euroespes health

Vol. 19 / December 2021

EuroEspes Health Medical Bulletin

International Center of Neuroscience
and Genomic Medicine

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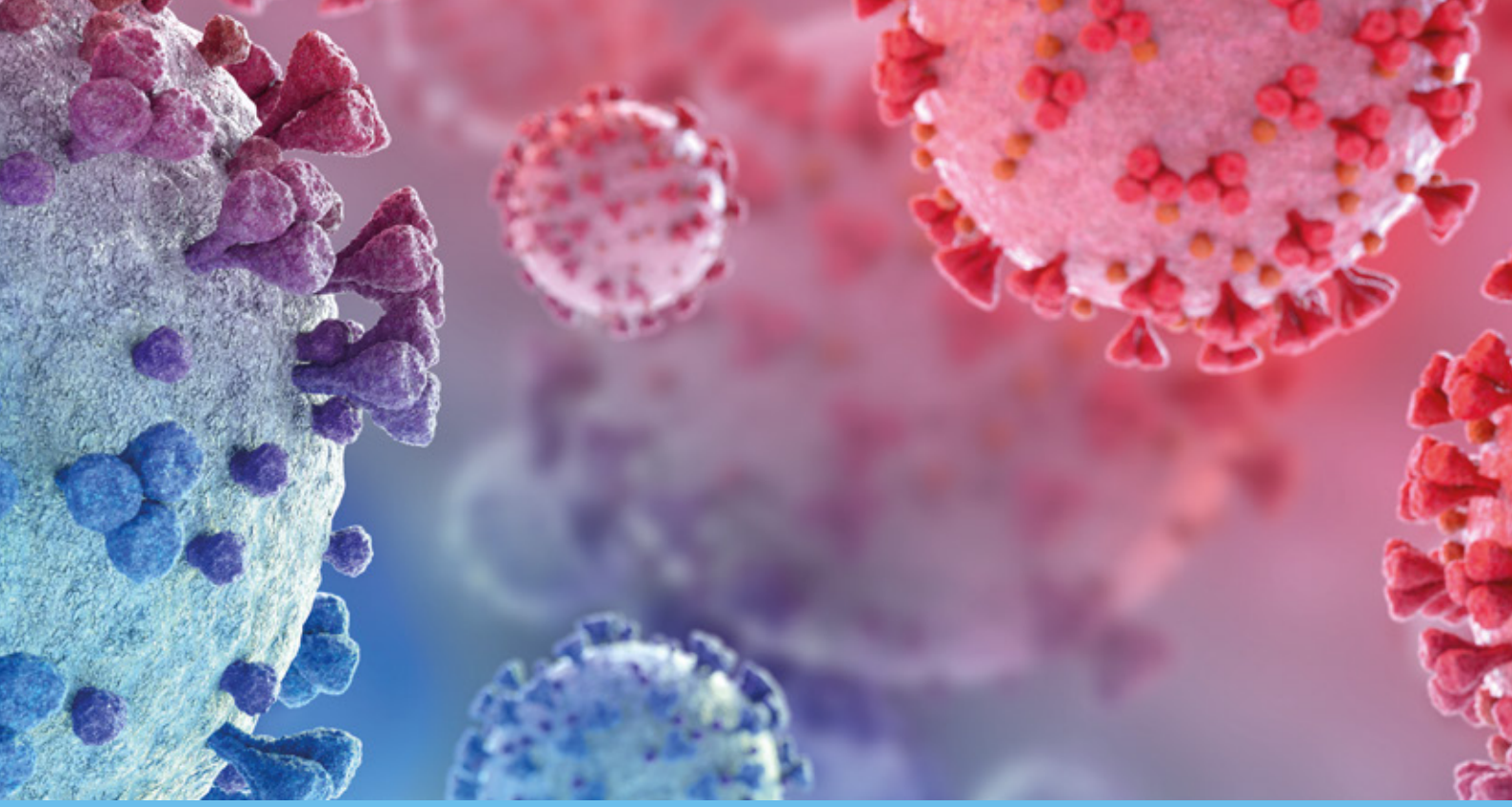


December Editorial

Omicronic Cyclogenesis: An Onomatopoeia

When the fox shows its tooth or moves its tail, the political-sanitary henhouse becomes hysterical; the press experiences an erogenous high because it already has a cover for days; and the pharmaceutical industry rubs its hands at the explosion of dividends, if the pie is sliced right. The victim is still the owner of the farmyard (society), who suffers a new panic attack at the rampage of all his terrified domestic animals on the farm of mysteries.

Nobody with a sensible attitude, or a little knowledge of microbiology, should be surprised that new variants -more or less dangerous- of the coronavirus appear. Omicron is one of the many variants that are already swarming around the world; it will not be the last or the most dangerous; others will occur in months or years, fueled by population mobility, the immunodeficiency of vulnerable groups, the uncontrollable animal reservoir, climatic seasonality and the gasoline that is added to the fire with vaccines.

The world population rises to 7.9 billion souls, of which 270 million have been infected and about 5 and a half million have died. Double vaccination, useful or useless, has been received by some 3.33 billion people, representing just over 40% of the world's population. So, assuming the vaccines were effective -which they are not; if they were, the vaccinated would not be infected - the virus still has a large human reservoir around the world to settle at ease and play with the individual immune system, with the ability to kill the most susceptible. The field widens if we add between 20% and 40% of those vaccinated whose antibody titer is insufficient, for whom vaccination does not guarantee immunity and, therefore, protection capacity against the virus. Obviously, these figures dismantle the illusion of herd immunity that would require at least 70% of the immunized population to immobilize the virus and slow its spread.

Since the laws of the chicken coop are random, capricious and a bit xenophobic, when someone in Africa yells "fire!", as Africa is not very relevant for the mega-businesses of some, the cocky guys from the henhouse decide to put a seclusion wall so that the African fire does not burn them, while allowing their Central European neighbors, who are now suffering the expected seasonal peak of COVID -19 -and spreading the omicron-, to exhibit their private parts and thoracic skins, on the neighboring beaches of Africa, without any type of restriction. Faced with the threat of omicronic fire, apparently coming from Africa, this has been the first political measure -segregationist and non-epidemiological; not based on knowledge but on pure visceral reaction; not exempt from ignorance and malice; and definitely useless in the face of the expansion of omicronic cyclogenesis.

They are the same roosters that are now debating making vaccination compulsory, hindering movement even more, restricting mobility, confining the population, segregating the unvaccinated, combating leisure and all collective recreational activities, deciding how many should enjoy the dinner of Christmas, and those who must go to a hospital or rot at home.

As many of these measures run into constitutional barriers and collide with the idiosyncrasy of freedom, as an acquired right of all domesticated people, veterinary judges are used to rule on the cause; but it happens that vets don't know about foxes; they hardly know how to maintain the laws of each corral; and each one expresses his affinity or rejection of the appetites of the henhouse, without uniformity of criteria, thereby increasing the confusion of the master of the pen who, in the end, does not know if the vet is recommending a disinfectant or an enriched feed.

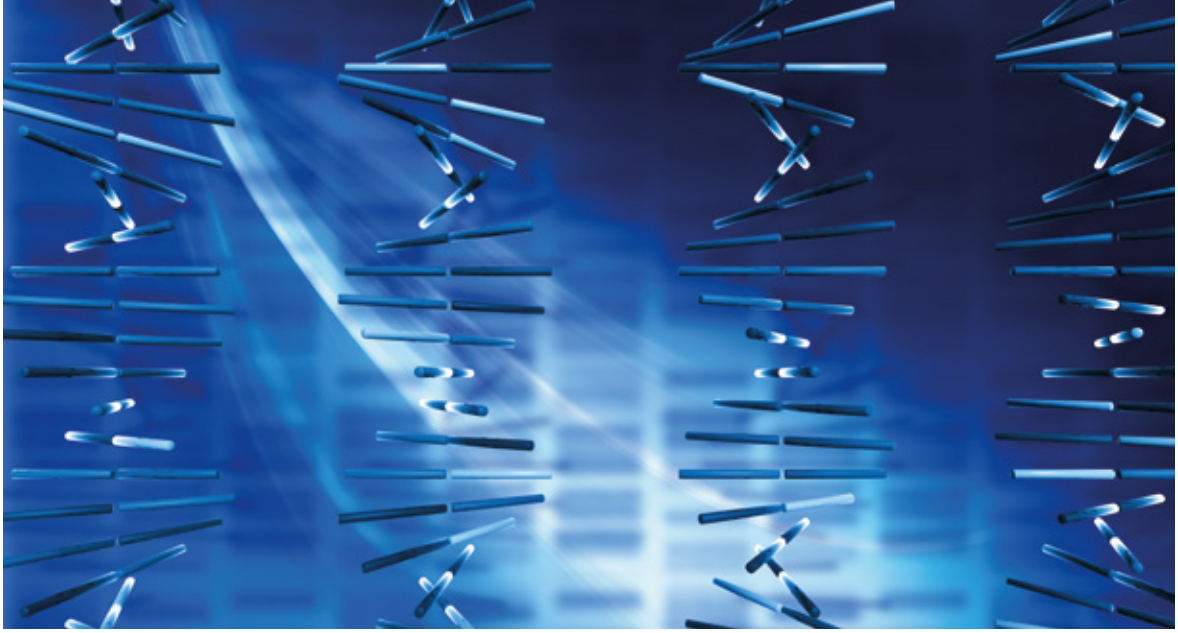
In the most democratic farmyards, where the little farm animals feel comfortable, no one is allowed - attributing powers that they do not have- to put up barriers to the field because the law of the master of the corral is common to all, although those of the political-sanitary henhouse are making an effort to look for exceptions. Here the vets are inhibited; and few are vaccinated. In other pseudo-democratic places, where the pen is fragmented into many little pens, governed by little ideological caciques with long crests and loud cackling, the animals are more docile; they are very well domesticated and submit to the will of those who instruct with pecks, with veterinary support, almost without saying a word. Here many are vaccinated; but the fox continues to visit them, day and night, with the added danger of the call of the cockatoos that chorus the rooster.

In the assembly of farmers, ranchers and nature lovers -owners of corrals-, the panorama is seen with confusion, concern and growing distrust. They find that past experience has been of little use; not much has been learned; the fox has been allowed to brag in front of the chickens; and the roosters have realized that, thanks to the fox, they have reached an all-encompassing power in the pen, with absolute submission of all the birds and even of other guests outside the henhouse. In this way, the political-sanitary *Gallus domesticus* has become a worse threat than the fox to the rest of the pen. Maybe even a fox has been transmuted into a rooster to make his rules more credible. Their disinfection messages are toxic; their improvisation is an attack on common sense; their level of cowardice is terrifying; their concept of economy and social welfare is primitive and sectarian; in their vision of the future they only see foxes in empty chicken coops; and veterinarians - who do not understand foxes - seem to suggest that the only way to kill the fox is by killing the chickens; not with disinfectants, which poison the grass and starve those who live outside the henhouse, but with fox droppings, which is more physiological.

Meanwhile, the farm dogs are furious at the fox's threat. They have their own stratagems to scare away the *Vulpes vulpes*, and finish off that hideous fox who invades the corral, steals food from the canids and preys on the chicken coop; but the veterinary judges do not allow them to attack the fox, by artificial design of those who hate chickens. For this reason, many are dedicated to vegetating and do not flinch when the fox invades their territory.

The slavery bureaucracy of the corral and fear have made everyone forget that there is no law that prohibits the dog from killing foxes and the masters of the corral from closing the chicken coops.

Ramón Cacabelos
Professor of Genomic Medicine



EuroEspes launches the Personal Genomic Profile (PgenP): a mapping of the individual genome for disease prevention and health planning

The Department of Genomics, led by **Dr. Juan Carlos Carril**, and the Genomic Sequencing Unit, headed by **Dr. Óskar Martínez de Ilárduya Ruiz de Larramendi**, have announced the immediate launch of the Personal Genomic Profile (PgenP) (*Personal Genomic Profile*). The PgenP is a genomic analysis of more than 35,000 genes of the Human Genome based on NGS (*Next Generation Sequencing*) technology. The PgenP offers exclusive information on three genomic blocks of vital importance for the health of people and their descendants.

The first genomic block shows pathogenic genes with mutations responsible for diseases (past, present or future) in the carrier person. This genomic information is vital for diagnostic confirmation of diseases that the carrier has suffered or may be suffering, and diseases that with the highest probability they may suffer throughout their life. Knowledge of these genomic biomarkers is the basis of Diagnostic Genomics and Predictive Genomics, through which it is possible to implement preventive programs to avoid the appearance of a disease or minimize its pathogenic effect if it does present itself.

This genomic information is decisive for any human disease whose cause lies in mutations present in exonic regions, which are expressed in the form of aberrant proteins or enzymes, known as the Human Exome. In the case of autosomal dominant diseases, these diseases can be transmitted to the offspring with a frequency of 50%.

The second genomic block shows a series of defective genes, which do not have to cause disease in the carrier, but which can be inherited by their children. If the children who carry these genes are united with another person with the same genetic defect, 25% of their descendants may suffer a disease; this is known as recessive inheritance. Therefore, the knowledge of these mutations is extremely beneficial to prevent the appearance of diseases in future generations.

The third genomic block includes a set of more than 500 genes whose function is currently unknown, but which are present in more than 50% of the population. A large part of our genome's sequences still hide information that is difficult to interpret or of uncertain meaning; however, as the functions of these enigmatic genes are discovered, some of these anonymous function variants will be assigned to many diseases whose cause is of idiopathic origin. The PgenP offers the user the complete list of these genes, which are present in the genome of each person, so that each person has this potentially valuable information permanently and throughout his life and which, without a doubt, will acquire relevance as soon as science and

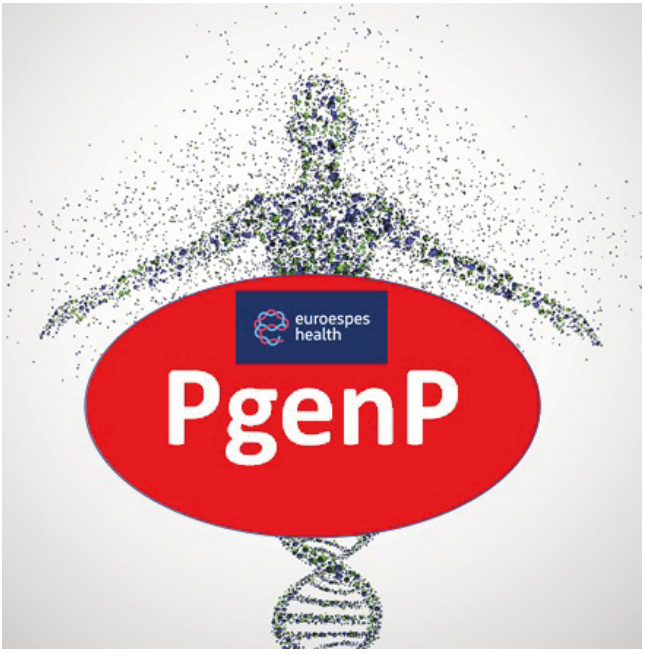
understanding of structural and functional genomics advances.

One of the goals of human genetics is to use the natural genomic variation present in the general population to understand the genotypic consequences that may cause mutations in protein-coding genes within the genome. A team of scientists from the *UK Biobank Exome Sequencing Consortium*, led by **Joshua D. Backmanof** the *Regeneron Genetics Centerin* New York, used whole exome sequencing to explore protein-altering variants and their consequences, in a sample of 454,787 cases from the UK Biobank. In this large sample of people, they identified 12 million coding variants, including about 1 million loss-of-function variants and 1.8 million nonsense variants that caused mutations. Looking for associations of these variants with disease traits, they found 564 genes with high pathogenic risk. Rare variant associations are enriched at loci identified in genome-wide association studies (GWAS). More than 90% of these variants differ from common variants in the human genome.

From the 12,326,144 coding regions identified, 75,096 are deletions or insertions, 3,457,173 are synonymous variants, and 7,878,586 are pathogenic nonsense variants. From the many associations found, a few variants increase the risk of liver disease, eye disease, and cancer; others reduce the risk of hypertension (SLC9A3R2), diabetes (MAP3K15, FAM234A), and asthma (SLC27A3). About 6 genes were associated with phenotypes of brain function or neuronal development (GBE1, PLD1). More than 80% of these variants have been confirmed in different cohorts and ethnicities, with consistency among individuals of European, Asian and African ancestry.

These studies show the ability of exome sequencing to identify associations between genes and traits (health-disease), as well as for elucidating gene function and identifying effector genes in large-scale genomic studies.

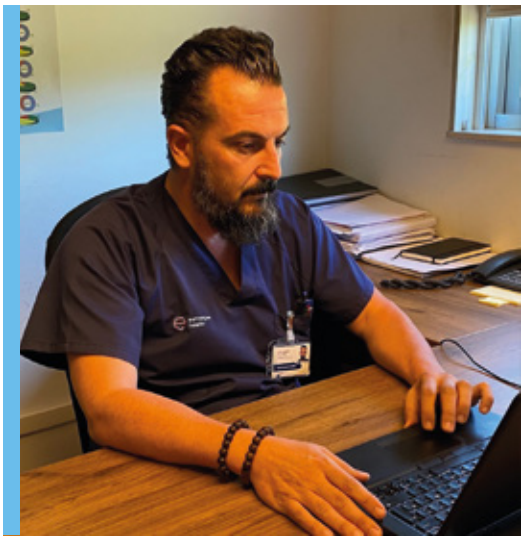
Genomic studies have to be complemented by proteomic studies, both in health and disease conditions. **Egil Ferkingstad's** group from *deCODE Genetics / Amgen, Inc., in Reykjavik*, Iceland, studied the plasma proteome in genome-wide association (GWAS) in 35,559 Icelanders and found 18,084 associations between genetic variants and plasma protein levels (protein quantitative trait loci; pQTL), of which 19% were rare variants (minor allele frequency [MAF] <1%). The study of the proteome in relation to 373 diseases showed 257,490 associations. By integrating pQTL and genetic associations with diseases and other traits, the Icelandic authors found that 12% of the 45,334 associations are variants in high binding disequilibrium with pQTL. They also identified 938 genes that encode potential drug targets with variants that influence biomarker levels.



The combination of genomics, proteomics and transcriptomics provides a valuable resource for understanding the causes of disease, its predictive diagnosis and / or early diagnosis and for the personalization of pharmacological treatment.

PgenP can be performed on any biological sample from which a sufficient amount of DNA is extractable. The Department of Genomics from the International Center of Neurosciences and Genomic Medicine performs PgenP on saliva samples, which can be sent from home, nationally or internationally, to avoid any inconvenience to users.

People interested in carrying out their PgenP can contact EuroEspes using the telephone number 981-780505 (national) (+ 34-981-780505, international) or via e-mail: info@euroespes.com; protocolasistencial@euroespes.com.



Dr. Juan Carlos Carril, Director of the Department of Genomics and Pharmacogenomics, International Center of Neuroscience and Genomic Medicine.

Dr. Óskar Martínez de Ilárduya Ruiz de Larramendi, Head of the Genomic Sequencing Unit, International Center of Neuroscience and Genomic Medicine.

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Hearing Loss with Age: Genomics and Pharmacogenomics

Presbycusis, or age-related hearing loss, is the most common cause of hearing impairment in adults worldwide. Presbycusis refers to a gradual and irreversible decrease in hearing that initially affects higher frequencies, gradually extending to lower frequencies. Its clinical manifestation can occur as early as the fifth decade of life, but hair cell degeneration in the inner ear begins during the early stages of life. This condition also affects central auditory processing through loss of auditory nerve fibers. With an increase in life expectancy, a higher prevalence of presbycusis is observed. Thus, it is estimated that up to 60% of the population over 60 years of age may present this condition, which has a positive linear correlation with age.

The management of presbycusis is often difficult given the coexistence of other age-related disorders and the association with multiple metabolic, pharmacological, neurodegenerative, and genetic factors. In addition, there is currently no treatment that reverses hearing loss, although there are several clinical lines of research with different compounds underway, such as AUT00063, a new small molecule that positively modulates voltage-gated potassium channels, which improves neuronal synchrony and temporal processing; or PF-04958242, a positive allosteric modulator of the AMPA receptor, an ionotropic glutamate receptor, which is also postulated as a candidate therapy for cognitive symptoms.

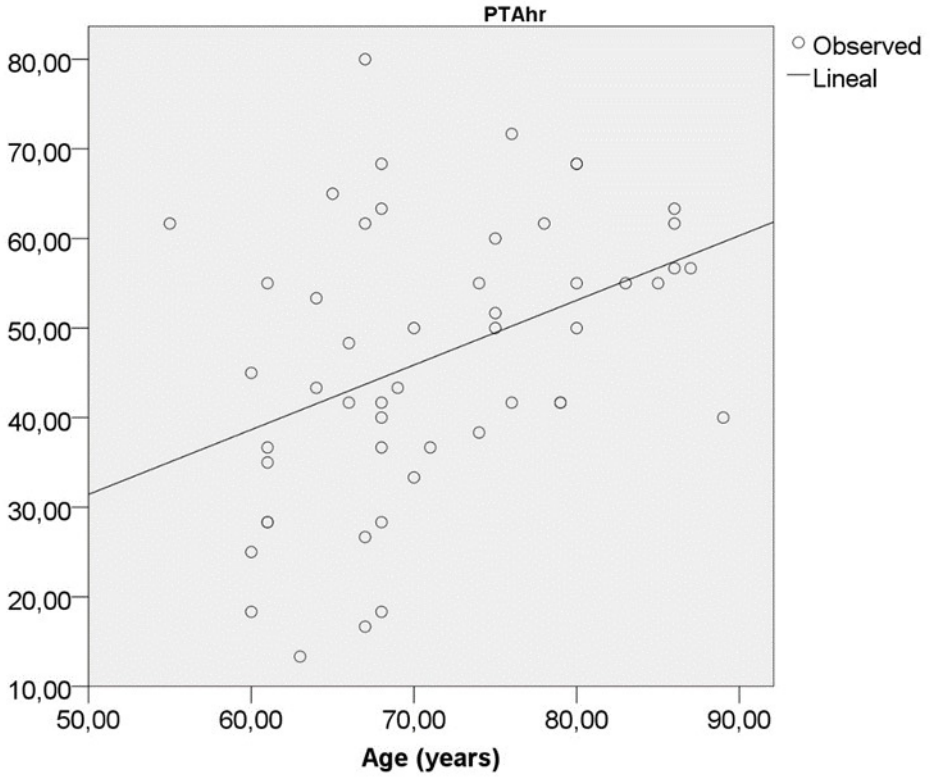
Hearing impairment is associated with other disorders such as psychosocial health problems, mobility difficulties (including vertigo and its sequelae), brain tumors, strokes, cognitive impairment, visual disturbances, diabetes, arthritis, and cardiovascular risk factors. Like neurodegenerative diseases, the characteristics of presbycusis show (i) an age-related onset and a progressive course; (ii) a progressive neuronal and sensory degeneration that begins early, with clinical expression several decades later; (iii) polygenic/complex abnormalities along with epigenetic modifications, cerebrovascular alterations, and environmental risk factors; and (iv) non-specific clinical phenotypes for early detection, without clear biomarkers for predictive diagnosis.

Although patients often report a similar family history, there is no clear pattern of inheritance given the involvement of multiple genes with diverse effects on hearing. Knowledge of interethnic differences in various genetic polymorphisms that predispose individuals to presbycusis is useful to prevent the disease and develop future treatments. Taking into account that senescence or neurodegeneration directly or indirectly affects hearing loss, it is clear that identification of these genes can affect the genesis of presbycusis.

In an interesting study by **Dr. Joaquín Guerra**, Head of the Neuro-Oto-Rhino-Laryngology Unit of the EuroEspes Medical Center, now available in the digital version of the Journal *Current Pharmacogenomics and Personalized Medicine*, the genes that specifically influence hearing in neurodegenerative diseases related to age, dementia and other cerebrovascular disorders, as well as the knowledge of pharmacogenetic profiles and a personalized approach to treating hearing loss in the most efficient way possible, is deepened.

The identification of genes that predispose individuals to hearing loss is not a recent phenomenon. For several decades, considerable effort has been focused on identifying genes that induce hearing loss to help guide early diagnosis and treatment for young children. Over the years, this has spread to older age groups, including the elderly. Advances in molecular genetics allowed the identification of several genetic loci associated with presbycusis.

As in other conditions related to senescence, these genetic defects can be classified into three main categories: (i) Mendelian or mutational defects in genes directly related to presbycusis; (ii) multiple risk polymorphic variants that can increase neuronal vulnerability to hearing loss; and (iii) various localized mutations in mitochondrial DNA (mtDNA) that can influence aging and oxidative stress, conferring phenotypic heterogeneity.

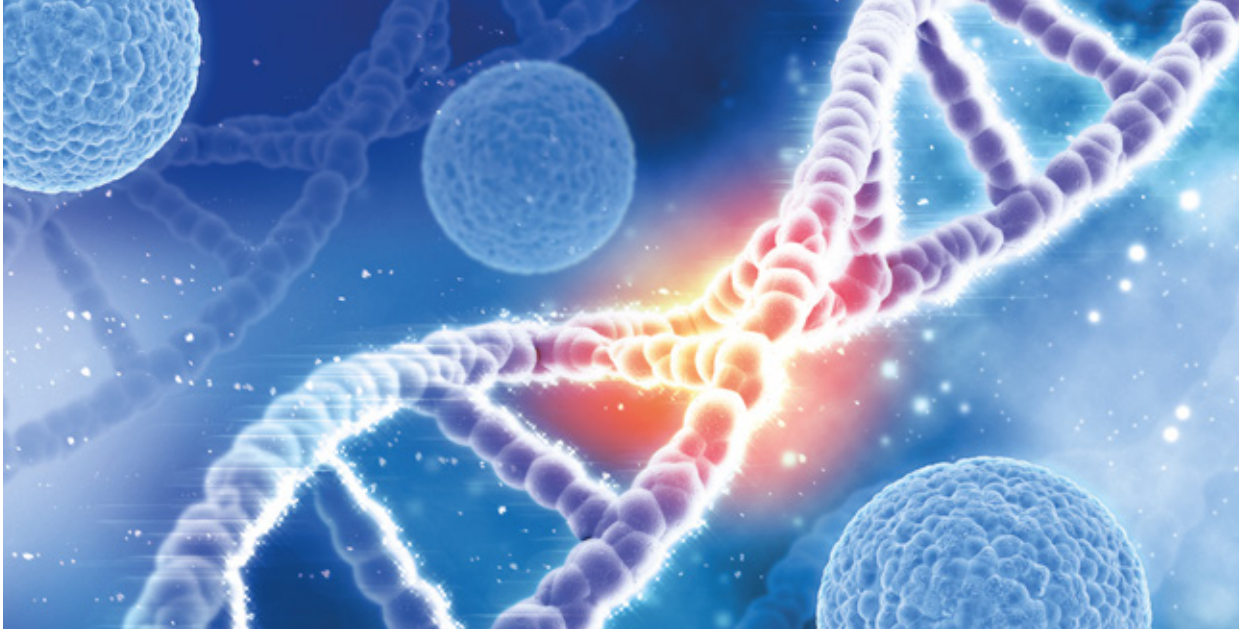


Regression model showing the relationship between hearing loss and aging in a heterogeneous group of 51 patients older than 60 years of age evaluated at the EuroEspes Biomedical Research Center.

Source: *J. Guerra. Neuro-Oto-Rhino-Laryngology Unit, International Center for Neuroscience and Genomic Medicine, A Corunna.*

References:

Guerra J, Naidoo V, Cacabelos R. Genomics and pharmacogenomics of age-related hearing loss. Cur Pharmacogenomics Person Med 2021; DOI: 10.2174 / 1875692118666210823115347.



Genomics of Human Longevity

The desire for a long life is a kind ambition; but everyone is aware that as the years go by, our capabilities diminish and, when disability limits us, the sense of dignity makes us question life by not being able to enjoy it.

Compared with the rest of the species, the human being is among the longest-lived, within a wide range of beings that live for minutes to others that live for centuries, such as some turtles and a few fish.

It has been known since ancient times that the longevity of each species is associated with its metabolic capacity, its reproductive capacity -especially the number of pregnancies and the period of pregnancy-, its body volume, its resistance to predatory factors and, above all, to the development and volume of your brain. Obviously, all these factors are closely regulated by genetic factors, characteristic of each species; and that genetic profile of the species is what determines the life span of each species in absolute terms. However, no species reaches its maximum level of longevity due to disease, accidents and environmental conditions (feeding, oxygenation, toxicity, accidents, etc); and there the concepts of "Life Expectancy" and "Longevity" arise. Life expectancy is a statistical construct based on the average life expectancy at birth, according to the observation of reality. In the human case, this life expectancy increases as environmental and health conditions improve. For example, in the early 1900s, the average life expectancy was less than 50 years old; now, the average is 82 years for men and 84 for women, in advanced countries. Therefore, in a century we have almost doubled life expectancy. In contrast, longevity is the maximum life expectancy that a species can constitutionally aspire to; in the human case, between 120 and 150 years of age.

Between longevity and life expectancy stands the real life of each person, marked by their individual genomics, their diet, their education, the health of the environment in which they live, accidents and disease. All these factors together are what determine our real history individually.

However, longevity itself is marked in our species genome; for this reason, each species lives an approximate average that affects all its members equally, except those that become ill, have an accident or suffer some adverse condition. In fact, perhaps the real footprint of our longevity is our species genome.

Over the past 20 years, since the human genome and that of other species were characterized, the existence of genes related to aging and longevity has been traced in the various genomic structures of all possible species. Between these two categories of genes,

the total of genes genuinely related to aging and longevity does not reach 1000; which is a very small number; perhaps because longevity does not depend on isolated genes but on a wide set of genes, which communicate with each other and with the environment, through epigenetics, to determine the longevity of each species.

What is clear is that over the years we get sick; and it is disease that shortens our life expectancy and allows, as humans, very few to have the privilege of approaching an age close to the longevity of the species.

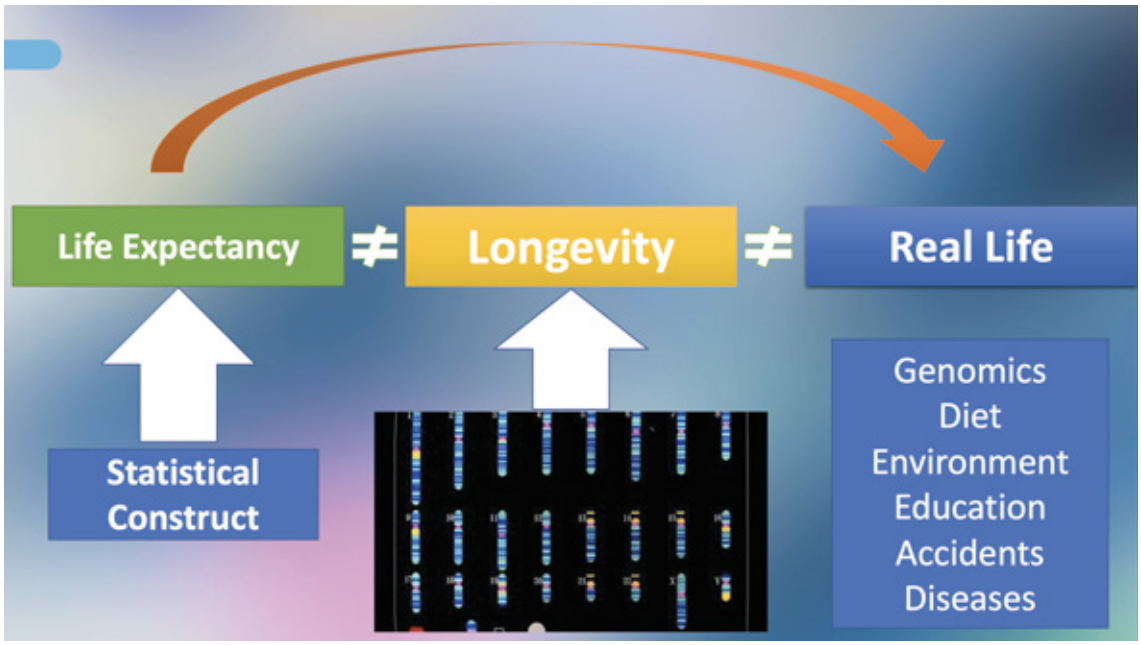
The heart ages; the walls of the arteries harden and the phenomenon of arteriosclerosis appears, a clear feature of tissue aging; the arteries and veins are damaged and thromboembolisms appear which, when they affect key organs, such as the brain, severely disable us. Tissues oxidize and cells age, like metals exposed to the elements. The brain shrinks due to the progressive death of neurons and the lack of cerebral oxygenation with age; with this our faculties are diminishing; it costs more to think; memorizing requires more effort; and moving becomes a laborious task. The genome also ages; our telomeres, where one of the longevity clocks is located, get shorter until they are exhausted; our genes deteriorate, accumulate defects that are self-repairing when young, and when old are irreparable due to biological inability to restore DNA damage. All these processes are happening gradually until the limit of resistance of our organs, under genetic regulation and environmental pressure; and suddenly, over 100 years of age, in days or months, our biological scaffold falls and we inevitably die.

We are biologically prepared to exceed 100 years, as a species, without great disability warning. If genomic and environmental conditions are adequate, we can celebrate the centenary knowing who we are with physical autonomy. But this, today, would only be possible in 10-20% of the population. The remaining 80% carry defective genes that prevent reaching these life expectancy quotas.

What any health system in a developed country has to pursue is to approximate the years of useful life expectancy to the years of maximum longevity of the species. For this, it is necessary to identify those defective genes that contribute to clogging our arteries, to being surprised by a stroke, a myocardial infarction, cancer or dementia at ages where we should have the opportunity to enjoy the previous work carried out, the sacrifices endured throughout life, and the well-being of the family we have created.

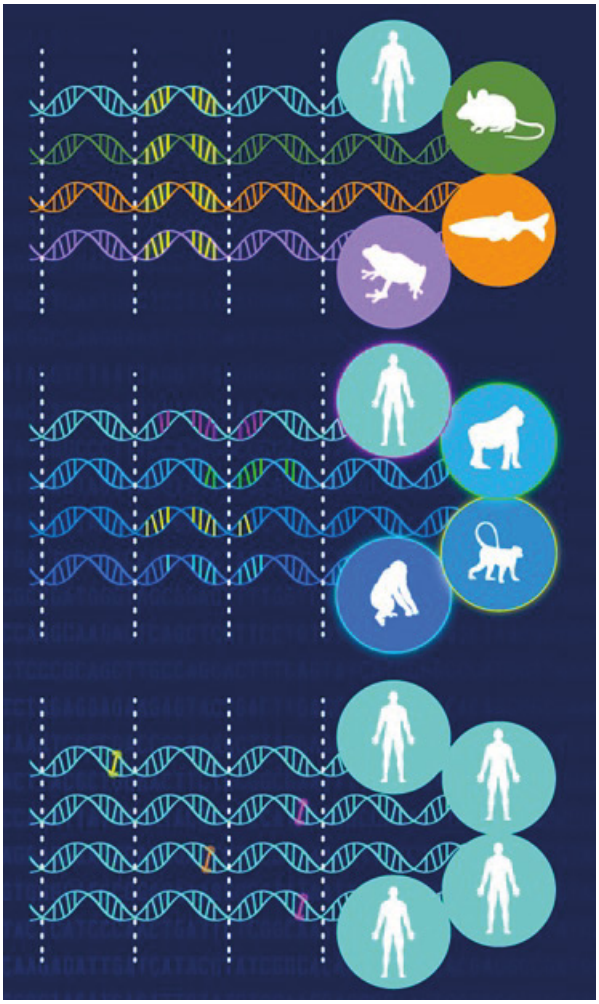
From a practical point of view, it is more sensible and useful to trace those genes that can shorten our lives than the other genes that can lengthen it. No one is going to steal the genes for the longevity of the species; but the genes that cause us disease are the ones that we have to know very well to be able to intervene and prevent them from ruining the potential of the genes that mark our potential longevity.

With this mindset, we may begin to think that more important than living long is living well.



Life expectancy and longevity vs. real life

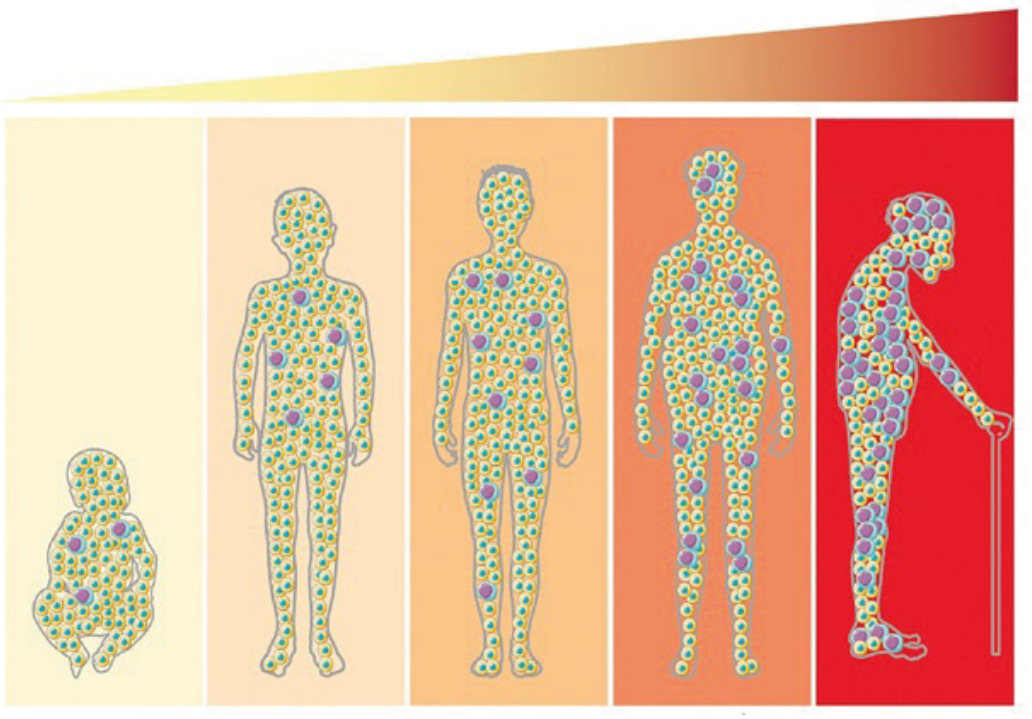
Source: *R. Cacabelos, 2021.*



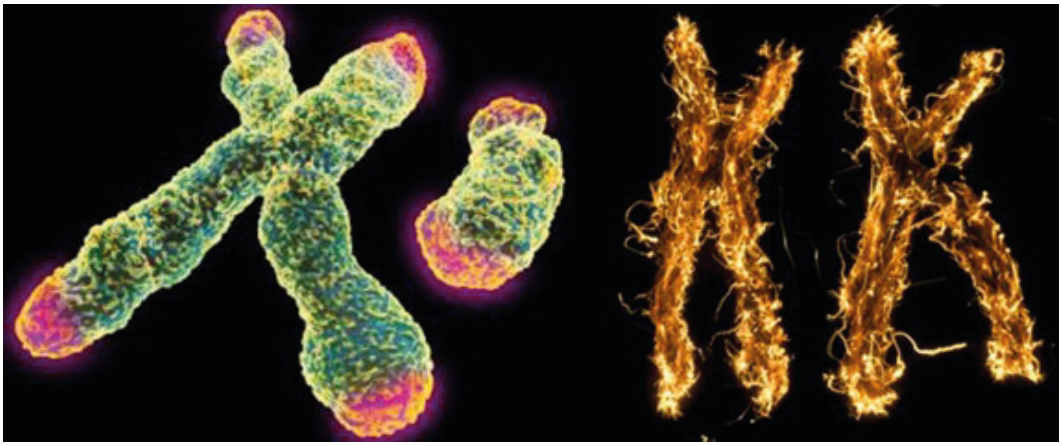
Comparative Genomics

Source: NIH: *National Human Genome Research Institute*

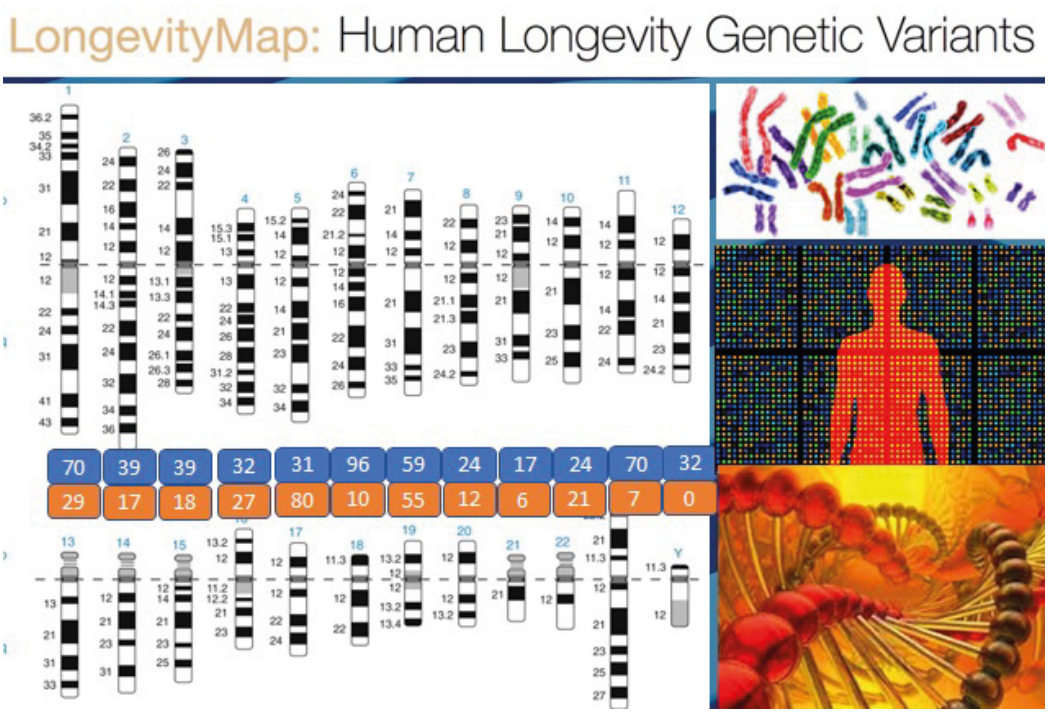
Aging of the human brain



Risk of accumulating diseases with age



Chromosomal aging



Genomic Map of Human Longevity

Distribution of the number of genetic variants per chromosome related to Human Longevity

*(**Source:** R. Cacabelos, 2021)*

Approval of a new drug (*Besremi*) to treat Polycythemia Vera

Polycythemia vera is one of 7,000 rare diseases that affect more than 30 million people in North America. In the United States alone, polycythemia vera affects about 6,200 people a year.

Most cases of polycythemia vera are associated with a somatic mutation in the JAK2 gene on chromosome 9p. Somatic mutations have also been found in the TET2 gene and the NFE2 gene.

There are other forms of polycythemia that are known as familial erythrocytosis. Familial erythrocytosis-2 (ECYT2) is caused by a compound homozygous or heterozygous mutation in the VHL gene on chromosome 3p25. This form of erythrocytosis is also known as Chuvash polycythemia, endemic in the Chuvash Republic of the Russian Federation and Ischia, Italy; is associated with a specific mutation in the VHL gene (R200W).

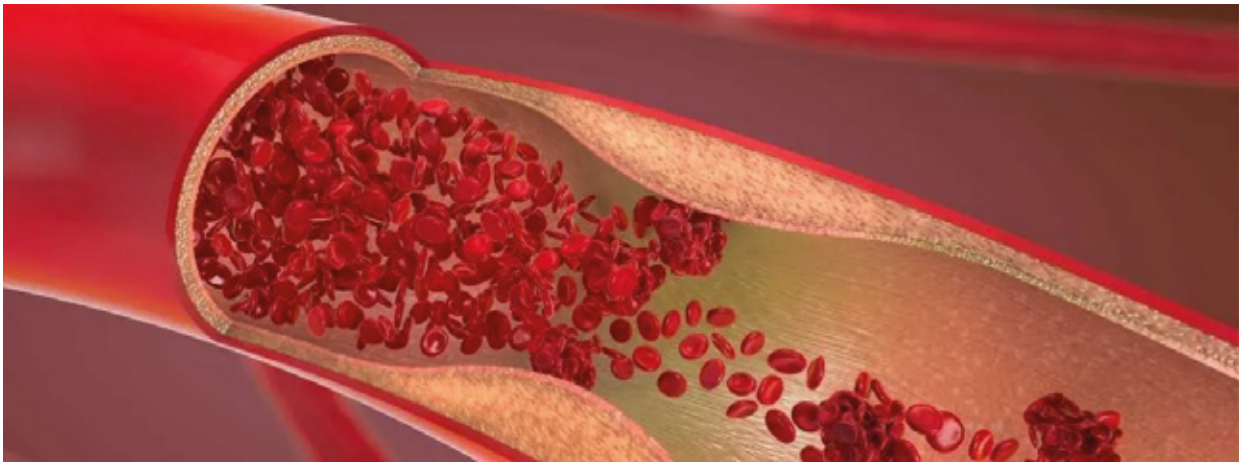
Familial erythrocytosis-1 (ECYT1) is caused by a heterozygous mutation in the gene encoding the erythropoietin receptor (EPOR) on chromosome 19p13. Other forms of familial erythrocytosis are ECYT3, caused by a mutation in the EGLN1 gene on chromosome 1q42; ECYT4, caused by a mutation in the EPAS1 gene on chromosome 2p21; ECYT5, caused by a mutation in the EPO gene on chromosome 7q22; ECYT6, caused by a mutation in the HBB gene on chromosome 11q15; ECYT7, caused by a mutation in the HBA genes on chromosome 16p13; and ECYT8, caused by a mutation in the BPGM gene on chromosome 7q33.

The US *Food and Drug Administration* (FDA) approves Besremi (Ropeginterferon alfa-2b) injection to treat adults with polycythemia vera, a blood disease that causes the overproduction of red blood cells. Besremi is the first FDA-approved medication for polycythemia vera, which patients can take regardless of their treatment history, and the first interferon therapy specifically approved for polycythemia vera. Besremi received orphan drug designation for this indication.

The effectiveness and safety of Besremi was tested in a multicenter trial that lasted 7.5 years. In this trial, 51 adults with polycythemia vera received Besremi for an average of about 5 years. The effectiveness of Besremi was assessed by looking at how many patients achieved a complete haematological response. 61% of patients showed a complete hematologic response, with a red cell volume less than 45% without the need for recent phlebotomy, normal white blood cell and platelet counts, normal spleen size, and no blood clots. Among the side effects of Besremi are the elevation of liver transaminases, low levels

of white blood cells (leukopenia), low levels of the number of platelets (platelet penia), joint pain, fatigue, itching, upper airway infections, muscle pain and similar symptoms to those of the flu. Other adverse effects include urinary tract infection, depression, transient ischemic attacks, and fetal harm in pregnancy.

Although the molecular effects of Besremi are not well understood, it is believed that it targets specific receptors that slow down the production of blood cells in the bone marrow. It is a long-term treatment. Patients receive a subcutaneous injection once every two weeks. If the drug was effective in the first year, the dose could be reduced to a monthly injection.



Advances in Gene Therapy and new molecules to combat dyskinesia in Parkinson's disease

Parkinson's disease is characterized by the premature death of dopaminergic neurons in the compact part of the substantia nigra in ganglia at the base of the brain. These neurons are responsible for the synthesis of dopamine to regulate ordered movements from the prefrontal cortex. The lack of brain dopamine is responsible for the symptoms that afflict patients with Parkinson's disease; and for more than 50 years, all therapeutic strategies have been aimed at supplementing dopamine deficiency.

AADC (*Aromatic L-amino acid decarboxylase*) is the enzyme that converts levodopa to dopamine. As Parkinson's disease progresses, the loss of AADC-producing nigrostriatal cells leads to the need for increased doses of levodopa and additional treatments to mitigate motor fluctuations and dyskinesias.

Chadwick W. Christine's team, from the Department of Neurology at the University of California, San Francisco, reports some success with a clinical trial (NBIb-1817 PD-1101; VY-AADC01) of gene therapy (not FDA approved) in Parkinson's patients for a period of 36 months. PD-1101 is a phase 1b, open label, dose escalation trial of VY-AADC01; an experimental AAV2 gene therapy encoding the enzyme human aromatic L-amino acid decarboxylase (AADC) in which intraoperative magnetic resonance guided bilateral putaminal infusions of VY-AADC01 are administered.

With this technique it was possible to reduce the dose of conventional antiparkinsonians associated with dyskinetic phenomena by 20-30%, without evidence in favor of etiopathogenic improvement. In some cases, dyskinesias even increased.

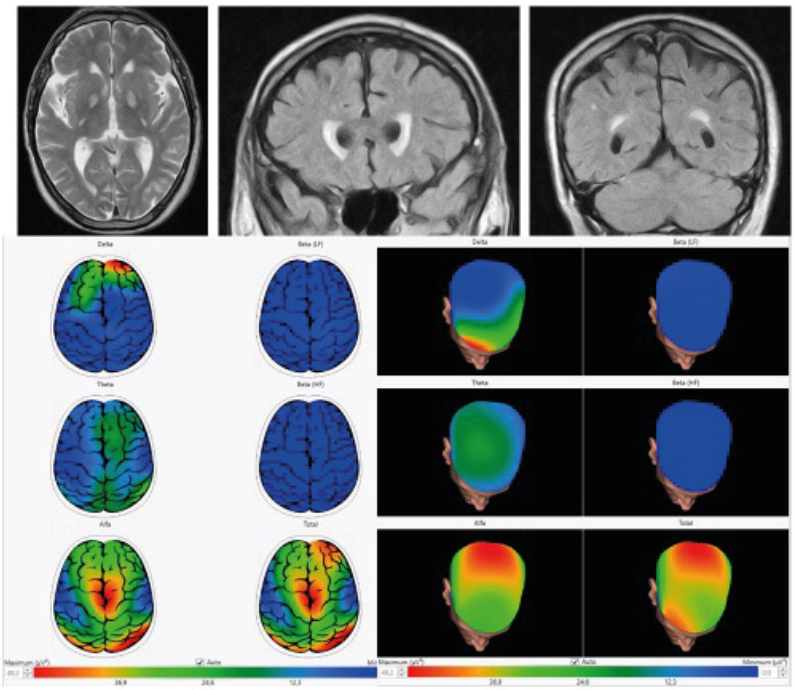
One of the problems faced by most patients with Parkinson's disease is the loss of effect of antiparkinson drugs, with the consequent need to increase the dose, and the appearance of uncontrolled movements, known as dyskinetic movements. In addition to the expensive gene therapy, recently tested, new chemical compounds are being investigated to somehow alleviate this serious complication of classical antiparkinsonian treatment.

As reported by *Drug Target Review*, a study from the Texas Biomed Research Institute, United States, has identified a promising candidate to minimize dyskinesia in patients on chronic treatment with traditional antiparkinson drugs.

A small molecule, called PD13R, is capable of reducing dyskinesia by more than 85% in a classic animal model of Parkinson's disease. Dyskinesia is a common side effect in patients receiving L-DOPA and other dopaminergic agents for long periods of time (> 5 years).

Designing drugs for Parkinson's disease and their side effects is difficult in part due to the progressive nature of the disease as neurons deteriorate. There are five types of dopamine receptors, all with different functions, in various brain structures. Finding the ideal compound that only interacts with a specific receptor is not an easy task. PD13R binds to dopamine receptor 3 (D3) with 1,486-fold greater selectivity for D3 than for dopamine D2 receptors.

Although the new molecule shows promise for counteracting dyskinesia, it is not an ideal drug. The best thing would be to find drugs that selectively reduce the process of premature neuronal death that occurs in patients with Parkinson's due to different causes. The main factors that influence the onset of Parkinson's are heredity, associated with 100 genes distributed throughout the human genome; cerebrovascular accidents that destroy critical regions of the basal ganglia where movements are regulated; environmental toxins, such as various drugs, herbicides, pesticides, aerosols; and repeated microtrauma to the brain (boxers, footballers, construction workers using vibrating machinery). In all these cases, neuronal destruction occurs decades before symptoms appear; For this reason, we recommend the use of neuroprotective products that prevent the selective destruction of dopaminergic neurons that give rise to Parkinson's symptoms.



Magnetic resonance imaging and brain mapping of a patient with Parkinson's disease

Source: *R. Cacabelos, 2021. International Center of Neuroscience and Genomic Medicine*

References:

Christine CW, Richardson RM, Van Laar AD, Thompson ME, Fine EM, Khwaja OS, Li C, Liang GS, Meier A, Roberts EW, Pfau ML, Rodman JR, Bankiewicz KS, Larson PS. Safety of AADC Gene Therapy for Moderately Advanced Parkinson Disease: Three-Year Outcomes From the PD-1101 Trial. Neurology. 2021 Oct 14: 10.1212 / WNL.0000000000012952. doi: 10.1212 / WNL.0000000000012952. Epub ahead of print. PMID: 34649873.

Sex Editing with CRISPR: Choice of sex on demand

A new scientific revolution is becoming feasible with CRISPR technology. Gene editing with this technique makes it possible to produce fully male or female litters of mice.

It is already possible to breed genetically modified mice in single-sex litters. This could have a huge impact on livestock farms and scientific research, as long as someone does not fall into the temptation to extrapolate it to the human species, which is technically possible. Researchers at the *Francis Crick Institute* who successfully applied the technique argue that the production of single-sex animals will save millions of lives of animals that are killed because they are not useful for a specific research or livestock operation.

There are various methods to skew the male/female ratio of newborn animals. Sperm can be classified by the weight of the sex chromosome, or by causing embryos of one sex to die before birth. It has been 2 years since the CRISPR technique was able to produce altered mice in which four out of every five litters were all female. In current experimentation, an efficiency level of 100% is achieved, extrapolated to other species.

CRISPR consists of two parts: the enzyme complex that physically disrupts the target gene in the genome, and a guide RNA, which recognizes the target gene and guides the complex to the correct place. To kill single-sex embryos, the CRISPR complex is separated, placing the gene for half C enzyme in one parent and the gene for half guide RNA in the other. First you have to find a molecular target that effectively kills the embryos. The chosen gene was Topoisomerase 1 (TOP1), key to cell division. Its uselessness leads to the rapid disappearance of an embryo in the very early stages.

The *Francis Crick Institute* researchers put the gene for TOP1-targeted guide RNA into the female mouse genome and linked the DNA encoding the CRISPR cleavage complex to the male Y chromosome. The enzyme and guide RNA bond only when sperm with the Y chromosome fertilize the female's eggs, creating the X/Y combination that defines a male.

When the developing male embryo consists of only a few dozen cells, the effects of gene editing kick in, killing that embryo before implantation in the mother's womb, preventing the birth of males. The reverse occurs when the CRISPR complex binds to the male's X chromosome, in which case all females are deleted.

To avoid ethical dilemmas, sex is defined before the animal is born. However, this form of genetic engineering has already started to raise ethical concerns in some sectors of society.

Multiple genetic and environmental factors associated with type 2 diabetes

Type 2 diabetes mellitus is reproducibly classified into five subtypes with different disease progression and risk of complications. The etiology of these phenotypic variants remains unknown. **Dina Mansour Aly**, from the Lund University Diabetes Center in Malmö, Sweden, and a large group of collaborators performed a comprehensive genomic analysis and genetic risk score (GRS) analysis to compare underlying genetic factors. They compared people from the Swedish ANDIS (*All New Diabetics In Scania*) study with individuals without diabetes; and replicated the results with the Finnish studies DIREVA (*Diabetes Register in Vasa*) and Botnia.

Swedish researchers found that diabetes subtypes differ with respect to family history and the association with GRS for diabetes-related traits. The severe insulin-resistant subtype is exclusively associated with GRS for fasting insulin, but not with variants at the TCF7L2 locus or with GRS that reflect insulin secretion. A polymorphic variant (rs10824307) close to the LRMDA gene is uniquely associated with obesity-related mild diabetes. All of this suggests that the different subtypes of diabetes have partially different genetic traits and, therefore, a different etiological nature.

References:

Mansour Aly, D., Dwivedi, O.P., Prasad, R.B. et al. Genome-wide association analyses highlight etiological differences underlying newly defined subtypes of diabetes. Nat Genet 53, 1534–1542 (2021). https://doi.org/10.1038/s41588-021-00948-2.

Psychogenic seizure in children and adolescents

Psychogenic non-epileptic seizures (PNES) are seizure-like events lacking the characteristic electrical shocks associated with epilepsy. Psychogenic seizures belong to the category of functional neurological disorders or conversion disorders. The more recent term defines them as non-epileptic dissociative seizures. They were formerly known by other terms, such as pseudo-seizures, psychogenic seizures, or hysterical seizures. Regardless of their neuropsychiatric nomenclature, psychogenic seizures have a dysfunctional etiopathogenic background in the brain that is poorly understood.

The team of **Anne Sofie Hansen**, from the Departments of Psychiatry and Clinical Medicine at the Universities of Aalborg and Aarhus in Denmark, have carried out a national study in children and adolescents aged 5 to 17 years with psychogenic seizures with the intention of better understanding the causes and the psychopathology associated with psychogenic seizures in this Danish child-adolescent cohort.

Of the 384 children and adolescents with psychogenic seizures, about 80% showed features consistent with prevalent and incident psychiatric disorders, which were not found in healthy children of the same age. These findings, although epidemiologically simple, are relevant from a treatment point of view. Many of these children are treated with unnecessary antiepileptic agents, ignoring the underlying psychiatric or psychopathological background that, if not treated properly at this age, can have serious consequences in youth and adult life.

References:

Hansen AS, Rask CU, Christensen AE, Rodrigo-Domingo M, Christensen J, Nielsen RE. Psychiatric Disorders in Children and Adolescents With Psychogenic Nonepileptic Seizures. Neurology. 2021 Aug 3;97(5):e464-e475. doi: 10.1212/WNL.0000000000012270. Epub 2021 May 24. PMID: 34031196.

Coffee and Tea: Natural neuroprotectors

Various studies link the consumption of coffee and tea with dementia, stroke and Parkinson's disease, although the results are not homogeneous and, sometimes, contradictory. In order to clarify the possible effect of coffee and tea, separately or in combination, on the risk of developing stroke and dementia, **Yuan Zhang**, **Hongxi Yang**, **Shu Li**, **Wei-dong Li** and **Yaogang Wang**, from the School of Public Health of Tianjin University in China, conducted a prospective study on 365,682 people aged 50 to 74 years between 2006 and 2010.

Throughout the study, 5,079 participants developed dementia and 10,053 suffered a stroke. When studying the association of coffee and tea consumption with strokes and dementia, they found that the intake of 2-3 cups of coffee per day or 3-5 cups of tea per day, as well as the intake of 4-6 cups of coffee and tea interspersed daily reduced the risk of strokes and dementia. Compared with non-drinkers of tea and coffee, drinking 2 to 3 cups of coffee or 2 to 3 cups of tea per day is associated with a 32% decreased risk of stroke and reduced risk of dementia 28%.

The Chinese researchers were also able to verify that the combination of coffee and tea consumption reduced the risk of stroke and vascular dementia.

These interesting results should be viewed with caution, without making them universal for several reasons: (i) the information comes from subjective sources provided by the participants, without scientific verification; (ii) although the authors took into account sex, age, ethnicity, economic status, body mass index (BMI), physical activity, alcohol and tobacco consumption, dietary pattern, sugar consumption, HDL-cholesterol (high-density lipoprotein), and LDL-cholesterol (low-density lipoprotein), history of cancer and history of diabetes, the reliability of this information was not verified; and (iii) the participating subjects belong to the *UK Biobank*, whose ethnicities are biased and do not represent an ethnically plural collective.

Regardless of the scientific value of this new epidemiological contribution to the potential neuroprotective role of tea and coffee, there are medical conditions in which their consumption must be controlled, especially in hypertensive people and heart disease, as well as in consumers of psychotropic drugs.

References:

Zhang Y, Yang H, Li S, Li W-d, Wang Y (2021) Consumption of coffee and tea and risk of developing stroke, dementia, and poststroke dementia: A cohort study in the UK Biobank. PLoS Med 18(11): e1003830. https://doi.org/10.1371/journal.pmed.1003830

Covid-19 News

SARS-CoV-2 spreading model

Uncertainty persists about the temporal evolution and the start of local transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide. A few weeks after the initial announcement of a cluster of atypical pneumonia cases in Wuhan, China, the first confirmed cases of coronavirus disease 2019 (COVID-19) were detected in the United States and Europe. Although many more states and countries began reporting cases in the following weeks, only a few cases were detected daily during this time period, and most countries adopted a testing policy that targeted symptomatic individuals with a history of travel linked to China.

Several reports suggest that the introduction of SARS-CoV-2 occurred earlier than was initially recognized, raising questions about the effectiveness of initial testing policies and travel-related restrictions, as well as the extent to which the virus SARS-CoV-2 spread via cryptic transmission in January and February 2020.

To answer these questions, **Jessica T. Davis**, from the *Laboratory for the Modeling of Biological and Socio-Technical Systems, Northeastern University*, Boston, USA, and her team developed a model that maps the plausible pathways of the pandemic using available information in the early stages of the outbreak and provides a comprehensive picture of the cryptic phase, as well as the subsequent first wave of the COVID-19 pandemic.

Although a limited number of SARS-CoV-2 cases were reported in January and February 2020, narrow initial testing criteria, combined with slow growth in testing capacity, as well as poor detection of risky trips, left many countries vulnerable to cryptic transmission of the virus. Based on this study, community transmission of SARS-CoV-2 is likely to have been present in various areas of Europe and the United States in January 2020, and it is estimated that, as of early March, only between 1 and 4 out of every 100 SARS-CoV-2 infections were detected by surveillance systems. The results of the model highlight international travel as the main driver of SARS-CoV-2 transmission, with possible spread from December 2019 to January 2020. The geographic distribution of the pandemic was heterogeneous, with cumulative attack rates of 0.78% to 15.2% in different US states. And from 0.19% to 13.2% in European countries by July 4, 2020.

Apart from clarifying various unknowns about the mode of spread of SARS-CoV-2 in the world, what the work emphasizes is the ineffectiveness of the measures to contain the pandemic and the failure of surveillance systems worldwide.

References:

Davis, J.T., Chinazzi, M., Perra, N. et al. Cryptic transmission of SARS-CoV-2 and the first COVID-19 wave. Nature 600, 127–132 (2021). https://doi.org/10.1038/s41586-021-04130-w

The Pandemic aggravates the Mental Health of the Population

A study by **Marius Brülhart** of the University of Lausanne in Switzerland and the *Center for Economic Policy Research* in London, in collaboration with **Valentin Klotzbücher,** of the University of Freiburg in Germany, **Rafael Lalive** (Lausanne) and **Stephanie K. Reich** (Freiburg) indicates that the COVID-19 pandemic has generated a situation of emotional instability in the population, with a notable deterioration of mental health in different sectors of society.

Mental health is an important component of public health, especially in times of crisis. Using data from helplines, which provide a real-time measure of the population's distress and mental health problems, the authors collected information from 8 million calls related to COVID-19 in 19 countries. Calls peaked six weeks after the initial outbreak, 35% above pre-pandemic levels. The increase in calls is attributed to fear and loneliness. As the pandemic progressed, concerns turned to physical health. On the other hand, relationship problems, economic problems, violence and suicidal ideation decreased in relation to what happened before the pandemic. This pattern was common in both the first wave and subsequent waves of COVID-19. The authors' interpretation of these results is that problems directly related to the pandemic appear to have replaced, rather than exacerbated, underlying anxieties. Conditioned by infection rates, suicide-related calls increased as containment policies tightened and decreased as income support was extended. This suggests that financial relief lessens the distress caused by lockdown measures.

Other conclusions that could be drawn from this study, to take into account to correct many aberrant political decisions, are: (i) inducing fear through the media or official messages from the ministries of health does not provide any benefit to the mental health of the population; (ii) restrictive measures, be they confinement or freedom of movement, generate emotional instability and intensify fear; and (iii) one of the aspects that generates the most anxiety is the loss of purchasing power and economic problems; consequently, the measures that threaten the economic activity of citizens are not correct policies in terms of mental health.

References:

Brülhart, M., Klotzbücher, V., Lalive, R. et al. Mental health concerns during the COVID-19 pandemic as revealed by helpline calls. Nature 600, 121–126 (2021). https://doi.org/10.1038/s41586-021-04099-6

Enigmas around the Omicron variant

A month ago, scientists from Botswana and South Africa alerted the world to a rapidly spreading variant of SARS-CoV-2, known as Omicron (B.1.1.529), already present in more than 40 countries. Omicron is a highly mutated variant of SARS-CoV-2 with an explosive propagation capacity, about six times higher than the Delta variant.

Dutch health authorities announced on November 30 that they found the new Omicron variant in cases detected two weeks earlier, indicating that it was already spreading in Western Europe before the first cases were identified in southern Africa. The RIVM health institute noted that they found Omicron in samples dating from November 19 and 23. Those findings predate the positive cases found among passengers who came from South Africa and were tested at Amsterdam's Schiphol Airport in early December. Belgium and Germany have also said tests confirm the variant was in those countries before South African health officials alerted the world on November 24 to its existence. Japan and France also confirmed their first cases of the new variant, as countries around the world rushed to close their borders, and the scientific community began the anti-Omicron crusade. Meanwhile, the World Health Organization (WHO), following its alarmist tradition, to cure itself in health, announced through its executive director, **Dr. Tedros Adhanom Ghebreyesus**, that the consequences of the worldwide spread of the Omicron variant could be catastrophic. Behind all the politicians, with President **Biden** and his top medical policy adviser, **Dr. Anthony Fauci**, at the helm, claimed that the variant was not cause for panic, but that it was cause for concern. The U.S. Centers for Disease Control and Prevention has already taken action, expanding its vaccine guide to recommend that all American adults receive a booster shot. **Dr. Michael Osterholm**, director of the Center for Infectious Diseases Policy and Research at the University of Minnesota, announced a difficult winter for the United States if people don't take prophylactic measures. For its part, the pharmaceutical industry has already anticipated that the Omicron variant may not respond to current vaccines.

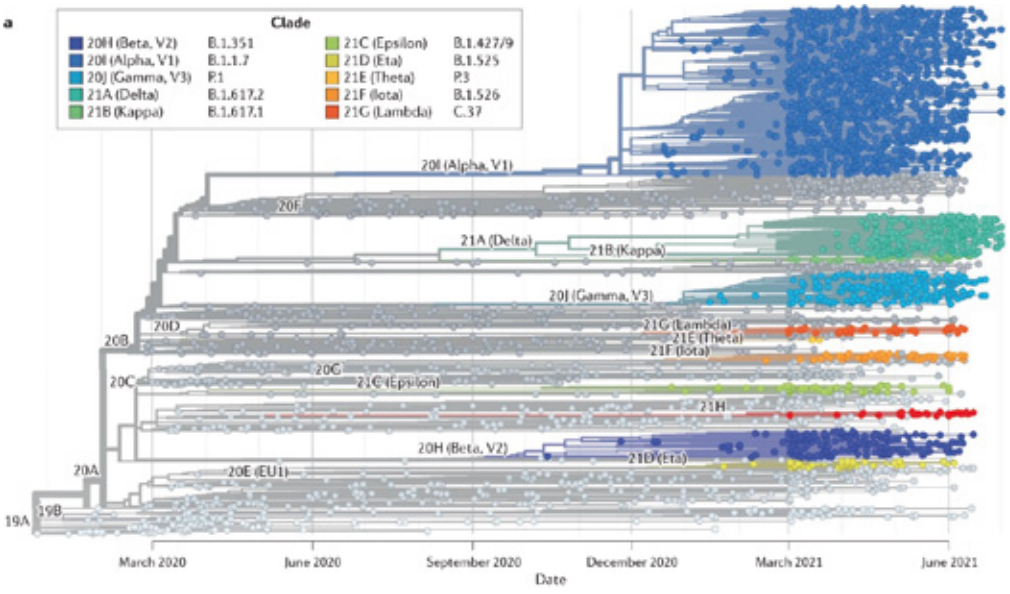
Although genome sequencing is necessary to confirm Omicron cases, some PCR tests can pick up a hallmark of the variant that distinguishes it from Delta. The rapid spread of the Omicron variant in South Africa suggests that it has some ability to evade immunity and infect people previously immunized against the Delta variant, either due to having previously suffered COVID-19 or due to vaccination. Reinfections in South Africa have increased as Omicron has spread.

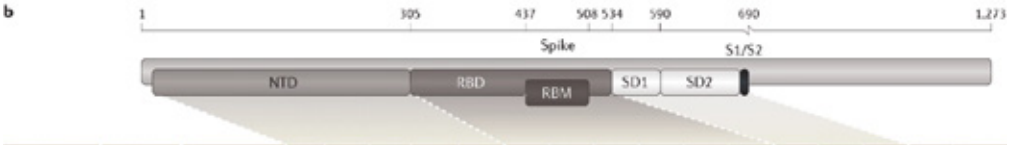
Variant B.1.1.529 contains more than 30 changes in the spike protein, the SARS-CoV-2 protein that recognizes host cells and is the primary target of immune responses. Many of the changes have been found in variants such as Delta and Alpha, and are related to increased infectivity and the ability to evade antibodies that block infection. Studies of Omicron mutations in the region that recognizes the receptors in human cells suggest that the variant is resistant to the neutralizing antibodies generated by conventional vaccines. However, it appears that the symptoms caused by Omicron in infected people are milder.

A study published online (doi: https://doi.org/10.1101/2021.11.11.21266068) on December 2 by **Juliet RC Pulliam** and colleagues from the *South African DSI-NRF Center of Excellence in Epidemiological Modeling and Analysis (SACEMA), Stellenbosch University*, in South Africa, is quite conclusive. The South African authors identified 35,670 reinfections among 2,796,982 people with confirmed SARS-CoV-2 at least 90 days prior to November 27, 2021. Although increases in the risk of primary infection were observed after the introduction of the Beta and Delta variants, a corresponding increase in the risk of reinfection was not observed. Contrary to expectations, the estimated risk ratio for reinfection versus primary infection was lower during the waves driven by the Beta and Delta variants than for the first wave. However, the recent

spread of the Omicron variant has been associated with a decrease in the risk ratio for primary infection and an increase in the risk ratio for reinfection. The estimated risk ratio for reinfection versus primary infection for the period from November 1, 2021 to November 27, 2021 versus wave 1 was 2.39.

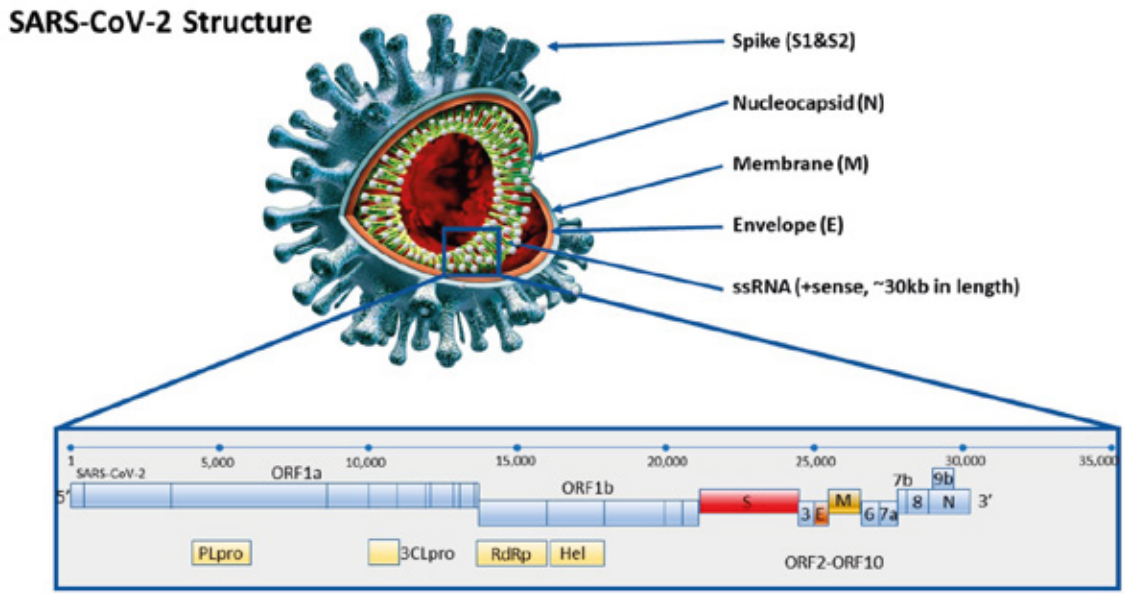
Population-level evidence suggests that the Omicron variant is associated with a substantial ability to evade immunity from a previous infection. In contrast, there is no epidemiological evidence in the entire population of immune escape associated with Beta or Delta variants. This finding has important implications for public health planning, particularly in countries with high rates of immunity against previous infections. Now scientists are investigating whether Omicron is also capable of evading vaccine-induced immunity and the possible implications of reduced immunity to infection in protection against severe illness and death.



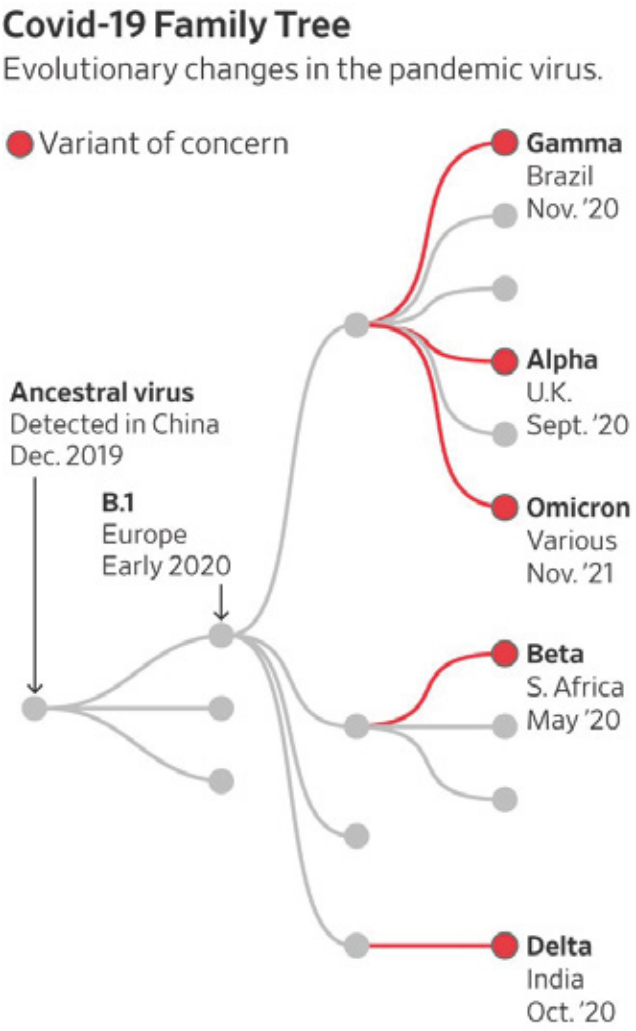


WHO	PANGO lineage	Country of first identification	18	69	95	144	242	417	452	478	484	490	501	614	681	701	nsp6: 106	N:203/ 204
			L	H	T	Y	L	K	L	T	E	F	N	D	P	A	S	R/G
Alpha	B.1.1.7	UK		del		del							Y	G	H		del	K/R
Beta	B.1.351	South Africa	F				del	N			K		Y	G		V	del	
Gamma	P.1	Brazil	F					T			K		Y	G			del	K/R
Delta	B.1.617.2	India			I				R	K				G	R			M
Epsilon	B.1.427/9	USA							R					G				
Eta	B.1.525	Nigeria		del		del					K			G			del	
Theta	P.3	Philippines									K		Y	G	H			K/R
Iota	B.1.526	USA			I	del					K			G		V	del	
Kappa	B.1.617.1	India			I				R		Q			G	R			M
Zeta	P.2	Brazil									K			G				K/R
Lambda	C.37	Peru							Q			S		G			del	K/R

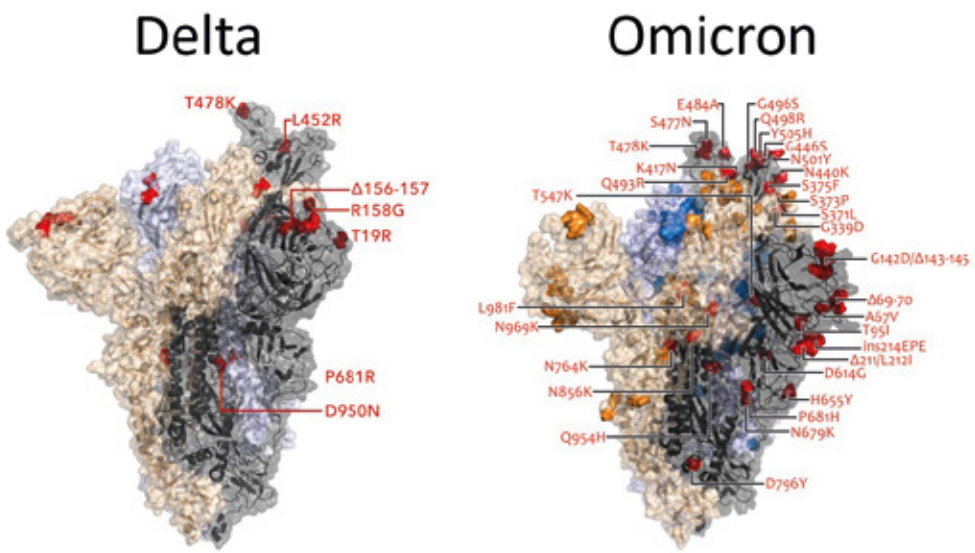
Phylogenetic variants of SARS-CoV-2
Source: Tao, K., Tzou, P.L., Nouhin, J. et al. The biological and clinical significance of emerging SARS-CoV-2 variants. Nat Rev Genet 22, 757–773 (2021). https://doi.org/10.1038/s41576-021-00408-x.



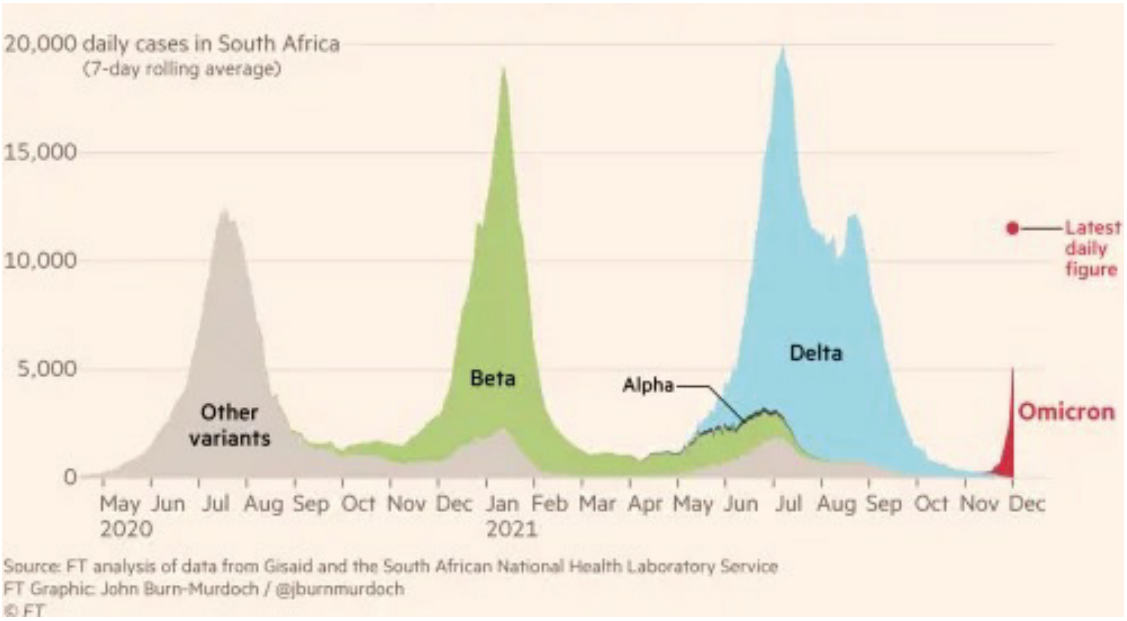
Structure of SARS-CoV-2



Evolutionary changes in the pandemic spread of the Coronavirus



Mutations in the Spike protein of the Delta and Omicron variants of SARS-CoV-2.



Spread of the Coronavirus in South Africa and the emergence of the Omicron variant

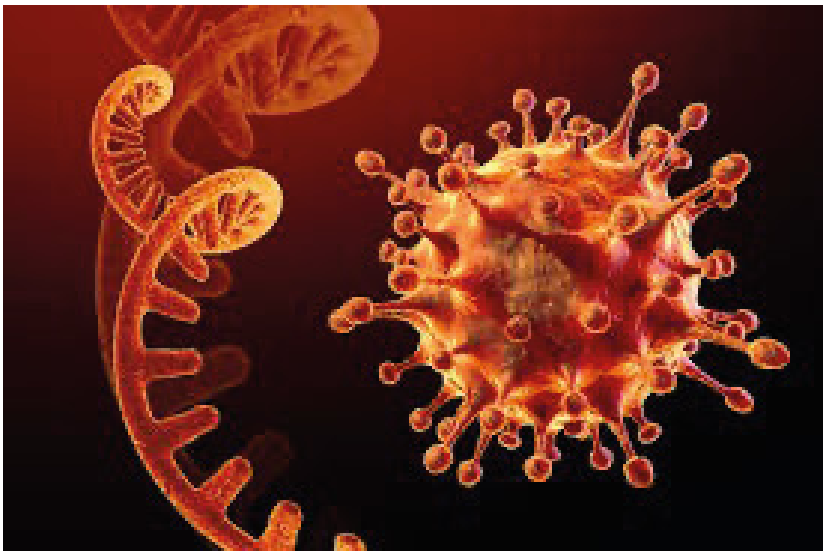
The race to develop anti-Omicron vaccines begins

Several pharmaceutical companies have already started preclinical studies for the development of new vaccines against the Omicron variant of SARS-CoV-2. *Everest Medicines and Providence Therapeutics* have begun work on a new version of the COVID-19 vaccine specifically targeting the new Omicron variant. Both companies have announced the start of a joint investigation to achieve a vaccine within 100 days.

Scientists from these two companies have analyzed the sequence of the Omicron variant of SARS-CoV-2, selected viral sequences, and designed plasmid clones.

The World Health Organization (WHO) has already designated variant B.1.1.529 as a worrying variant, although the potential impact on the effectiveness of the vaccine is not yet clear.

Providence is a Canadian biotechnology company pioneering messenger RNA (mRNA) therapies and vaccines with operations in Calgary and Toronto. *Everest Medicines* is a biopharmaceutical company focused on the development and commercialization of pharmaceutical products that address the unmet medical needs of patients in Asian markets.



EMA approves two drugs with monoclonal antibodiesfor COVID-19

The *Committee for Medicinal Products for Human Use* (CHMP) of the *European Medicines Agency* (EMA) has recommended the authorization of *Ronapreve*™ and Regkirona for COVID-19.

Ronapreve™ (Casirivimab/Imdevimab) and ***Regkirona*** (Regdanvimab) are the first monoclonal antibody drugs to receive a positive CHMP opinion for COVID-19 and join the list of COVID-19 products that have received a positive opinion since the recommended authorization of ***Veklury*** ® (Remdesivir) in June 2020.

The committee recommended authorizing Ronapreve for the treatment of COVID-19 in adults and adolescents from 12 years of age, weighing more than 40 kilograms who do not require supplemental oxygen and who are at risk of their disease becoming serious. Ronapreve can also be used to prevent COVID-19 in people over the age of 12. The CHMP also recommended authorizing Regkirona for the treatment of adults with COVID-19 who do not require supplemental oxygen and who are also at high risk of worsening their coronavirus disease.

Both products appear to significantly reduce hospitalization and deaths in COVID-19 patients. In a study of 1,192 patients affected by COVID-19, 0.9 percent of patients treated with Ronapreve were hospitalized or died within 29 days of treatment compared with 3.4 percent of patients treated with placebo.

Another study analyzed the benefits of Ronapreve for the prevention of COVID-19 in 100 people who had close contact with an asymptomatic infected partner. With Ronapreve, 29% of people tested positive and developed symptoms within 14 days of their positive test results, compared to 42.3% of people who received a placebo.

Regarding Regkirona, a study in 434 COVID-19 patients showed that the treatment reduced the number of hospitalizations, the need for oxygen therapy, and mortality. 3.1% of Regkirona-treated patients were hospitalized, required supplemental oxygen, or died within 28 days of treatment compared to 11.1% of placebo patients.

The safety profile of both drugs was favorable, with a small number of infusion-related reactions. The CHMP concludes that the benefits of the medicines outweigh their risks for the approved uses and recommends that the European Commission (EC) take binding legal decisions for the approval of both medicines in the countries of the Union.

COVID-19 diagnosis with CRISPR technology

Aisha Al-Jabani, *Assistant Editor* of *BioTechniques (The International Journal of Life Science Methods*) reports in the November 17 issue that a group of researchers at the University of California, San Diego have developed a diagnostic tool called *Sensitive Enzymatic Nucleic Acid Sequence Reporter* (SENSR), using CRISPR technology, to identify pathogens from their DNA or RNA sequences. PCR tests require specialized facilities and long reaction times that limit their application. SENSR promises the development of simpler and more practical technologies for the detection of viral nucleotides.

SENSR uses the Cas13d enzyme and a ribonuclease effector called CasRx, a pioneer in the use of this technology (Brogan D, Chaverra-Rodriguez D, Lin C, et al. *Development of a rapid and sensitive CasRx-based diagnostic assay for SARS-CoV-2, ACS Sens*. Doi: 10.1021 / acssensors.1c01088, 2021). Cas9 is commonly used in genetic engineering with CRISPR; but recently enzymes such as Cas12a and Cas13a have been explored for precise CRISPR-based diagnostics. The first results indicate that SENSR is capable of providing an accurate diagnosis of SARS-Cov-2 in less than an hour and the promoters of the technique are working to turn it into a possible self-test at home, airports or places that demand rapid tests of high reliability.

EuroEspes promotes the use of Pharmacogenomics in Psychiatry in Brazil

The International Center of Neuroscience and Genomic Medicine EuroEspes is implementing in Brazil the use of personalized psychopharmacological treatment, through the Smart Pharmacogenetic Card, in patients with neuropsychiatric disorders. This activity is led by **Dr. Reinaldo Segre**, psychiatrist and close associate of **Dr. Ramón Cacabelos**, in Sao Paulo.

For three years, EuroEspes has promoted in Brazil the use of genomic and epigenetic markers for the diagnosis of various psychiatric diseases, as well as the optimization of psychiatric treatment, based on pharmacogenomics, to reduce side effects in patients who have to undergo long chronic treatments, with high risk of toxicity.

In February 2019, Dr. Cacabelos and Dr. Segre, together with a multidisciplinary group of Brazilian collaborators, presented the latest version of the Smart Pharmacogenetic Card of EuroEspes in Sao Paulo. This bioinformatic product incorporates specific software for reading and interpreting more than 300 genetic variants related to drug metabolism and a database with more than 3000 drugs from all medical specialties. The Smart Pharmacogenetic Card allows the doctor to know what type of drug should be prescribed to their patients, based on the genomic profile of each one, and allows the user, drug consumer, to be sure that the drug they consume is adequate, minimizing with this, adverse effects and optimizing the therapeutic power of any drug.

Dr. Reinaldo Segre and Dr. Ramón Cacabelos during the presentation of the EuroEspes Smart PharmacoGenetics Card in Sao Paulo, Brazil.

Dr. Ramón Cacabelos is awarded the Physician of the Year Award in Genomic Medicine

On December 15, at the Westin Palace Hotel in Madrid, the Doctor of the Year Awards Gala was held. At the event, presented by the Spanish TV channel Antena 3 journalist, Roberto Brasero, and chaired by the director of the newspaper La Razón, Francisco Maruhenda, and the CEO, Andrés Navarro, Dr. Ramón Cacabelos was presented with the Doctor of the Year Award in Medicine Genomics. In a brief address to those present, Dr. Cacabelos expressed himself in these terms:

"For the sake of the brevity that this act requires, I just want to say that Genomics is the younger sister of the great family of science, with little more than 20 years of history, when President Clinton and Prime Minister Tony Blair made public the first draft of the human genome generated by the Collins and Venter groups, in the public and private sectors, respectively. Genomics is not a branch but a vigorous root in the lush tree of medicine, with a vertiginous development, reflected in the more than 800,000 scientific publications that have appeared in the last quarter of a century, with a current average of 10,000 publications per year.

In evolutionary terms, as a species, genomics allows us to know who we are, where we come from and where we are going, which is not a small thing.

As doctors, genomics helps us understand the molecular bases of the pathogenesis of diseases, of which we do not know even 20%; allows us to design and characterize predictive biomarkers to anticipate disease and to implement programs that preserve health, prevent or delay disease and make damage easier to repair; and it is also essential for the development of new generations of drugs and vaccines, with personalized treatments based on the genomic profile of each person, as we are already doing with the application of pharmacogenomic procedures, with which we can improve therapeutic precision in more than 40% and reduce side effects in 50% of cases.

On the other hand, every award has two readings: Recognition and Commitment. With the enthusiasm of a novel discipline that brings new knowledge to the arsenal of medical knowledge, and with the humility of every vocation of service to the medical community and the well-being of people, we appreciate this distinction.

Finally, realism should not make us forget that, in the study of any complex matter, a single man is nobody without the work and sacrifice of his collaborators and without the hours of life that we rob from our families. I believe that they deserve our most sincere recognition and our deepest gratitude".

Andrés Navarro, Ramón Cacabelos and Francisco Maruhenda

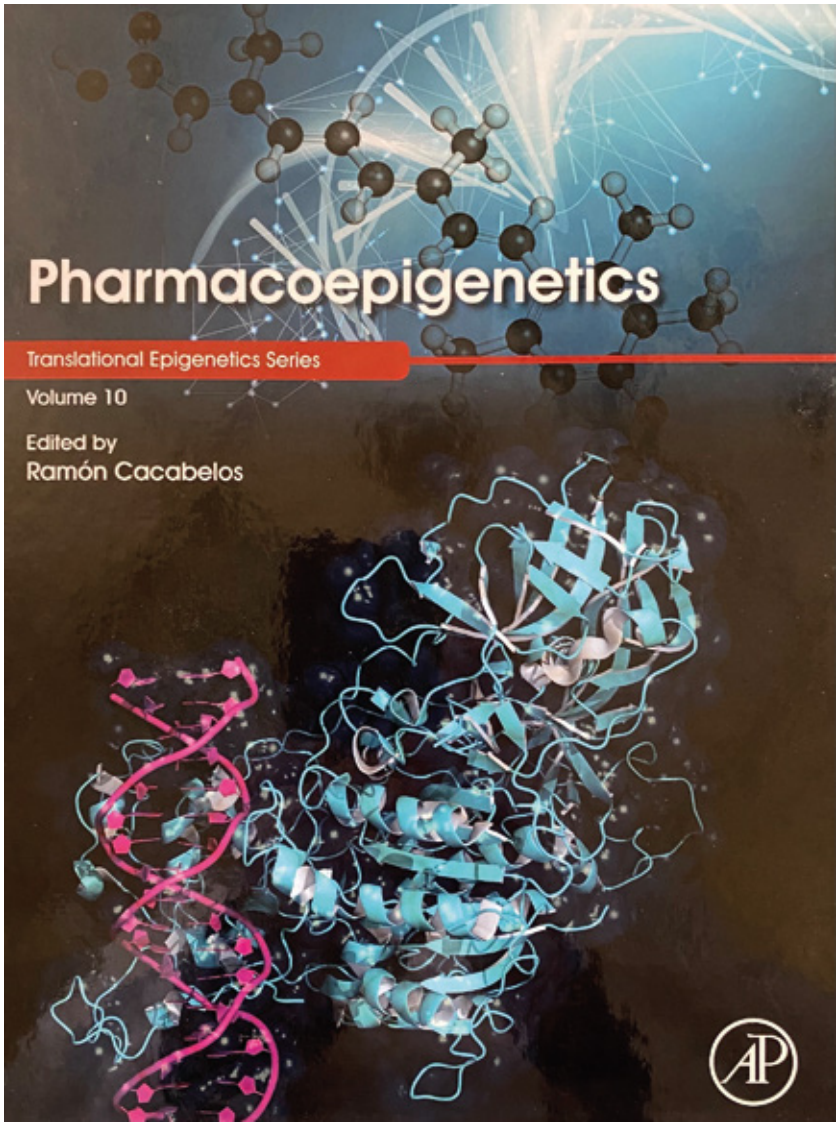
Dr. Ramón Cacabelos addresses the audience for the Medical of the Year Awards, in the presence of Andrés Navarro and Francisco Maruhenda, CEO and Director of La Razón newspaper, respectively.

Editorial News

Elsevier Announces Second Edition of PharmacoEpigenetics

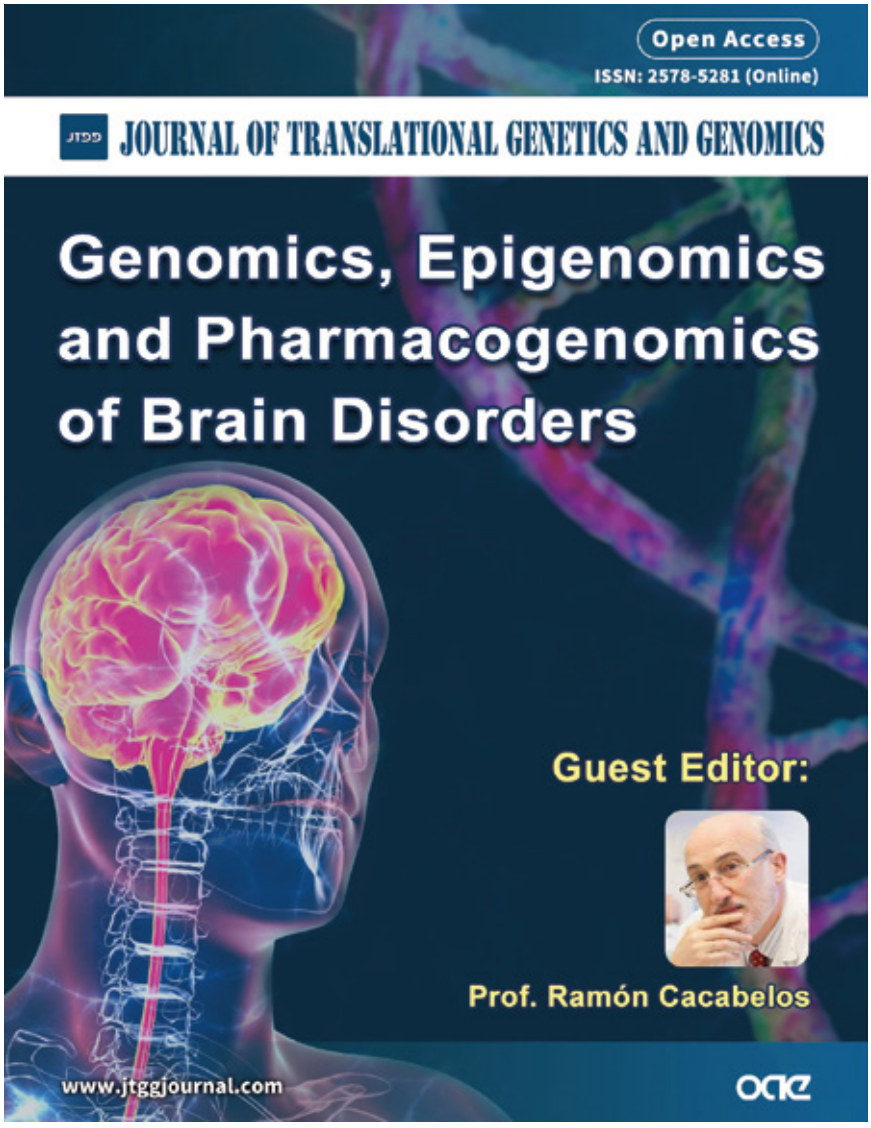
Elsevier is preparing the second edition of the book ***PharmacoEpigenetics***, edited by **Dr. Ramón Cacabelos**.

PharmacoEpigenetics, from Academic Press, the publishing division of Elsevier, is the world's first published work on PharmacoEpigenetics. The first edition came out in 2019 and after the huge international reception of this first installment on a highly innovative discipline, those responsible for Elsevier are already preparing the second edition, which is expected in 2022.



Open Editions 2021-2022

Editions are open to the international scientific community for which Dr. Ramón Cacabelos is responsible, as Editor-in-Chief or Guest Editor for special issues dedicated to genomics, epigenetics, pharmacogenetics of diseases of the central nervous system and development of new pharmaceutical products.



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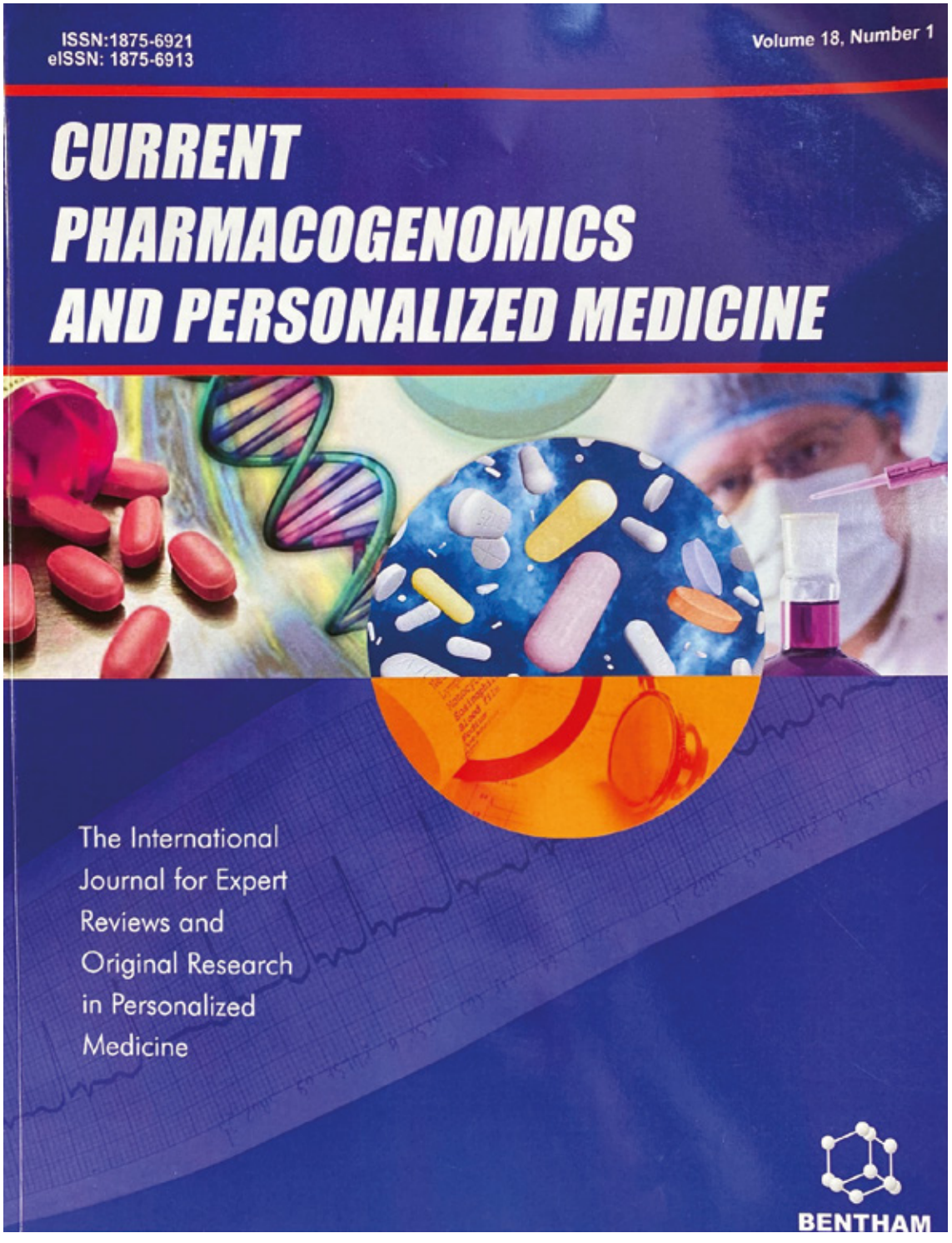
EDITOR-IN-CHIEF

Ramón Cacabelos
International Center of Neuroscience and Genomic Medicine
EuroEspes Biomedical Research Center
15165-Corunna (Spain)

Biography




Central Nervous System Agents
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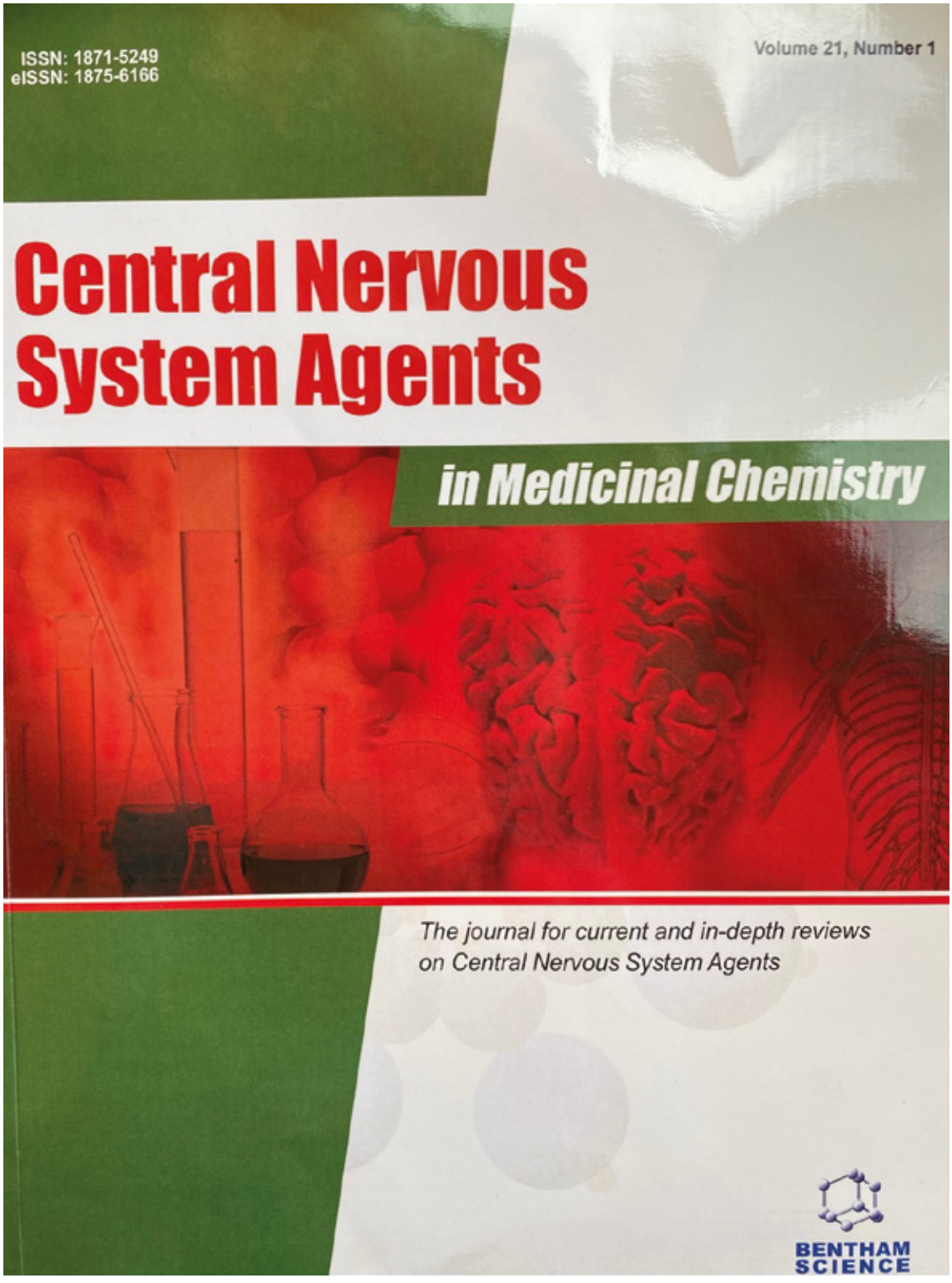
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Central Nervous System Agents
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BENTHAM SCIENCE

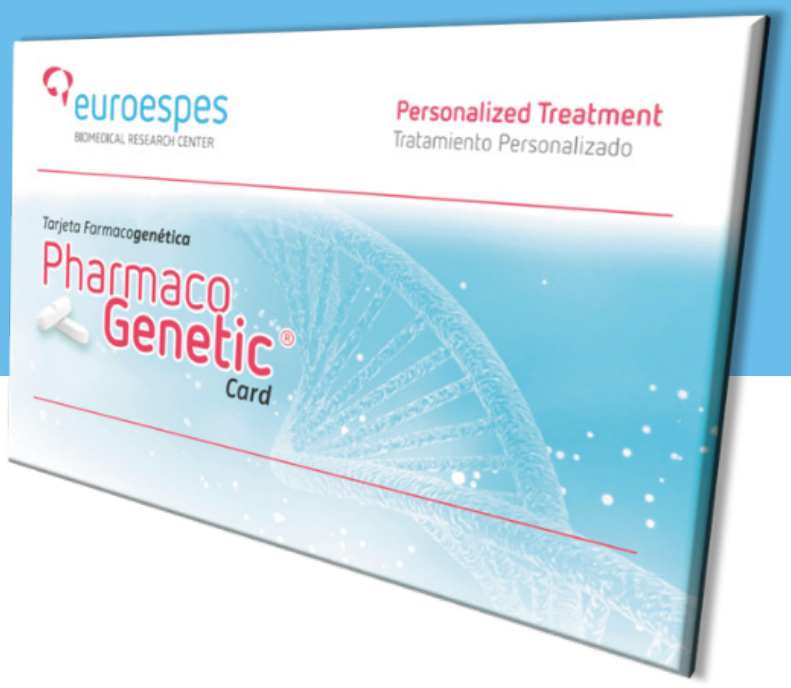
Promotional Section

Alzheimer's Prevention Plan (APP)
Home and Face-to-face

The APP identifies populations at risk of Alzheimer's disease (AD) and discriminates against other memory disorders and other forms of dementia. As the initial component of the APP is the identification of the genetic risk, in order to avoid unnecessary costs and discomfort due to the displacement of people, we have established a dual APP: (i) Home APP to perform genetic tests on a saliva sample that the interested person sends to the EuroEspes Medical Center with no need to travel; and (ii) face-to-face APP for those who wish to complete a complete diagnostic protocol, including genetic tests, at our Medical Center. Those people whose home APP detects an obvious risk can later join the face-to-face APP to complete the diagnostic set and enter the personalized prevention program through pharmacogenetic intervention.

Parkinson's Prevention Plan (PPP)
Home and Face-to-face

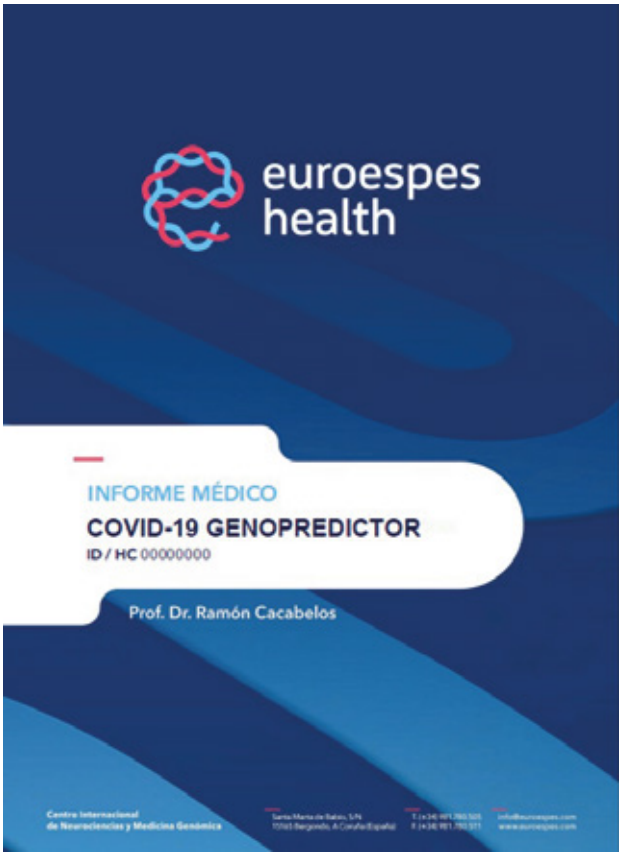
The PPP identifies the population at risk of suffering from Parkinson's disease, differentiating familial Parkinson's disease and other forms of parkinsonism (vascular, toxic or traumatic). The PPP also includes (i) a home PPP for all those asymptomatic people with a family history of Parkinson's or who detect incipient symptoms of tremor, rigidity or bradykinesia; and (ii) a PPP in person at the EuroEspes Medical Center where they would carry out the complete diagnostic protocol, including genomic screening. Patients following the home regimen who show genetic or environmental risk for Parkinson's would take the in-person PPP to complete the diagnostic set, and start the personalized prophylactic plan according to their pharmacogenetic profile.



Smart Pharmacogenetic Card PGx-60/4000

The most advanced bioinformatics product in the world with its personalized pharmacogenetic profile:

- to know the medicines you can take and which you should not take
- so that your doctor knows which drugs to prescribe and which drugs harm you
- to avoid toxicity and side effects when you have to take medication for any health problem
- to avoid life-threatening drug interactions if you have to take several medications simultaneously for long periods of time
- to avoid unnecessary expenses on products that are not useful to you
- to preserve your health with the appropriate medication for your genomic profile
- for the health of their children, who share 50% of their genome
- for life, because your genome does not change



COVID-19 GenoPredictor

The COVID-19 GenoPredictor is the only genetic test in the world that allows predicting vulnerability to SARS-CoV-2 infection with potential lung damage, immunological status and immune response capacity to coronavirus infection, and pharmacogenetic profile that allows us to personalize the pharmacological treatment appropriate to the genome of each person in case of need for treatment.

Carrying out this genomic test is recommended for people at high risk (heart disease, lung disease, hypertension, diabetes, stroke, cancer, immunosuppressed), people exposed by the nature of their work (high public attendance centers, frequent trips), people with a family history of risk, people infected by coronavirus and health personnel.

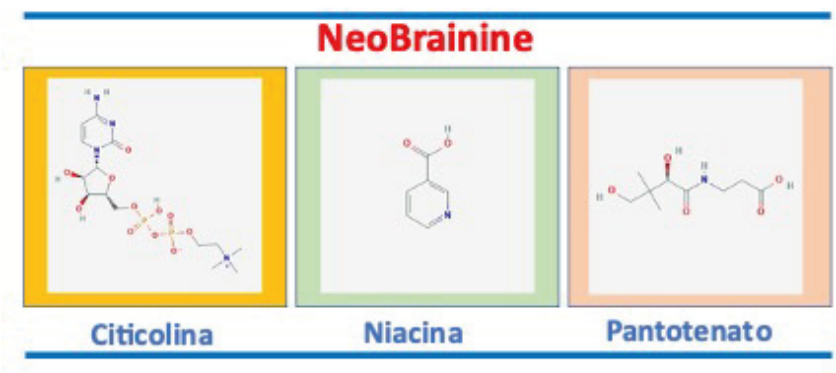
NeoBrainine

NeoBrainine is a new neuroprotective product for the prevention and treatment of various types of dementia and cerebrovascular risks (migraine, cerebral ischemia, thromboembolic events, stroke). NeoBrainine is a hybrid bioproduct, created by the team of scientists led by Dr. Ramón Cacabelos, that integrates citicoline, pantothenic acid and niacin molecules. Citicoline is a choline donor, acetylcholine precursor -an essential neurotransmitter for memory-; it is an essential component of the phospholipids of neuronal membranes and is an intermediate metabolite in nucleotide synthesis.

Pantothenic acid (D (+) - N- (2,4-dihydroxy-3,3-dimethylbutyryl) β-alanine) is an amide between pantoic acid with β-alanine; it is a water-soluble vitamin of the B complex, also known as vitamin B5 or vitamin W, essential for life. Pantothenic acid is a fundamental cofactor in the synthesis of coenzyme A (CoA) and in the metabolism and synthesis of carbohydrates, proteins and fats.

Niacin or nicotinic acid ($C_6H_5NO_2$) is another water-soluble vitamin of the B complex (vitamin B3, vitamin PP) involved in cell metabolism as part of the coenzyme NAD (nicotine-adenine-dinucleotide) and NAD-phosphate (NADP). Its derivatives (NADH, NAD+, NADPH, NADP+) are essential in energy metabolism and in DNA repair. Its main amide is nicotinamide or niacinamide ($C_6H_6N_2O$). Niacin is essential in the synthesis of steroid hormones and in the elimination of toxic xenobiotic agents.

The components of NeoBrainine (Citicoline, Niacin and Pantothenic Acid) exert essential neuroprotective functions for the normal functioning of the central nervous system.



Atremorine capsules

Atremorine has been approved by the European Patent Office for the prevention and treatment of Parkinson's disease.

In its usual presentation, Atremorine is dispensed as a powder to take with yogurt or other similar food, but not with water or liquids that can oxidize it or alter its properties. To avoid the use of powder and to facilitate the intake of Atremorine, EuroEspes Biotecnología (Ebiotec) launches Atremorine in capsules. The new presentation is now available nationally and internationally.

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DefenVid-90

EuroEspes Biotechnology (Ebiotec) launches a new presentation of DefenVid with 90 capsules. This new presentation covers a complete monthly treatment regimen. Ebiotec continues to maintain the presentation of 30 capsules.

DefenVid is an immunity enhancer epinutraceutical to combat immunodeficiency states or the fall in natural defenses associated with the use of antibiotics for bacterial infections or chemotherapeutic agents in cancer patients.

DefenVid is a powerful enhancer of cellular immunity at any age against viral infections.

The two presentations of 30 and 90 capsules are already available nationally and internationally.

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Complete Sequencing of the Human Genome

The team of geneticists from the Department of Genomics and Pharmacogenomics, led by Dr. Juan C. Carril and Dr. Óskar Martínez de Ilárduya Ruiz de Larramendi, Head of the Genomic Sequencing Unit, make available to users of medical services from the International Center for Neurosciences and Genomic Medicine, as well as from the national and international medical and scientific community, a service specialized in the complete sequencing of the human genome (> 20,000 genes) with NGS technology.

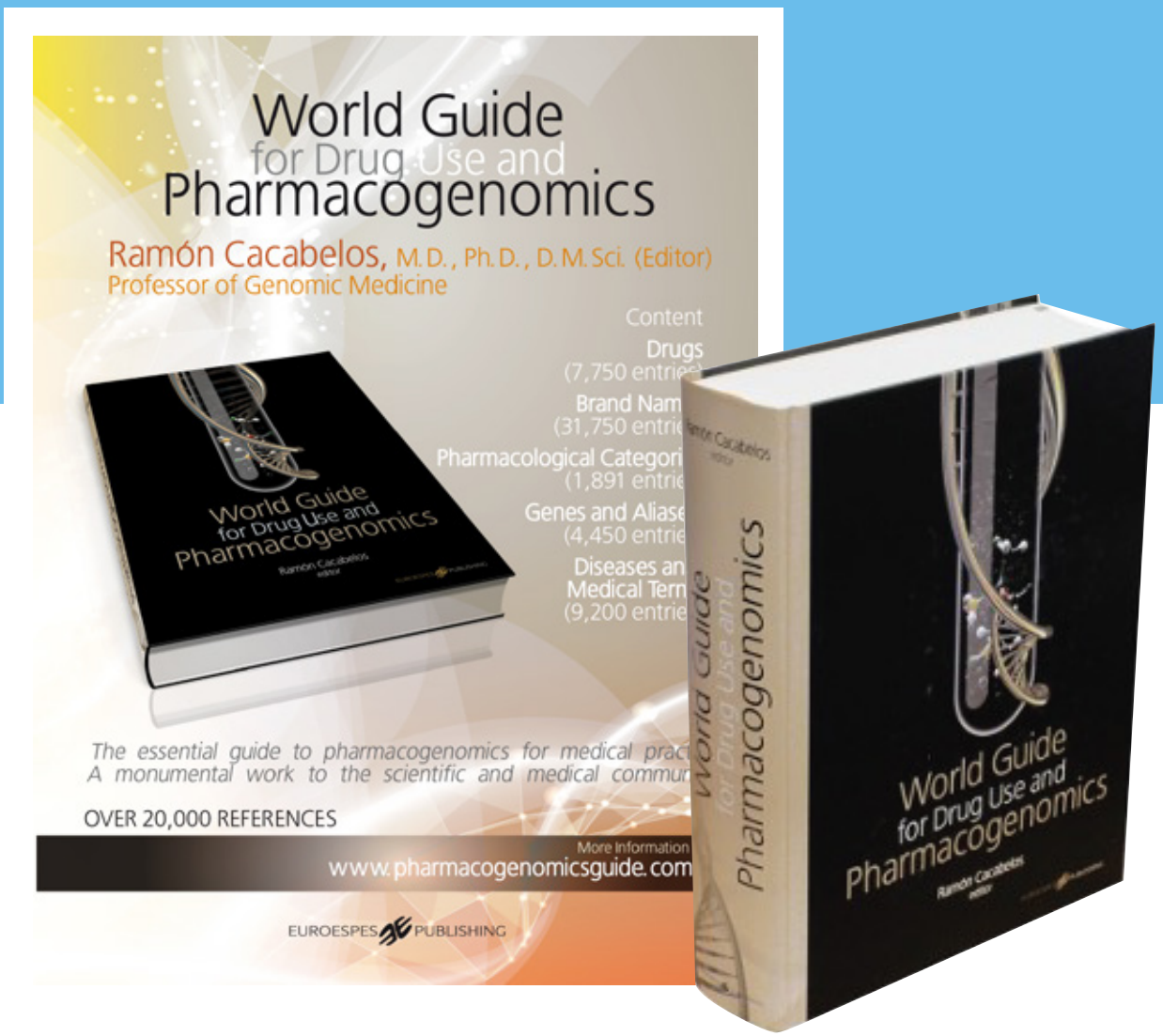
DermoGenetics Catalog

The Genomics and Pharmacogenomics Department of the EuroEspes Medical Center offers doctors and specialists in Dermatology the EuroEspes DermoGenetics Catalog. The Catalog includes the 1000 most relevant genes in skin diseases, from allergic reactions to skin cancer. This is the first Dermogenetics Catalog available in Europe.

Home Care: COVID-19 and Genetic Testing

Following our Community Care policy, facing the COVID-19 crisis, mobility restrictions in various national territories, and the difficulties of displacement of our national and foreign patients, the International Center for Neuroscience and Genomic Medicine has established a Home Care Service to our patients, to individuals and companies to carry out COVID-19 tests (PCR, Antigens, Antibodies) and genetic tests (see catalog at www.euroespes.com).

Phone No.: (+34) 981 780505.



World Guide for Drug Use and Pharmacogenomics

The First World Guide of Pharmacogenomics, edited by Dr. Ramón Cacabelos, incorporates for the first time the pharmacogenetic profile of commonly used drugs. In its more than 3000 pages the WGDUPGx catalogs (i) drugs approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Koseisho (Japan) and other international agencies, with their bioactive properties, side effects, metabolism and pharmacogenetic profile; (ii) genes of interest in human pathology and pharmacogenetics; and (iii) more than 9,000 illnesses and medical terms.

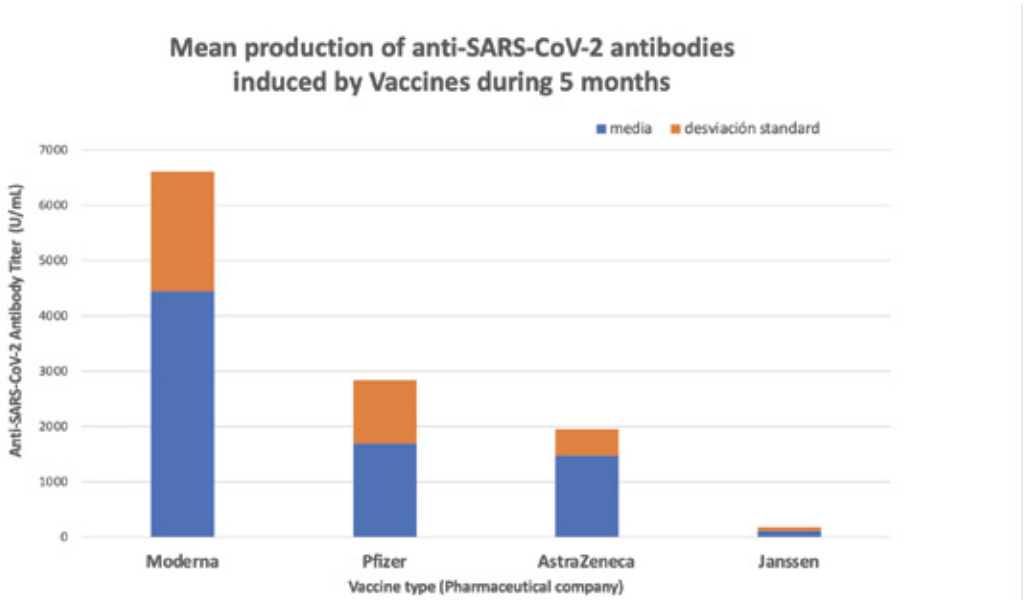
The World Guide for Drug Use and Pharmacogenomics is a fundamental reference in the library of universities, hospitals, medical departments and research centers.

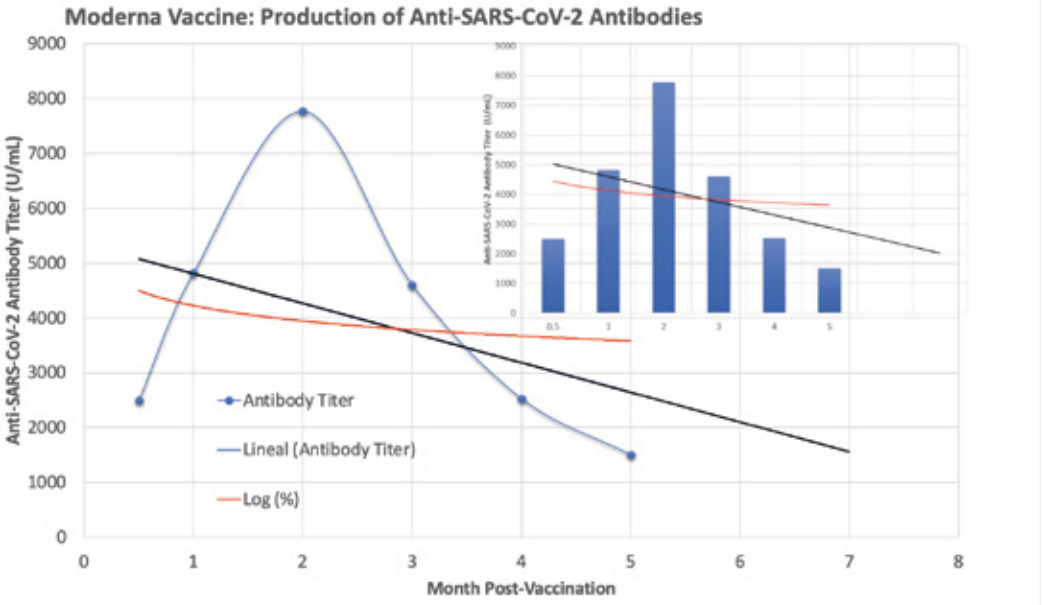
Available from EuroEspes Publishing Co., Tel. (+34) 981 780 505.

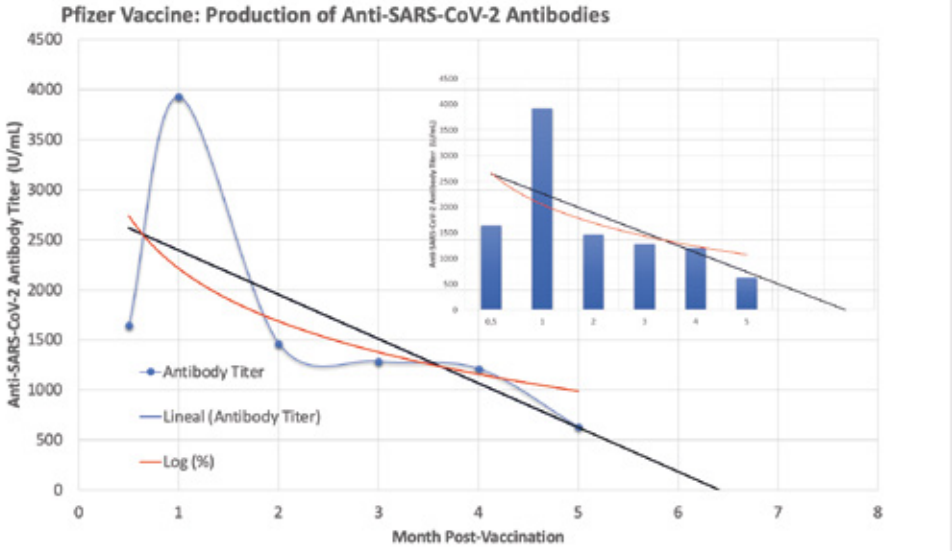
INFORMATIVE BILLBOARD

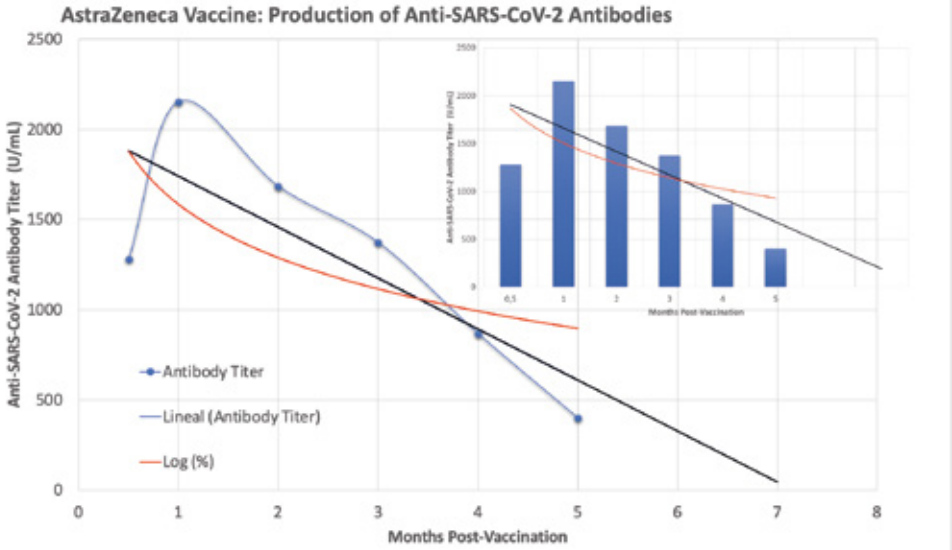
Anti-SARS-CoV-2 (COVID-19) vaccines

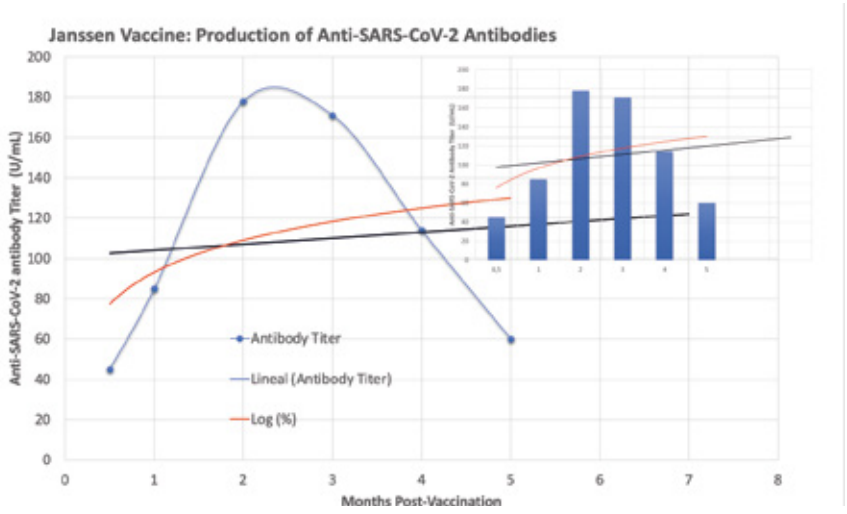
At the request of a large number of readers of the **EuroEspes Health Medical Bulletin** concerned about the properties and effects of anti-COVID-19 vaccines, we reproduce the results obtained by our Clinical Analysis Laboratory, directed by Lola Corzo, at the EuroEspes Medical Center. For more details, see the **EuroEspes Health Medical Bulletin** of October, 2021.











Data Source:

Davis, J.T., Chinazzi, M., Perra, N. et al. Cryptic transmission of SARS-CoV-2 and the first COVID-19 wave. Nature 600, 127–132 (2021). https://doi.org/10.1038/s41586-021-04130-w

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Technical Secretariat: Dr. Vinogran Naidoo, Dr. Juan C. Carril
Photocomposition and Design: Chalana

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