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# THE ROLE OF ASSORTATIVE MARRIDGES AMONG DEAF IN THE PREVALENCE OF HEREDITARY HEARING LOSS

The article presents an overview of the role of assortative deafness marriages in the spread of hereditary hearing loss. In 1883, Alexander Graham Bell, the famous inventor of the telephone, first suggested that frequent marriages between deaf people could lead to an increase in the incidence of deafness, but this hypothesis was not recognized by his contemporaries. In the 2000s, with the development of molecular genetic studies, which made it possible to identify one of the most common forms of hearing loss due to gene mutations GJB2, connexin 26, which encodes the interstitial contact protein, has been reinterpreted by Walter Nance. In the series of studies, he and his coauthors were able to show that the reproductive capabilities of the deaf have increased, and marriages between the deaf occur not by chance, but by the principle of assortativity, which in total could lead to an increase in the prevalence of one of the most frequent "connexin" forms of hearing loss.

**Keywords:** hereditary deafness, sign language, assortative marriages.

*The emergence of systematic sign language education for deaf people.* The earliest known case of education for the deaf dates back to XVI$^{th}$ century. The lord of the city of Onya in the province of Burgos in Spain, Juan de Velasco, sent his two deaf sons, Francisco and Pedro, to the monastery of San Salvador [29]. They were taught by the priest Pedro Ponce de Leon. In teaching the brothers, he applied more than 360 gestures which were used during the vow of silence in the monastery in various everyday situations. It is also assumed that additional gestures were used, which the brothers developed at home with their two deaf sisters. In total, de Velasco had 9 children, four of whom were deaf. His wife, Juana Enrique de Riviera, was related by blood to him, which was a common practice for preserving wealth within the family at that time. The father of the deaf boys wanted to give them the opportunity to inherit the property in the event of the death of the eldest hearing son and received permission from the emperor to do so. In this regard, he provided his sons with a high level of education, as a result of which they were able to learn to read and write in Spanish, Greek and Latin. De Leon used a mixed approach that included writing, the sign (dactyl) alphabet, monastic gestures, and the" home" gestures of the brothers. He later published his experience as a manuscript *Doctrina para los mudos sordo,* the original and copies of which are now considered lost [29].

In 1615, Manuel Ramirez de Carrion was invited to Madrid to teach Luis Fernandez de Velasco, the great-nephew of de Leon's first students. De Carrion taught Luis using the dactyl alphabet. De Carrion was forced to leave and Luis de Velasco was trained by Jean Pablo Bonet, who learned methods of de Carrion. In 1620, he published *Reduction de las letras y arte para enseñar a ablar los mudos* (trans.: "Letter reduction and the art of teaching the mute to speak"), which later became very important, being the first book on ways of teaching the deaf. Luis de Velasco himself also played an important role in showing how highly educated a deaf person can be [29].

The recognition of sign language as a distinct language, as well as the development and implementation of a curriculum for its training, begins with Charles-Michel de l'Épée. l'Épée was born to a wealthy family in Versailles and was studied to be a priest, but was forbidden to preach. He found his vocation by chance when he met two deaf girls who were taught from pictures. He believed that faith and salvation of the soul should not depend on hearing and can be achieved through gestures. Using his father's house and his own funds, l'Épée founded the first free school for the deaf in 1760. His first publication appeared in 1774, in which he defined and published the syntax of sign language [1]. At the same time, the first school for the deaf in Germany was opened in 1778. Its founder was Samuel Geinicke, who began teaching the deaf in 1754. He considered the sound method and spoken language necessary for a full-fledged education. In turn, it was based on the writings of the Dutch physician Johann Conrad Ammann, who left two works "*Surdus Loquens*" (Amsterdam, 1692) and "*Dissertatio de loquela*"(Amsterdam, 1700). These two works were reprinted many times (7th edition in 1740) and were translated into French and German. They served as a basis for subsequent teachers of the deaf and dumb, especially Geinicke, in their further research.

*Alexander Bell's hypothesis on the relationship between congenital forms of deafness and marriages between deaf people.* In 1883, Alexander Graham Bell, the famous inventor of the telephone, in his speech at the National Academy of Sciences of the United States for the first time suggested that frequent marriages between deaf people can lead to an increase in the incidence of deafness [3]. Bell himself was quite familiar with the problems of the hard of hearing and the deaf, as his mother began to lose her hearing when he was 12 years old [12]. To communicate with her and help her understand others Bell learned sign language [17]. Alexander Bell at the beginning of his career followed in his father's footsteps, a linguist who developed the so-called "visible speech" system. Visible speech is a phonetic alphabet and writing system, the main feature of which is a visual representation of the position of the organs of the articulatory apparatus in the pronunciation of phonemes [5]. Alexander Bell significantly improved the system of visible speech. In 1871, Alexander Bell was invited to the school for the deaf and dumb in Boston (USA) to teach their teachers this system. In 1872, he opened the" School of Voice Physiology and Speech Mechanics" in Boston, which attracted a large number of deaf students.

Like many scientists of the time, Bell was very interested in the science of heredity, which had become popular since the publication of Charles Darwin's work. On his estate, he conducted long-term experiments in breeding [5]. Bell's observations on deafness showed that the proportion of deaf children born to deaf parents is many times higher than the

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proportion of deaf children born in the general population. He published his observations and reflections in a report of 1883, which caused heated discussions. But at the end, he was unable to develop any theory to explain his assumptions and observations [19].

Bell's initiative was continued by Edward Allen Fay, Vice President of Gallaudet College for the Deaf (Gaulladet) and the editor of "American Annals of the Deaf" journal [18, 19]. Bell gave him all the pedigrees he had collected. Over a six-year period, Fay and his assistants were able to collect information on more than 8,500 people from an analysis of the pedigrees of 4,471 marriages among Gallaudet College graduates and graduates of other boarding schools for the deaf across the United States, from 1803 to 1894 [13]. Their findings did not support Bell's arguments, but neither did they refute his critics. As Bell had suspected, there was a link between deafness and heredity. For example, among the sample of children with one or both deaf parents, 9% were also deaf, compared to the incidence of hearing loss in the general population, which was approximately 1 per 1000 newborns. However, a smaller percentage of deaf offspring were born to couples in which both parents were deaf than to deaf-hearing couples. At the same time, 76% of the analyzed marriages were between two deaf people. The presence of deaf relatives and consanguinity of parents were the factors most strongly increasing the probability of having a deaf child [13], but these studies were not continued.

*Confirmation of the hypothesis by Walter Nance.* Later the scientific community usually ignored Bell's suggestion, given the assumed large number of genes associated with deafness. So, James Crow and Joseph Felsenstein, based on the classic works of Ronald Fischer and Sewell Wright [14, 31], showed that assortative marriages (marriages based on similarity of traits), in the absence of selection pressure, affect only genotype frequencies, and not gene frequencies [31]. Regarding deafness, they concluded that if the phenotype is due to genes with the similar frequency in 35 loci (as was then considered [11]), then even intensive assortative marriages, in the absence of selection, will give only a 2-3% increase in the incidence of deafness [31].

In the 1970s, a comparative analysis of the work of Edward Fay was published [13] with up-to-date data from the annual study of children with hearing loss at Gallaudet University, which included information on 12,665 cases [27;28]. In the works of Susan Rose, for the first time, the concept of *complementary* and *noncomplementary marriages* is used when analyzing assortative marriages of deaf people based on the state of hearing of their offspring. *Complementary* marriages are defined as marriages between deaf married partners with different etiologies of hearing loss (acquired hearing loss in one of the partners or mutations in various genes associated with hearing loss); in such marriages, there may be only hearing or, in some cases, both deaf and hearing children. *Noncomplementary* marriages are marriages between deaf people who share the same genetic cause of hearing loss – the presence of biallelic recessive mutations of the same gene. All children of such a married couple will also be deaf and have the same genetic etiology of hearing loss as their parents (Fig. 1).

The results of Susan Rose show that between XIX and XX centuries, the proportion of children with one or two deaf parents has increased by 38% from 0.064 to 0.089. Among assortative marriages, the proportion of noncomplementary marriages also increased by 23% from 0.29 to 0.36. In these two large-scale samples, Susan Rose conducted a segregation analysis and concluded that 49% of cases of deafness were sporadic. Among inherited forms, 12% - 14% were classified as autosomal dominant with incomplete penetrance, and 86% - 88% of cases were identified as autosomal recessive. It was assumed that they are caused by genes in 10 independent loci, probably distributed with the same frequency [27;28].

In the end of the XX$^{th}$ century, ideas about the high heterogeneity of hereditary hearing loss have changed dramatically. It became clear that hereditary deafness associated with the DFNB1 locus (autosomal recessive deafness type 1A), in which the *GJB2* (Cx26) gene was mapped, is the most frequent one [7;16]. Mutations in this gene have been found to be a major cause of autosomal recessive nonsyndromic congenital hearing loss in many populations [6-9;20;22;23;26]. New molecular genetic data suggesting that up to half of all cases of inherited hearing loss are caused by mutations in a single gene – *GJB2*, became a big discovery [16 – 23], and subsequently led to a rethinking of many previously existing concepts about the extremely high heterogeneity of this pathology.

The very fact of identifying one major form of hearing loss provided an opportunity to rethink Alexander Bell's hypothesis that assortative marriages between deaf people can contribute to an increase in their number due to an increase in the proportion of noncomplementary marriages in which hearing loss in both spouses is due to the same genetic cause. So, in 2000, Walter Nance suggested that in all noncomplementary marriages from the Edward Fay data sets [13] and Susan Rose [27;28], hearing loss may have been caused by mutations in the gene *GJB2* ("connexin deafness"). In this case, it is possible to indirectly estimate the contribution of these mutations by the proportion of noncomplementary marriages. The proportion of such marriages will be equal to the fourth power of the frequency of the corresponding mutant allele in a given population, i.e. $q^2 \times q^2$, where $q^2$ it is the proportion of "connexin deafness" in the population. Rose's data showed that among 1,299 fertile assortative marriages, 4.2% were noncomplementary, and then the contribution of connexin form of hearing loss to XIX it was approximately equal to $q^2 = \sqrt{0,042} = 0,204$ (20.4%) [24]. Walter Nance and his colleagues noted a significant increase in the proportion of "connexin deafness" in the United States between XIX and XX centuries, by comparing the 20.4% with modern, at that time, data - 35.6% [4].

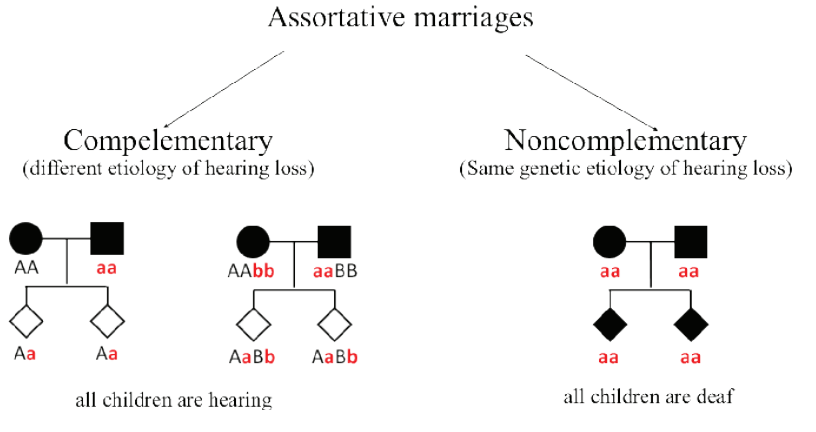


**Fig. 1.** Types of assortative marriages for deafness

Based on this, it was hypothesized that frequent assortative marriages between deaf individuals, combined with their increased fitness (genetic fitness), could lead to an increase in the incidence of hereditary hearing loss in the United States [24;25]. Walter Nance and his colleagues suggested that in the previous millennium, the fitness of individuals with congenital deafness was very low, and that the frequencies of deafness genes were in balance [25]. Introduction of sign language in Europe ~300 years ago [29] is one of the key events that significantly improved the social and economic conditions of the deaf, as well as their fitness. Genetic fitness of the deaf, in the works of Walter Nance, is measured by relative fertility, which is defined as the ratio of the average number of children in a sample of deaf and hearing individuals. An example of calculating relative fertility is shown in the fig.2.

In many countries, schools for the deaf and hard of hearing have been established, which has facilitated the choice of a marriage partner based on sign language skills, i.e. linguistic homogamy. The increased fitness of deaf individuals, in turn, can be interpreted as a relaxation of the selection pressure directed against deafness. In this connection, it has been suggested that the combination of "relaxed selection" and assortative marriages should give an advantage to the most common form of autosomal recessive deafness in the population [24], and may also be relevant to the evolutionary hypothesis about the mechanism of speech gene fixation in *Homo Sapiens* [25].

*Computer modeling of the prevalence of hereditary hearing loss with relaxed selection.* To test their hypothesis, Walter Nance and his colleagues conducted computer simulations aimed at assessing the impact of assortative marriages and reducing deafness selection pressure on the prevalence of autosomal recessive deafness [25]. The results of modeling showed a change in the frequency of deafness since the beginning of attenuation of selection, both in the presence and absence of assortative marriages [25]. In addition, it is known that assortative marriages increase the phenotypic expression of alleles, then they modulate the effect of selection pressure on these alleles, therefore, increased fitness will contribute to an increase in the number of deaf individuals [25]. At the same time, the increase in the occurrence of deafness was accompanied by an increase in the frequency of the recessive allele and significantly accelerated in the presence of assortative marriages, which may explain the doubling of the occurrence of the "connexin" form of deafness in the United States within 200 years [25]. At the same time, it was shown that the effect of assortative marriages is limited to the form of recessive deafness that was most common at the beginning [25].

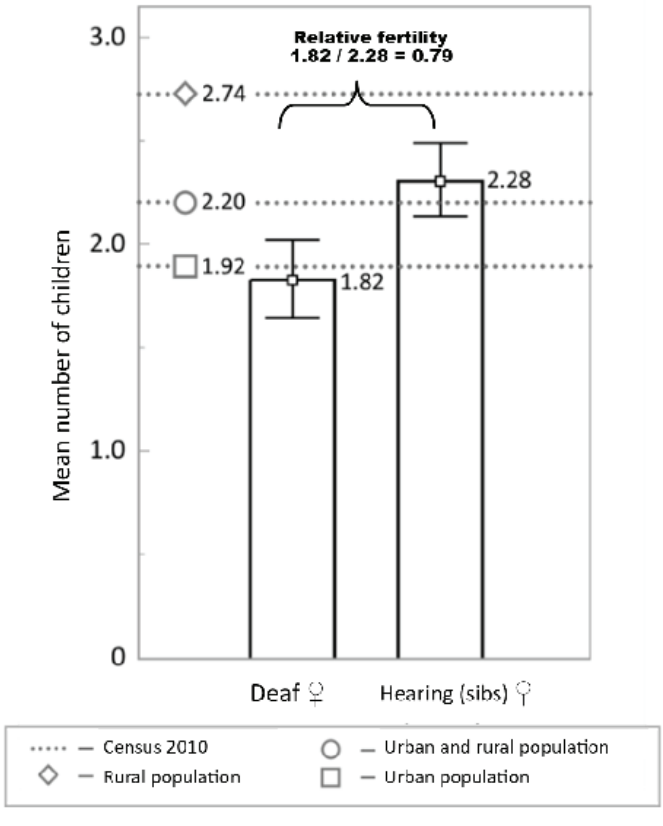


**Fig. 2.** Relative fertility (genetic fitness). Note. The figure shows the average number of children of deaf and control women (hearing siblings) aged 35–69 in Yakutia. "♀" - women. Confidence intervals at the 95% significance level [27]

The next study devoted to this topic was the analysis of modern data on 311 marriages of graduates of Gallaudet University (Gallaudet University) in comparison with the data of Edward Fay [13], which revealed a more than 5-fold increase in the proportion of noncomplementary marriages: from 4.2% to 23% [1]. From these data, we can estimate the increased contribution of the "connexin" form of hearing loss to the etiology of deafness in the United States. The proportion of noncomplementary deafness marriages, equal to 4.2% in XIX century [8] and 23% at the beginning XX centuries [28], approximately correspond to 20.5% and 47.95% of the contribution *GJB2* due to hearing loss, respectively (√0,042 = 0,2049, √0,23 = 0,4795). As a result, the share of connexin deafness increased by 134% over 100-200 years in the United States [1;13]. At the same time, it was shown that this growth is associated with linguistic homogamy [1].

Later, up-to-date data on reproduction and marital structure in deaf individuals were published based on a sample of Gallaudet University graduates [15]. The average number of children who were deaf was lower than that of their hearing Siblings, and the relative fertility rate was 0.88 [15]. However, it was higher than the figures of the US Census of deaf people thirty years ago – 0.74 [30], which indicated increased fitness (fitness) deaf people and reducing the selection pressure for deafness [15]. The proportion of assortative marriages was 0.79, and an analysis of fertility rates after stratification by type of marriage showed that more children are born in assortative marriages (2.11) than in marriages between deaf and hearing individuals (1.85), suggesting the influence of many factors on the fertility of deaf people [15]. Thus, in the presented series of works [1;15;24;25]. Walter Nance and his colleagues were able to provide evidence for the hypothesis that frequent marriages between deaf people, combined with a relaxed selection pressure, may indeed have led to an increase of the "connexin" deafness in the United States since XIX century (fig. 3).

Another group of researchers from Gallaudet University also studied the effect of assortative marriages between deaf people on the prevalence of auto-

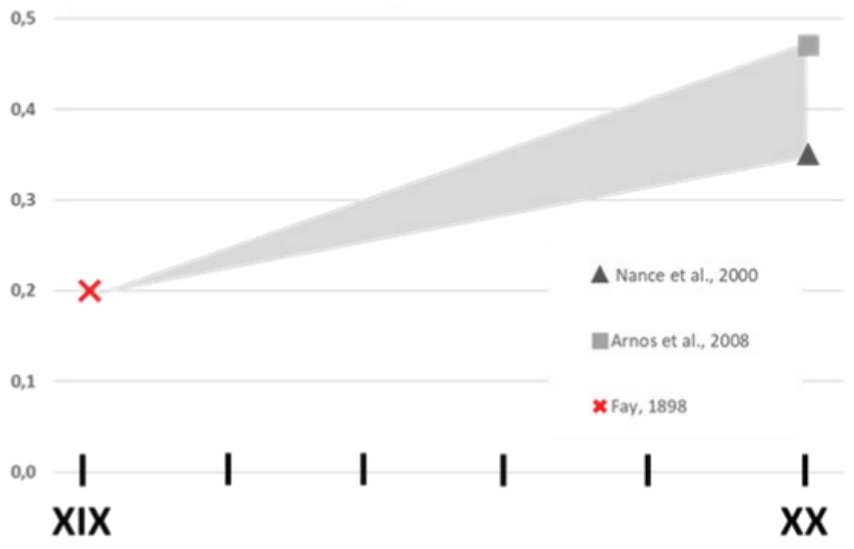


**Fig. 3.** *GJB2* mutation frequency increase in the USA over 200 years [1;13;24]

somal recessive deafness and the frequency of corresponding alleles to double-check Walter Nance's hypothesis based on Alexander Bell's assumption [12]. Using data from the modeling work of Nance and Kearsey [25], Derek Brown et al. conducted computational experiments using an agent-based model. They showed that the proportion of recessive homozygotes was 23% higher in the population with 90% assortative deafness marriages ($q^2$ = 0.022%) than in the population without assortative marriages ($q^2$ = 0.017%) when modeling over 20 generations [12]. It was shown that the increase in the occurrence of autosomal recessive deafness is limited to the first three generations, which also corresponded to calculations performed according to the theoretical calculations of Crow and Felsenstein (1968) [10]. Additionally, modeling was performed with different values of the average number of children in deaf people, as a result of which it was shown that the frequency of the recessive allele increased with a relative fertility value of 1.5 times or higher, when combined with assortative marriages [12]. The conclusions drawn in the work of Brown and his colleagues are generally consistent with the data obtained by Nance [25], adding some clarifications regarding the impact of reduced reproduction and the proportion of non-hereditary forms of hearing loss [12].

In conclusion, it should be noted that the simulation models proposed by Nance [25] and Braun [12], are based on retrospective data from the XIX century. These studies have been aimed at confirming the role of assortative marriages by deafness in increasing the incidence of the "connexin" deafness that has occurred since the emergence of permanent communities of deaf people more than 200 years ago. Currently, there are no models to assess the prevalence of inherited forms of hearing loss in the future, taking into account the changed social environment and current trends in society aimed at improving social equality. Development and growing availability of modern medical technologies, such as cochlear implantation and various social rehabilitation programs for the deaf, leads to their greater inclusion into society and, as a result, unreduced reproductive capabilities. In such conditions, predicting the prevalence of inherited forms of deafness can be used from a practical point of view to plan the amount of necessary medical and social care. In this regard, it is relevant to develop mathematical models that predict the dynamics of hereditary deafness under the influence of relaxed or complete absence of selection pressure for deafness using modern data.

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# THE ROLE OF NEUROPILIN-1 (NRP1) IN THE DEVELOPMENT OF SARS-COV-2 INFECTION

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A review of the literature on the role of neuropilin-1 in the development of SARS-CoV-2 infection and a search for probable links between polymorphic variants of the *NRP1* gene and SARS-CoV-2 are presented. This review presents the characteristics of polymorphic variants of the *NRP1* gene, which demonstrate the possibility of their association with the course of SARS-CoV-2 infection.

**Keywords:** SARS-CoV-2 infection, neuropilin-1, polymorphic variants of the *NRP1* gene.

**Introduction.** With the onset of the SARS-CoV-2 coronavirus infection pandemic, it was necessary to understand the mechanisms of penetration of this pathogen into the cell and the mechanisms of their interaction as early as possible. In 2020, it was found that the furin-cleaved S1 fragment of the SARS-CoV-2 spike protein directly binds to cell surface neuropilin-1 [6].

Neuropilin-1 (NRP1) is a transmembrane glycoprotein. The neuropilin-1 receptor plays a key role in the development of the nervous and vascular systems, as neuropilins mediate VEGF (vascular endothelial growth factor) dependent angiogenesis and semaphorin-dependent axonal growth direction. In addition, the participation of neuropilins in a wide variety of signaling and adhesive functions has been studied, which indicates their high role as pleiotropic coreceptors [12].

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NRP1 consists of 923 amino acids and has a massive extracellular portion that includes two tandem CUB domains (a1/a2), two tandem domains homologous to coagulation factors V/VIII (b1/b2), a linker sequence, and one MAM domain (C) that supports dimerization and multimerization of neuropilin molecules and promotes the formation of signal receptor complexes [27]. The cytoplasmic domain, which includes 44 amino acid residues, contains a sequence of three C-terminal amino acid residues (SEA-COOH) and demonstrates high phylogenetic conservatism [30].

**Neuropilin-1 promotes the breakdown of the spike protein.** Cleavage of the SARS-CoV-2 S protein at the S1-S2 site results in the C-terminal sequence TQTNSPRRAR-OH. AgNP nanoparticles coated with the TQTNSPRRAR-OH peptide sequence were efficiently taken up by the neuropilin-positive cell culture. Intensive uptake of AgNP-TQTNSPRRAR-OH by the olfactory epithelium, neurons, and blood vessels of the cerebral cortex has also been shown [6]. NRP1 can modulate SARS-CoV-2 infection by stimulating the separation of the S1 and S2 subunits. Additional sites of interaction between neuropilin-1 and the spike protein, which function as additional points of connection with the lipid bilayer of the infected cell, play a significant role [21]. In turn, the results of isothermal titration calorimetry demonstrate a direct relationship between the b1 domain of NRP1 and the synthetic S1 peptide (679-NSPRRAR-685) with an affinity of 20.3 μM at pH 7.5, and this crystal structure showed significant similarity [7] with the crystal structure b1 domain of NRP1 in complex with its endogenous VEGF-A ligand [28].

**Functional and structural diversity of binding sites for neuropilin-1 and spike protein.** The analysis of interaction sites between SARS-CoV-2 S-protein and human neuropilin-1 deserves special attention: amino acid residues GLN280, ASP289, TYR322, ARG323, TRP325, GLN327, ASP329, LYS359, ASP361 have been identified as potential binding sites in the b1 domain of NRP1. Relationships are also observed between GLN3, ILE8, PHE29, ALA30 RBD of SARS-CoV-2 S-protein domain and ARG402, ARG405, LYS407 of NRP1 b1 domain [2]. The overlap of SARS-CoV-2 RBD checkpoints with the VEGF-associated NRP1 site is confirmed, and interaction with GLN280 can serve as an example [18]. In turn, the amino acid residues TYR322, ARG323, TRP325, GLN327, ASP329, LYS359, ASP361 are structurally close to the VEGF-binding site of NRP1; moreover, TYR297, ASP320, SER346, THR349, TYR353 play a leading role in its structure [33]. All this indi-