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Genomic Variant of COVID 19 are Asymptomatic

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ABSTRACT

Genomic variation or variants are the differences that make each person's genome unique (0.1% different) otherwise we are 99.1 have identical according to Human Genome Projects (DOE: USA) DNA sequencing identifies an individual's variants by comparing the DNA sequence of an individual to the DNA sequence of a reference genome maintained by the Genome Reference Consortium (GRC). Mutation were defining earlier as a heritable change in phenotype now current technology has shown difference in the DNA sequence and its could be polymorphic (SNPs) or Pathogenic (CNVs) and recent studies "Genome wide association studies (GWAS)" have linked single nuc Genomic variant of COVID-19 analysis has showed COVID-19 variants from publicly available 48 genomes. Co-occurrence of 8782C>T and 28144T>C variants nucleotide polymorphism (SNPs/CNVs) with virus disease like COVID 19.

Keywords: SNPs, CNVs, Human Genome Projects, Genomic variant

BACKGROUND

With reference to current literature in Genetics, many well-known genetic diseases are not following mendelian inheritance pattern, they are known as multifactorial or complex trait are not caused by one specific gene or mutation. Their genotypes represent multiple genes and environmental factors. So complex traits are so important they affect everybody. For example, complex disorders such as heart disease type II diabetes and obesity are the leading cause of death all over the world and also huge burden on the economy. Current understanding of these disorders has limitation and daunting task due to the complexity of the factors involved in individual genome in addition to these traits do not follow traditional principles and predictable pattern of inheritance causing to the need to approach modern methods of research.

HUMAN GENOME VARIATION

Understanding of our genome after Human Genome Project (DOE: USA) was over in the year 2003, made a revolution in modern biology or life science in understanding of our own genome. Now we know the difference between two individual genomes are almost 99.9% identical in DNA level but 0.1 % difference are many of the things that make us unique! Now we know the people's genome differ from each other in genomic level (DNA level) These difference in your DNA help to determine what look (phenotype) like and what your risk might be for various diseases. Genome analysis (DNA sequencing) has shown that human genomes differ from one other in nucleotide level sometimes at single base and sometimes in chunks of thousands of bases. Even today researchers are still discovering new type variants (difference between two genome) within human genome. So human genome variation is more important because a very small set of these Variants are linked to difference in various trait: height, weight, skin color, type of earwax and even with specific genetic disease.

Human Genome Project

Human Genome Project has made change in our understanding of human trait and how we to reach them – one example is eye color. We used to know that one dominant gene controlled brown or blue eyes and that blue-eyed parents could not have brown eyed children. Now we know due to genomic variants the determine eye color. In fact, at least ten genes each of which comes in several "flavors" contribute to eye color. So, the combination of these gene variants in a person's genome that produces the wonderful range in human eye color (Human Genome Variation: NHGRI; USA).

HapMap Project

The first draft of DNA sequencing is over in the year 2003 and it was not understood the genetic language (code or

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sequence) of nucleotide sequence of first draft by the researcher involved in the same project. So **HapMap project** was launched to understood the meaning of DNA nucleotide sequence and biology of the genetic code. It was applied to understood genetic variant affecting health and diseases along with interaction of drug and environment.

1000 Genome Project (1K GP)

The same project was launched in January 2008, was an International Research effort to make catalogue of **Human Genetic Variation in World population**. Scientists planned to sequence the genomes of at least thousand genomes of anonymous participants from number of different ethnic group using advanced genetic technology. The Project (Pilot phase) was over in the year 2010 which was published in journal Nature. After three years in 2015, two papers were published in Nature and reported many **variant**s, restricted to closely related groups, were identified and eight **structural-variation** classes were analyzed **(Figure 1)**.

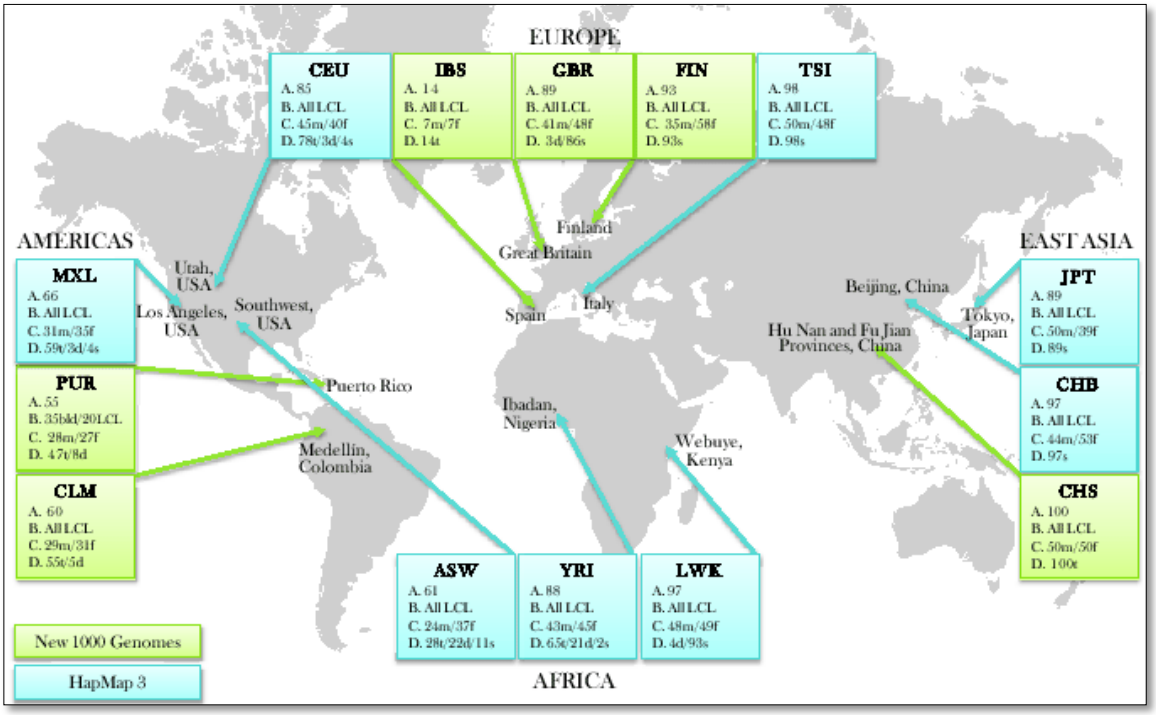


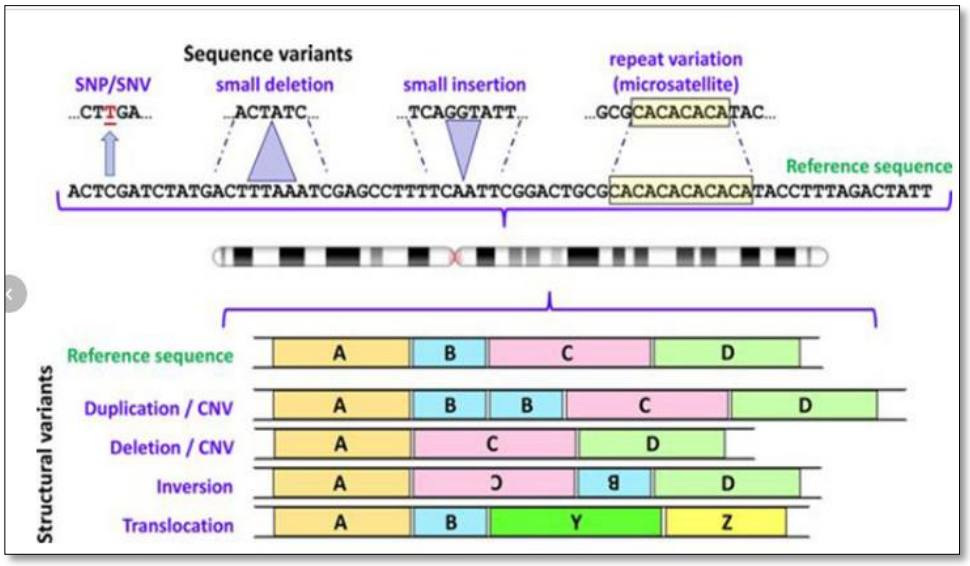
Figure 1. Map indicating the locations of the populations the 1000 Genomes Project phase.
Source: http://www.bioinf.jku.at/research/sharingShortIBD/hapFabia1000Genomes_html/node34.html

HUMAN GENETIC VARIATION ASSESSMENT

Genetic variation among human (individual) observed in DNA level in many scales from gross alteration in human karyotype to Single Nucleotide changes in above 1000 genome project reports. The same chromosomal abnormalities observed in 1 in 160 live human birth The Nucleotide diversity (DNA level) differ between two individuals was estimated (year 2004) to be 0.1 to 0.4% base pairs and later in year 2015, the 1000 genome project which sequenced one thousand individuals and reported typical individual genome differ to 0.6% of total number of base pairs. Nearly all (>99.9%) of these sites are small differences, either single nucleotide polymorphisms or brief insertions or deletions (indels) in the genetic sequence, but structural variations account for a greater number of base-pairs than the SNPs and indels. As of 2017, the Single Nucleotide Polymorphism Database (dbSNP), which lists SNP and other variants, listed 324 million variants found in sequenced human genomes **(Figure 2)**.

Single-Nucleotide Polymorphism (SNP)

A nucleotide sequence consist of four nucleotide (known symbol is A,T,G,C) and usually these letters make sentences (known as genetic code) instruct living cell in our body to work .So in Single Nucleotide Polymorphism (SNP) make a change in genetic code i.e. make a substation of a single nucleotide that occurs at a specific position in the genome, which is very common up to 0.5% variation among normal population has shown in 1000 genome project. For example, at a specific base position in the human genome, the C nucleotide may appear in most individuals, but in a minority of individuals, the position is occupied by an A. This means that there is a SNP at this specific position, and the two possible nucleotide variations – **C or A** – are said to be the **alleles** for this specific position **SNPs pinpoint**



Source: https://www.researchgate.net/figure/Some-types-of-variants-found-in-human-genomes-Variation-involving-one-or-a-few_fig1_329379756

Figure 2. Some types of variants found in human genomes: Variation involving one or a few nucleotides are shown above the chromosome icon, and structural variants below; in each case the variants are depicted in relation to the reference sequence. For depiction of structural variants, A, B, C and D represent large segments of DNA; Y and Z represent segments of DNA from a different chromosome. Note that differentiation between CNVs and deletions/insertions depends upon the size of the relevant DNA segment (see text for further details). Abbreviation: CNV, copy number variant. Chromosome ideogram from NCBI Genome Decoration Page.

differences in our susceptibility to a wide range of diseases (e.g. sickle-cell anemia, β-thalassemia and cystic fibrosis result from SNPs). The severity of illness and the way the body responds to treatments are also manifestations of genetic variations. For example, a single-base mutation in the APOE (Apo lipoprotein E) gene is associated with a lower risk for Alzheimer's disease **(Figure 3)**.

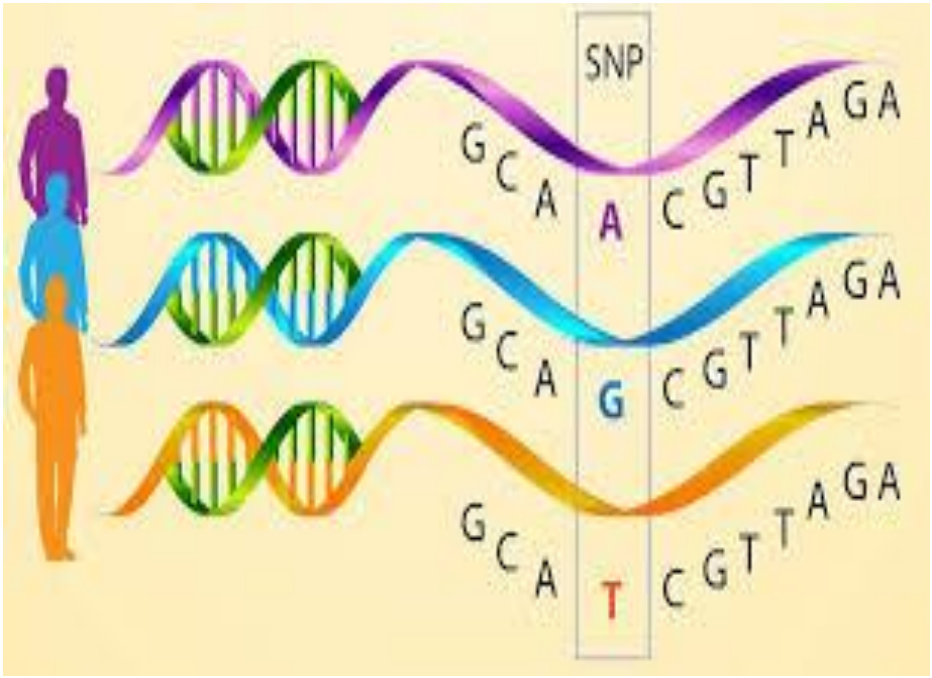


Figure 3. SNP Genotype.

Structural variation (CNV/SV)

With reference to 1000 genome project reports (Nature; 2015), observed SVs in normal human DNA sequence are Copy Number variation (CNV) , Deletions, Inhersions and duplications are much more common than SNPs diversity This observation was confirmed in 2007 studies of diploid genomes of two famous Geneticist : Craig Venter and James D. Watson (their DNA sequence was donated for research) and published in Human Genome Project and Celera Genomics respectively. So according to 1000 genome project, a typical human has 2,100 to 2,500 structural variations, which include approximately 1,000 large deletions, 160 copy-number variants, 915 Alu insertions, 128 L1 insertions, 51 SVA insertions, 4 NUMTs, and 10 inversions.

Copy number variation (CNV)

Large number of human genome sequence studies has shown CNVs a phenomenon in which section of the genome are repeated and the number of repeats in the genome varies between individual. So, it is defined that CNV is type of structural variation specifically, it is a type of duplication or deletion event that affects a considerable number of base pairs (may be Exon/Intron). So, genome studies have shown, approximately two-thirds of the entire human genome may be composed of repeats and 4.8-9.5% of the human genome can be classified as Copy Number Variation. In mammals, these CNVs play an important role in making different variant (phenotype) in population as well as disease phenotype. However large population studies have demonstrated that there are two main groups of repeats (CNVs) observed they are short repeats and long repeats in human genome and have definite effect on phenotype (? Disease or Variant) **(Figure 4)**.

Asymptomatic Carrier of COVID-19 are Genomic Variant

Let's start with the famous quote by Charles Darwin: ***"It is not the strongest of the species that survives, nor the most intelligent, but the one who is most adaptable to change."*** *Same statement was made about 200 years before Ultimately present Genomic science (post-human genome project era) has accepted him as a father of our Genomic Science.* **Present Genomic Science** *has defined our Genome – consist*

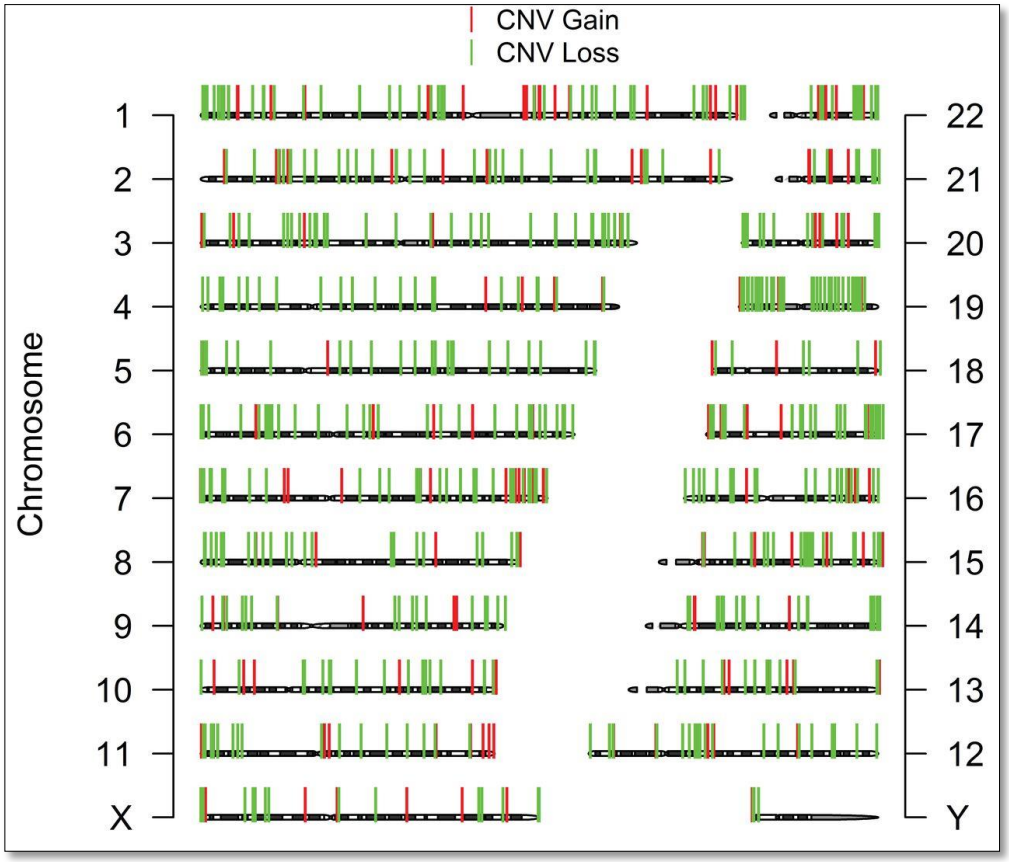


Figure 4. Genome-wide aCGH analysis reveals copy number variation (CNV) in the SSc population. Significant SSc-associated CNV identified by aCGH array were noted in the human genome. Red bars represent high copy number in SSc, while green bars represent low copy number in SSc. aCGH: array comparative genomic hybridization; SSc: systemic Sclerosis.

Source: http://www.jrheum.org/content/43/5/880

of complete set of DNAs, including all of its genes. Each **genome** contains all of the information needed to build and maintain that organism. In humans, a copy of the entire **genome**—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus. So, **genetic variation** is caused by **variation** in the order of bases in the nucleotides in genes. New technology now allows scientists to directly sequence DNA which has identified even more genetic **variation** than was previously detected by protein electrophoresis. These differences are called genomic variants **(Figure 5).**

There are three sources of genetic variation: Mutation, gene flow and sexual reproduction. A mutation is simply a change in the DNA. Mutations themselves are not very common and are usually harmful to a population. Human genomic variation is particularly important because a very small set of these variants are linked to differences in various physical traits: height, weight, skin or eye color, type of earwax, and even specific genetic diseases.

Molecular mechanism of infection in cells

The cellular entry of coronaviruses depends on the binding of proteins with viral spicules (S) to the cellular receptors and the priming of the S protein by the host cell proteases. The SARS-CoV-2 virus has been shown to use the ACE2 receptor from the level of pulmonary alveoli, for entry and an enzyme, TMPRSS2 serine protein for initiating protein S. A TMPRSS2 inhibitor approved for clinical use blocked entry and could be a treatment option. Some results revealed an important communication between SARS-CoV-2 and SARS-CoV. About 80% of COVID-19 infections are mild **(Figure 6)**.

The infectivity varied between two individuals are due to Genomic variation (Genomic Variant patient) has showed various clinical studies (clinical phenotype variation). So largely asymptomatic patient is most likely Genomic variant. It is known that sickle cell patient does not get malaria infection due to same genomic variation.

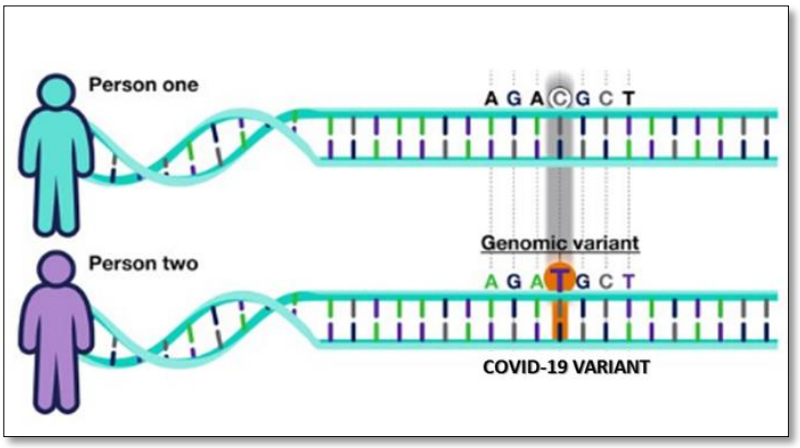


Figure 5. Genomic variants.

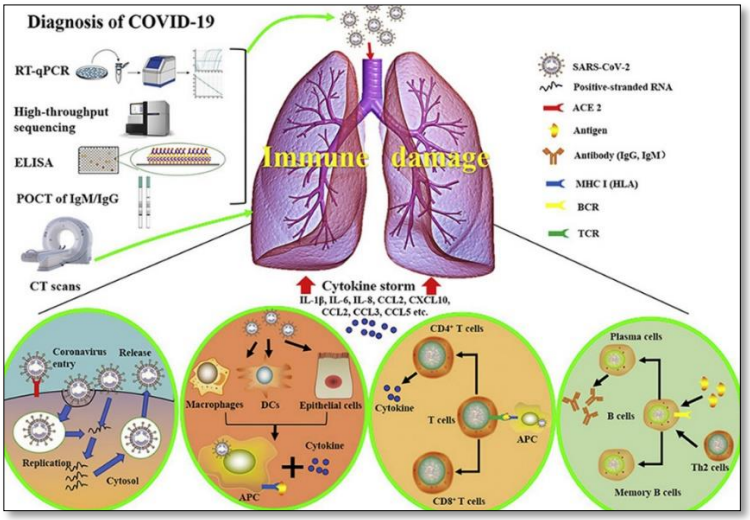


Figure 6. Molecular immune pathogenesis and diagnosis of COVID-19.
Source: [1]

Recent paper published by Takahiko Koyama [2] about Genomic variant of COVID 19 analysis has showed COVID-19 variants from publicly available 48 genomes.

Co- occurrence of 8782C>T and 28144T>C variants are frequently found among travelers but not from Wuhan samples, Thus, we named it traveler sub strain

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