Short Communication

May the SARS-COV2 OMICRON Variant Signal the End of the Pandemic – A Fibonacci Fractal analysis

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The emergence of the Omicron variant of SARS-CoV2 identified first in South Africa was announced with anxiety in media following alarm and concern by many researchers in the scientific community and the WHO has declared it a variant of concern (VOC): “The discovery of a highly mutated coronavirus variant in South Africa has triggered a global scramble” [1]. The main reason for this turmoil is the exploding number of non-synonymous mutations in the gene coding the spike protein causing lungs and other organs cell entry. However, objectively, although this variant may be very contagious it has not yet demonstrated any particular killing capability as the WHO reports: “There is currently no information to suggest that symptoms associated with Omicron are different from those from other variants. Initially reported infections were among university students—younger individuals who tend to have a more

mild disease—but understanding the level of severity of the Omicron variant will take days to several weeks" [2]. A report deposited on medRxiv indicates that the mRNA vaccine is 4 to 6 fold less neutralizing Omicron than for the wild-type virus [3]. Another report by the University of Hong Kong shows that it replicates considerably less in the lung tissue compared with bronchus which may diminish the lethality [4]. So the question we discuss here is the potential causes and effects of a heavy mutational rate on the virus contagiousness and infectiousness.

1. Delta and Omicron variants exhibit an increased number of mutations in the spike protein gene

Compared with the first identified COVID-19 strain (Alpha strain) the Delta variant of SARS-CoV-2, B.1.617.2, presented 23 mutations [5]. Twelve of those mutations are in the spike protein gene. One study has reported that this variant is 60% more transmissible than the Alpha variant. As of August 2021, the Delta variant has quickly become the dominant strain [5].

The number of mutations found in the spike of the Omicron variant is exceeding by far that found in other variants of concern. "Non-synonymous mutations were identified in the spike (S)–encoding (n = 35) and other viral protein-encoding (n = 22) regions. Among the non-synonymous mutations in the S protein, 43% (n = 15) were also identified in other VOCs/variants of interest, and 31% (n = 11) were found only in VOCs (Alpha, n = 6; Beta, n = 4; Gamma, n = 5; Delta, n = 4). Some of the point mutations and deletions found in other regions are not novel and can also be found in other variants at different frequencies" [6].

2. Genome Instabilities and Epidemic Endings are A General Law of Virus Evolution

The genome of a rapidly mutating RNA virus may become unstable and provoke the end of an epidemic. The general mechanisms governing this process are unknown, but it seems that they act in parallel with the development of collective immunity or as a consequence of it. We are referring here to viruses that mutate at a rate much faster than the human life span, like flu viruses and SARS coronavirus, excluding retroviruses that can mutate extremely rapidly, like HIV because they integrate the genome and thus infect permanently their host. The collective immunity tends to exert a positive evolutionary pressure on classical RNA viruses to force their adaptation to the more resistant fraction of the population untouched by the virus, despite having been in contact with it, or to the population already immunized, naturally or via vaccination, or after having developed marked symptoms [7, 8].

However, fortunately, it is observed until now that the efficiency of a perpetual adaptation process is not guaranteed. Virus genomes do not have infinite adaptive resources and the acute phase of epidemics always fades away even-though virus variants continue to circulate for quite many years, having a marginal lethal impact. This was the case with the Spanish Influenza A deadly world pandemic of 1918-1919, the basis of the infectious and pathogenic character of which remain unanswered and that disappeared progressively. Research indicates that descendants of the 1918 virus persist enzootically in pigs and probably also circulated continuously in humans, undergoing gradual antigenic drift and causing annual epidemics, until the 1950s [9].

This fact, observed for the Spanish Influenza H1N1 virus, has a direct and profound implication on the understanding of the stability of the viral genome. Would the immunity escape process be always guaranteed then the virus would circulate endlessly along the years with potentially the same level of contagiousness and pathogenic character? The fact that this scenario does not seem to happen means that viruses that mutate much faster than the human lifespan do not possess a capacity of infinite adaptation. As the collective immunity spreads, they cannot continuously generate new viable and efficient variants issued from mutation and recombination of themselves and end up generating defective genomes [10, 11]. To survive this programmed decline they need to re-assort with a viable "helper" virus, a situation not necessarily fulfilled [8, 12].

Thus, it is logical to hypothesize that having explored all possible mutations the genomes of SARS-CoV2 will inevitably become defective and not able anymore to generate new efficient variants in the absence of such rescue mechanisms. Thus it may become dormant in an intermediate host until it disappears and/or is replaced by another virus. There is a priori no scientific reason to think otherwise even though individual lock-down and mass vaccination have biased the evolutionary pressure on the virus giving it more time to find adaptive mutation/re-assortment. It must be considered that the deadly epidemic of SARS-CoV of 2003-2004, by many aspects a virus close to SARS-CoV2, has ended without the need for mass vaccination and general lock-down. The end of the epidemic was marked by an increasingly defective genome with a progressive deletion in the accessory Orf8 gene, at the end of the genome sequence, that participates in viral replication. "A 29 nucleotide (nt) deletion within ORF8 occurred in all strains involved in the middle and late phase of the human epidemic" [13-15].

The reason why deletion and truncation may occur at the 3' extremity of the viral genome is not known. One theoretical hypothesis is that the viral replicase generates many copy errors or arrests in this end section due to an overall destabilization of the RNA strand. This may be caused by the disruption of the cohesive electrostatic interactions, at medium and long-range, with dynamical implications for the coherence of the RNA structure, all that being forced by the evolutionary pressure mutations needed to escape immune resistance [16-19].

3. Loss of Fibonacci long-range fractal meta-structures in the Californian Omicron variant

It is mathematically demonstrated that a hidden fractal order exists in DNA and RNA genomic sequences [16]. It consists of long-range Fibonacci meta-structures that are being thought to be associated with genome overall stability concerning their conformational structure and dynamic. Effectively, these meta-structures translate genome adaptation to the human host. They have increased with successive variants from the Wuhan initial strain [17].

When we apply the Fibonacci meta-structure analysis we observe that these fractal meta-structures (except for the California case) remain high at the whole-genome level (data and results presented in extenso elsewhere [20]). Meanwhile, the spike genes are all very weak in terms of long-range meta-structures compared with the Wuhan spike and all the other previous variants.

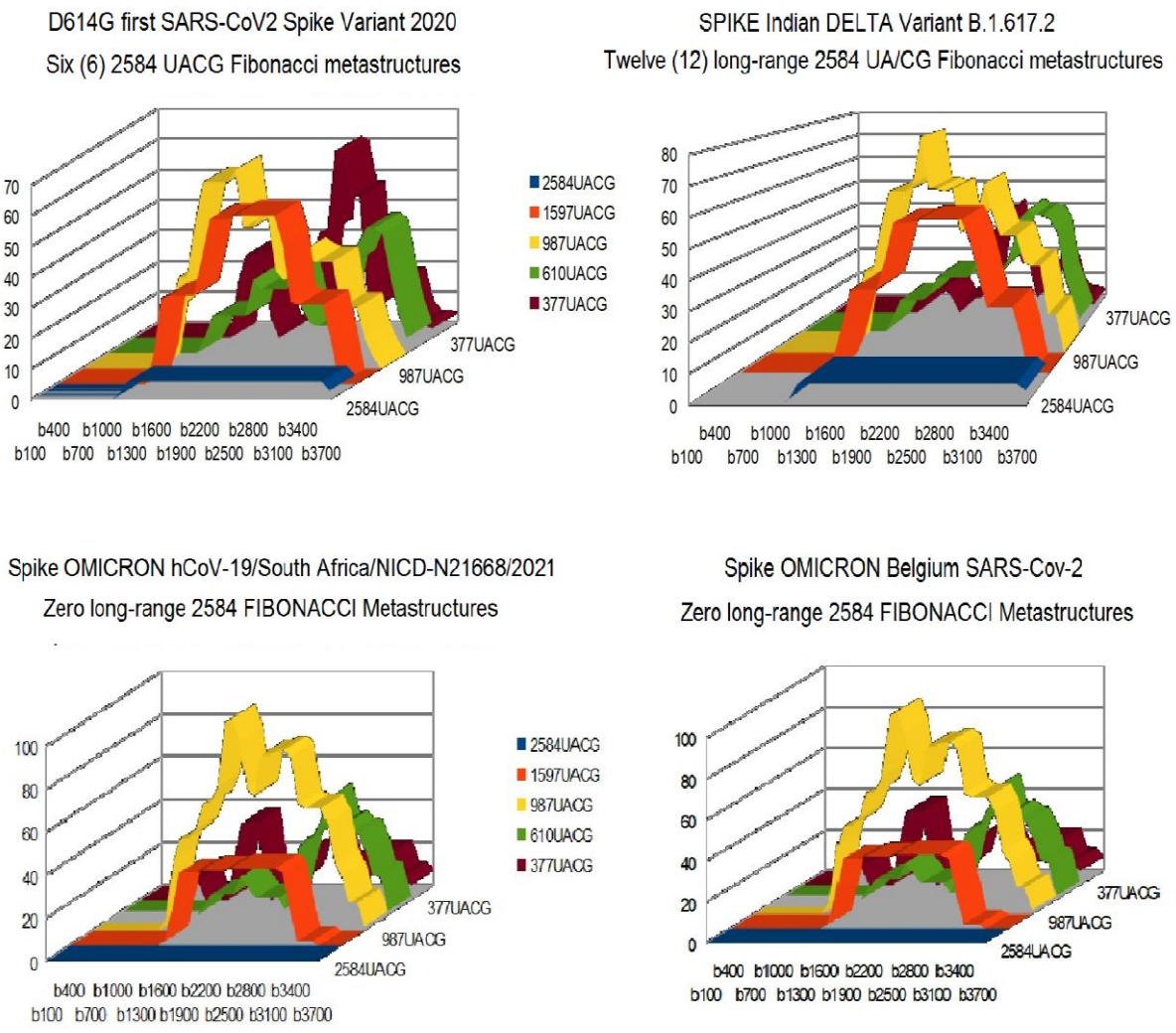

Figure 1: Comparison of Fibonacci fractal meta-structures of the spike protein gene between the D614G consensus variant of the initial stage of the pandemic with the Delta variant and two Omicron 21K sub-clade variants.

Figure 1 illustrates the progressive loss of meta-structures in the S gene essential for infectiousness along the course of the pandemic. From D614G to Delta the short-range meta-structure at 377 UA/CG nucleotide length drops considerably during a first phase (2020-2021) and subsequently very recently, with the Omicron 21K sub-clade, the long-range meta-structures of 1797 and 2584 UA/CG lengths tend to disappear marking the disruption of the virus genome fractal cohesion, in relation with a loss of RNA secondary structure conformation (hairpin loops) in this particular gene [20].

4. Discussion

Does this loss of Fibonacci long-range coherence results in a low pathogenic character, or at least not more pronounced than for the Delta variant, as the first observations seem to show in South Africa and California?

Due the variable extent and timing of mass vaccination across countries along the year 2021 it is impossible to decipher whether the increased number of mutations along with enhanced contagiousness has actually corresponded to a decreased pathogenic character of the variant Delta. Countries like Israel and the USA had completed a level of full vaccination (2 doses) in 50% of the population at the end of March and July, respectively. However, these 2 countries have both experienced dramatic waves of Covid-19 related deaths with the Delta variant beginning at the end of July [5].

Whereas in France, at the end of July as vaccination had reached hardly 48% of 2 doses, after having been lagging behind with only 4% at the end of March, the virus death toll was extremely weak compared with Israel and the USA. This was the case as well in many other European countries and seems to indicate a lower pathogenic character. Proponents of the catastrophic epidemic scenario would argue that this low death toll is the result of the enforcement of the use of vaccination and of the sanitary pass in France and in other European countries.

With the third vaccine injection becoming mandatory by January 15, 2022, for everybody over 18 years in France, the same scenario of denial of the possible natural ending of the epidemic may arise together with an impossibility to measure the real level of pathogenic character of this mutant. However it will be possible to measure it in the coming months in some states in USA, and in other countries in the world, where a third injection is not going to be mandatory.

Conflict of interest: none

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