<0.0001$), the lengths 4-7 nucleotides are around random 50%, and the lengths of 9-13 nucleotides are enriched in the population ($p<0.0001$).

In summary, our results demonstrate a very robust dependence: in SNPs, the alleles containing longer purine stretches are more frequent and the alleles containing shorter purine stretches are less frequent in the population.

Discussion

The difference in allele frequencies in the population can result from three causes.
The first possible cause can be a fresh admixture of a smaller population containing a minor allele into a large population containing the major allele. This cause works only for a single SNP and the signal would disappear when millions of SNPs are averaged.
The second possible cause is stereochemical: purine stretches could proliferate by a known effect of polymerase stuttering: sometimes a polymerase gets stuck and inserts extra copies of the same nucleotide (a short pattern of nucleotides) into a sequence. This is a typical cause of tandem repeats also known as microsatellites.
This could possibly explain effects at short distances, but would unlikely explain the phenomenon illustrated in Fig. 1.
Specifically, it would be hard to explain the effects happening at longer distances, such as 9-13 nucleotides from the SNP. The graph in Fig. 3 shows that the interrupted allele is removed from the population more efficiently at a distance of 13 nucleotides than 9 nucleotides, $p<000.1$.
This suggests the third possible cause, that longer purine stretches on average give an evolutionary advantage to individuals. In other words, there is an evolutionary pressure towards the elongation of purine chains longer than 16 nucleotides.
This result supports our hypothesis developed over the years (Myakishev-Rempel, 2020; Polesskaya, 2018; Savelev, 2020b), that delocalized electron clouds harbored by purine stretches (continuously stacked purines) play a functional role in resonance signal transmission and regulation of the genome.

Author contributions

Principal investigator MR. Conception and interpretation MR, IS, and OP. Background and discussion MR, IS, RAM, and AN. Main programming and data analysis AK. Additional programming LY and LS. GWAS data parsing and interpretation by AK, VB, IS, AVo, and OP. DNA modeling AS, MR, IS, and AVe.

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