

The Remote Isolate of The Croatian Littoral – 50 Years of Research on The Island of Susak with New Insights into its Genetic Diversity

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ABSTRACT

This paper presents a review of the 50-year long anthropological and epidemiological research of the Susak population. Island of Susak is an example of extreme genetic isolate, with a very low level of heterozygosity and a significantly high level of inbreeding, due to the practice of endogamy. Its specific features have put the island in the focus of diverse research during the last five decades and in this study we additionally present new insights into the island's maternal genetic heritage. For this purpose, mitochondrial DNA (mtDNA) haplogroup diversity was defined based on SNPs of the control and coding region on the sample of 64 autochthonous individuals from the island. Only three main haplogroups were detected – H, T and one W sample, with a limited number of haplotypes, and certain typical European haplogroups (U, K, J, V, X,) were completely absent. Haplotype analysis revealed five possible founder lineages of altogether 16 different haplotypes. Island of Susak also has the second lowest reported GDV (gene diversity index) among Croatian isolates, which is in line with its reduced mtDNA diversity. Since such island communities are most likely to disappear in the near future, we see these results as a valuable contribution for further population genetics and epidemiological studies.

Key words: island of Susak, review, mtDNA, inbreeding, genetic isolates, genetic diversity

Introduction

Geographical, historical and demographic background

The island of Susak (ital. Sansego) is the most remote inhabited island of the Croatian Littoral, located in the Kvarner Bay, in the proximity of Croatia's two biggest islands – Cres and Krk (Figure 1). The island spans over an area of only 3.5 km², and has a single settlement of the same name. Susak's uniqueness is widely known throughout Croatia. It is genetically unique and serves as an example of extreme isolation and inbreeding, but it is also geologically unique. Its surface is a limestone plateau covered by thick sand deposits, not common in the rest of Croatia. The genesis and the composition of these deposits have been a matter of interest and discussion for the last two centuries. Most recent mineralogical and geochemical investigations suggest that the area of the island was exposed to a strong input of fluvial Alpine material carried by the river Po, while the upper layers are of volcanic origin (related to Italian volcanic provinces), blown and de-

posited on top¹. The island is also known for its archaic dialect, its costume resembling the Greek Fustanella and ancient marriage customs².

First known inhabitants of the island were the Illyrians and after them the Romans. Don Turčić³ claims Susak was used by wealthy Roman families from the mainland and other islands as a summer resort. Under their domination, Susak and other Eastern Adriatic islands fell under the jurisdiction of the Province of Dalmatia and together they became a part of the Illyrian Province. The Croats started to populate these islands in the early Middle Ages and they lived together with other Susak inhabitants under the supreme rule of the Byzantine Emperor. During 10th and 11th century the island became a part of the Croatian Kingdom and after that the territory was first under Hungarian and later Venetian rule. The Venetian Republic ruled over the island until late 1797. At that time it became part of the Napoleon's Illyria and stayed under its rule until 1815, when the Austrian-Hungarian Monarchy annexed this region. Susak stayed under Monarchy's domination until the end of World War I, when it came under the Italians. In World War II, German army occu-

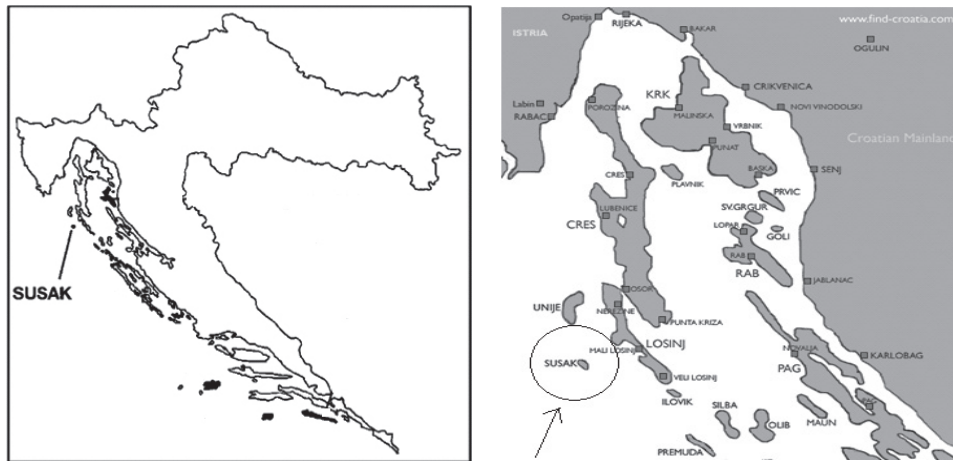


Fig.1. Geographic location of the island of Susak.

pied Susak and after the war Susak became part of SFR Yugoslavia, and finally of Republic of Croatia⁴.

Historic reports of the island of Susak are relatively late. First written evidence comes from the early 11th century, when Ivan the Deacon wrote about Saracens who destroyed a Venetian fleet near the island in 844. Afterwards Susak was mentioned several times in various documents, charts and official papers of Venetian dodges (in 1208, 1229, 1280 and 1356)^{3,4}. The wars with the Turkish Empire in the 16th and 17th century especially led to the forced immigration from the Croatian mainland towards the islands – among others also to the small island of Susak. In the year 1771 it had 300 inhabitants, while in 1880 the number increased to 1111 and till the end of World War II its population expanded to a total of 1876 inhabitants^{4,5}. With a population density of over 400 inhabitants *per km*², it was at that time the most populated island of former Yugoslavia. However, it still remained isolated and the only link with the outside world was a small wooden boat that sailed to the nearby island on working days. Besides that, there were no other, telephone or radio, connections with the outside world^{4,5}. Due to the worsening of the economic situation and the overpopulation of the island, massive exodus of the younger generation started in the 50's of the past century. Until the 80's 90% of the population emigrated to the USA (Figure 2). Interestingly, the emigration process was directed to one specific place, more or less – Hoeboken, New Jersey, USA. The cohesion of the islanders who still live on Susak and those in New Jersey remained tight and the emigrants insisted on keeping their traditions alive through the collective activities of the »St. Nicholas Society of Sansego« in Hoeboken, and by visits to Susak. According to the most recent census (2011), Susak currently has 151 permanent residents and only a limited number of surnames: Busanić, Hrončić, Lister, Matešić, Mirković, Morin, Picinić, Sutora, Skrivanić, and Tarabokija⁶. Two additional socio-psychological have also contributed to the reduced gene flow between the island and the rest of the land. The Susak islanders are perceived as highly consanguineous and peculiar and have developed a strong, archaic dialect of the Croatian language because

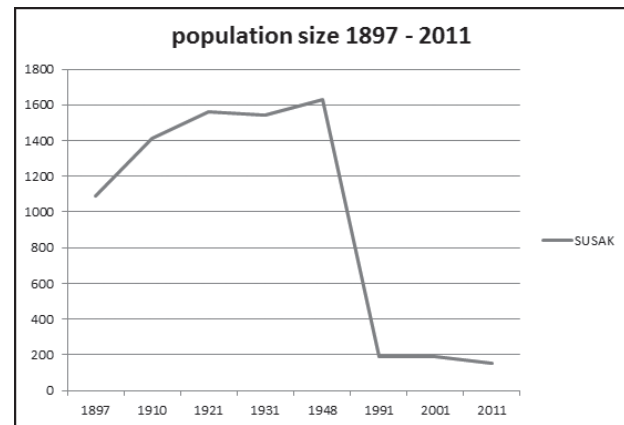


Fig. 2. Demographic changes in the Susak population 1897 – 2011 (evidence of the massive exodus after WW2).

of their long life under Italian rule, which made their communication with other islands and the mainland difficult and therefore limited^{2,4,5}.

Anthropological and epidemiological studies of the island of Susak

In the early 50's of the last century the population of Susak was thoroughly studied by a multidisciplinary research team of the Yugoslavian Academy of Sciences and Arts. The results of those extensive studies were published in a monograph in 1957 and this book presented an in-depth analysis of the island's geographical, ecological and geological distinctions, socio-economic status and lifestyle, population dynamics, demography, medical conditions etc. An important part of the study was a pedigree analysis and construction of genealogical trees. The results were quite interesting and shocking – they confirmed a significant number of consanguinity cases on the island. Among 1400 inhabitants there were only 5 surnames, with two dominant ones^{4,5}. At the same time, in 1953, Susak's ge-

neological data were collected by the University Institute of Anthropology from Ljubljana, Slovenia and from 279 constructed genealogical charts, 67 or 24% showed consanguinity between husband and wife. In the second generation, 48 consanguineous matings of various kinds have been detected, with sometimes two or three in the same pedigree. The frequency of red-haired individuals was also higher than usual (14% of carriers with visible components for red-hair) and the proportions of blood groups were untypical – mostly individuals with A or O blood group were present⁷. A first study of genetic diseases was undertaken on Susak by the Department of Psychiatry and Neurology of the University of Zagreb in the 50's as well. This study produced 129 cases considered to be related to oligophrenia (mental retardation), which accounted for 9.2% cases of oligophrenia in the total population of the island. This was considered a higher percentage than that of the mainland population and islanders recognized only first cousins as real blood relatives².

In 2004, Croatian School of Public Health conducted an anthropological assessment of this extremely isolated community over the period 1951 – 2001. Their work also included analysis of microsatellite DNA polymorphisms (STRs) – they analyzed 18 autosomal STR markers in 70 individuals and gave first insight into their genetic structure⁵. Results were in accordance with the starting hypothesis: a low average heterozygosity compared to the outbred non-Croatian populations, signature of a recent severe bottleneck, reduced allele diversity (consistent with the reduced gene pool) and a significant level of linkage disequilibrium (LD) that was among the highest reported in island isolates. A subsequent study conducted by Vitart et al.⁸ (2006) showed similar results considering the level of gene diversity in comparison with other Croatian island villages.

Another relevant article published by Saftić et al. (2006) was dedicated to indigenous diseases and specific medical conditions in four Croatian island populations (Susak, Mljet, Krk and Lastovo)⁹. Population isolates are in general highly suitable for mapping Mendelian disease genes in comparison with the outbred population – they exhibit a higher degree of inbreeding, higher prevalence

for certain diseases, more uniform genetic background, wider intervals of linkage disequilibrium, less migration, higher occurrence of consanguinity and a more uniform environment¹⁰. As for the island of Susak, this study has shown a strikingly higher prevalence of learning disability (hereditary mental retardation) – five times higher than expected, as well as frequent congenital anomalies in children. Also, 10% of the population has some kind of psychiatric disorder (oligophrenia, senile dementia, psychoses, schizophrenia etc.) and 95% of the population was blood type A or O. These data are significantly different from those found in surrounding populations⁹.

Isolated island populations in the Eastern Adriatic could also be exceptionally suitable population for the investigation of epidemic-induced changes in the population structure. In this context, a research has been conducted in 2009 to test the hypothesis that an epidemic of lethal infectious disease in the past increased the current frequencies of CCR5Δ32 mutation (which leads to resistance to HIV infection in a homozygous form) on Croatian islands¹¹. The research involved scanning through all historic documents from 1300-1700 period, also known as the period of the most lethal epidemics in the European history, when 3 major outbreaks of „plague” occurred. According to historic records, the epidemics in 1449 and 1456 were the most disastrous ever to hit the Croatian coastal region. On the islands of Susak and Rab they caused the deadliest epidemic ever recorded on Dalmatian islands, with a cumulative mortality of more than 70%. It seems the disease arrived from northern Europe through the »amber route« and had inflicted recurring lethal attacks throughout the whole 15th century. Genetic-epidemiological evidence presented in this study points to the conclusion that these recurring epidemics could have acted as a selective pressure upon the rare CCR5Δ32 mutation and resulted in the unusually high frequencies that are observed across Europe today¹¹.

MtDNA research in Croatia started more than a decade ago and numerous publications based on the research of Eastern Adriatic isolates have been published so far¹²⁻¹⁶. This study presents a continuation of this work based on

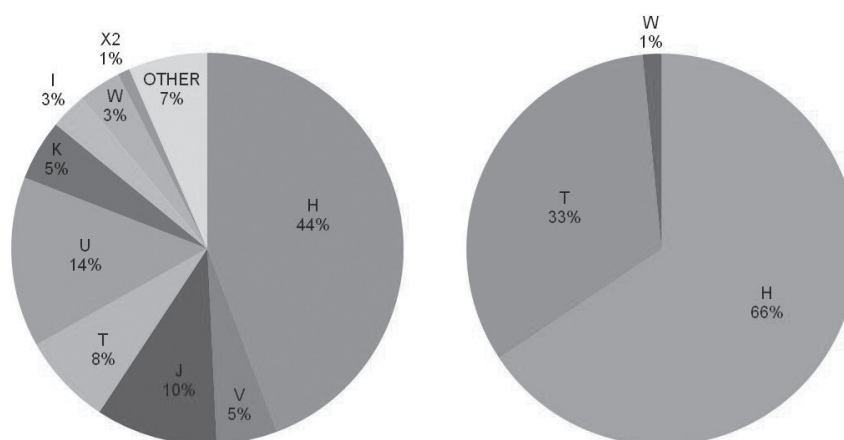


Fig. 3. Comparison of the mtDNA basic hapogroup distribution in continental Croatia (left) and on Susak (right).

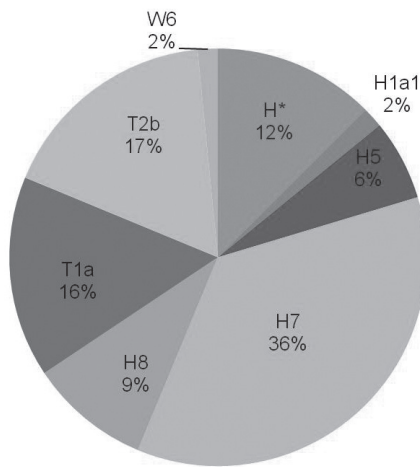


Fig. 4. MtDNA sublineages on the island of Susak.

the mtDNA analyses of the Susak population and the obtained results have also been put in a wider Croatian context.

Sample and Methods

Blood samples were taken from 64 adult individuals, randomly chosen and autochthonous. Individuals were chosen based on genealogical data and first siblings were

avoided in order to get the most representative sample possible. All volunteers gave their informed consent prior to inclusion in the sample. The sample was collected during the fieldwork on Susak conducted by the Croatian School of Public Health in 2001. Genomic DNA was extracted from whole blood samples using the »salting out« method (Miller et al., 1988) at the Institute for Anthropological Research in Zagreb. Further analyses were performed in the Estonian Biocentre, Tartu, Estonia.

The hypervariable segment I (HVS-I) of the control region of mtDNA (nucleotide positions 16000 – 16400) was PCR amplified by Biometra Thermocycler (Biometra, Goettingen, Germany) using the primer set V3/HVSI R. After purification by shrimp alkaline phosphatase (SAP; Fermentas, Fisher Scientific-Finland, Vantaa, Finland) PCR products were sequenced directly from both strands on the Applied Biosystems 3730xl DNA Analyzer using the BigDye Terminator sequencing kit (Applied Biosystems, Warrington, UK). RFLP typing was performed by restriction endonuclease analysis using the primer pairs and PCR conditions as previously described by Finnilä et al. (2000).

Haplogroups and subhaplogroups affiliations were determined based on single-nucleotide polymorphisms from the coding and non-coding region of mitochondrial genome, according to the mtDNA tree Build 17 (www.phylotree.org) (Van Oven & Kayser, 2009). In order to enable comparison of our results with the ones from the other mtDNA studies, HVS-I sequences were aligned and ana-

TABLE 1
MTDNA HAPLOGROUP DISTRIBUTION AND FREQUENCIES IN THE ISLAND OF SUSAK

HAPLOGROUP	HVS-I SEQUENCE (+16000)	DEFINING POSITION (detection method)	N	%
H*	311	7028CT (7025 AluI)	1	1.6
	CRS*	7028CT (7025 AluI)	7	10.9
H1a1	162-209	7028CT (7025 AluI)	1	1.6
H5	304	7028CT (7025 AluI), 456CT (seq)	1	1.6
	261-304	7028CT (7025 AluI), 456CT (seq)	1	1.6
	92-304	7028CT (7025 AluI), 456CT (seq)	2	3.1
H7	126	4793AG (4793 BsuRI)	4	6.2
	305	4793AG (4793 BsuRI)	4	6.2
	109C-305	4793AG (4793 BsuRI)	1	1.6
	126-261*	4793AG (4793 BsuRI)	14	21.8
H8	68-288-362*	13101AC (13100 MspI)	6	9.3
	126-163-186-189-294-390*	12633GA (12629 Eco47I)	6	9.3
T1a	126-163-186-294-390	12633GA (12629 Eco47I)	4	6.2
	126-294-304*	930GA (seq)	10	15.6
T2b	126-304	930GA (seq)	1	1.6
	172-192-223-292-325	4093 (seq)	1	1.6

* possible founder lineages

TABLE 2
GENE DIVERSITY INDEX OF DIFFERENT CROATIAN ISOLATES

POPULATION	GDV	SOURCE
Mljet	0.857	Šarac et al. 2012
Susak	0.897	present study
Cres	0.937	Jeran et al. 2009, Havaš Auguštin 2011
Korčula	0.956	Jeran, 2010
Lastovo	0.958	Šarac et al. 2012
Hvar	0.980	Jeran, 2010

lyzed according to the Cambridge Reference Sequence (rCRS, NC_012920; Andrews et al. 1999) by using ChromasPro software (Technelysium Pty Ltd, Tewantin QLD, Australia) (Figure 3 and 4).

A phylogenetic network based on mtDNA haplotypes was constructed using program Network 4.502 (Fluxus Engineering Web site), applying both reduced median and median joining algorithms (Figure 5). Different weights were assigned to substitutions. Gene diversity was calculated according to the standard formula (Nei, 1987) (Table 2). Genetic differences between Croatian insular subpopulations were visually represented using Principal Component Analysis (PCA) (Figure 6). PCA plot was constructed using the free software POPSTR (<http://harpending.huamnevo.utah.edu/popstr/>) based on biallelic markers.

Results and Discussion

In the sample of 64 individuals (42% of the current Susak population), we found an interesting mtDNA haplogroup and subhaplogroup distribution and prevalence. Detected haplogroups were all Europe and Near East-specific, but their frequencies were deviated – complete absence of certain haplogroups and excess frequencies of others have been recorded. The only detected major haplogroups in our sample were H, T and W, with the following percentages – 66% of H, 33% of T, and 1.6% (only 1 individual) with haplogroup W affiliation. U or J individuals were complete absent (Figure 3). Deviations from the usual frequency distribution pattern have been found previously in other Croatian isolates¹⁴⁻¹⁶, but no study conducted on Croatian samples so far noted such a reduction in basic haplogroup diversity. A higher resolution of detected haplogroups is presented in Table 1 and Figure 4.

Altogether, 8 subhaplogroups and 16 haplotypes were found on the island (Table 1). Most prevalent subhaplogroup was H7, encompassing 36% of the total sample and about 55% of the H hg sample). The predominance of the H7 subclade is striking and much higher than the Croatian average, where about 1% of H7 was recorded¹⁶⁻¹⁹. The only other Croatian island with elevated H7 frequency is the island of Brač, with 9.5% of H7 individuals. Since

Susak and Brač are not neighboring islands, it seems most likely that the higher prevalence of this clade is due to different migration events or simply to the effect of random genetic drift. Another interesting finding is the high frequency (9%) of the usually quite rare subclade H8, present with <2% in other Croatian subpopulations¹⁶⁻¹⁹. It has been previously recorded that sublineages H4, H5, H7, H8 and H11 indicate a Near East influence²⁰, with very low percentage in Europe. Peak H8 frequencies have been found among Central Asian and Altaian populations²¹. The frequency of the paraphyletic H* clade represents 12% of the total Susak sample and 18.2% of the total hg H sample, which is significantly less than in other Croatian populations. Also, we found only one inhabitant with H1 subhaplogroup, a subclade that comprises about 30% of H hg and 13% of the European mtDNA pool in general²¹.

The percentage of T hg in the Susak population significantly exceeds the average frequency of this haplogroup in Europe. Subclades T1 and T2, present in Susak islanders with similar frequencies (15.5% and 17.2%, respectively), usually account for around 10% of mtDNA in Europe and about 6% in other Croatian subpopulations^{16-19,22}. Both T1 and T2 most likely originated in the Near East and date to ~21 kya, although the origin of T2 is the least clear and an ancient presence in Europe is possible. T1 represents ~2% of overall genetic variability in Western Europe and ~3% in Eastern Europe and the Near East, whereas T2 reaches ~8% in Western Europe and ~5% in the Near East. Recent results from whole mtDNA genomes suggest T2b is predominantly European and dates to ~10 kya, while T1a clade (dated to 7 kya) is a clear Neolithic signal²³. We can suggest that a Neolithic signal is evident in the Susak's gene pool based on the frequencies of H7, H8 and T1a, which have all been brought in connection with Neolithic dispersals into Europe. This also corresponds to a finding on the neighboring island of Cres, where a high percentage of a Neolithic signal has also been recorded¹⁴.

As for the W6 subclade, only one individual has been detected in the general Croatian population, in contrast to the most common W subhaplogroup, W1¹⁶⁻¹⁹. Interestingly, of all the Croatian islands, W6 individuals have been detected only on the islands of the Croatian Littoral – Krk (4.5%), Cres (3.4%) and Susak (1.6%). This suggests they have most probably been brought through a single migration event and dispersed afterwards via maritime connections between the islands. In general, W haplogroup is rather sparse (< 5%), but widespread throughout Europe and with higher diversity in southern than in northern European populations²².

We have also been able to detect possible founder lineages (Table 1) based on haplotype analysis, since only two haplotypes out of 16 account for 37% of the sample and five lineages (possible founder lineages) account for 67% of the sample. The gene diversity index of the island of Susak was calculated (0.897) and compared with other Croatian and European »genetic outliers« (Table 2). The population of Susak has the second lowest level of diversity among Croatian isolates. Only the island of Mljet (0.857) has even

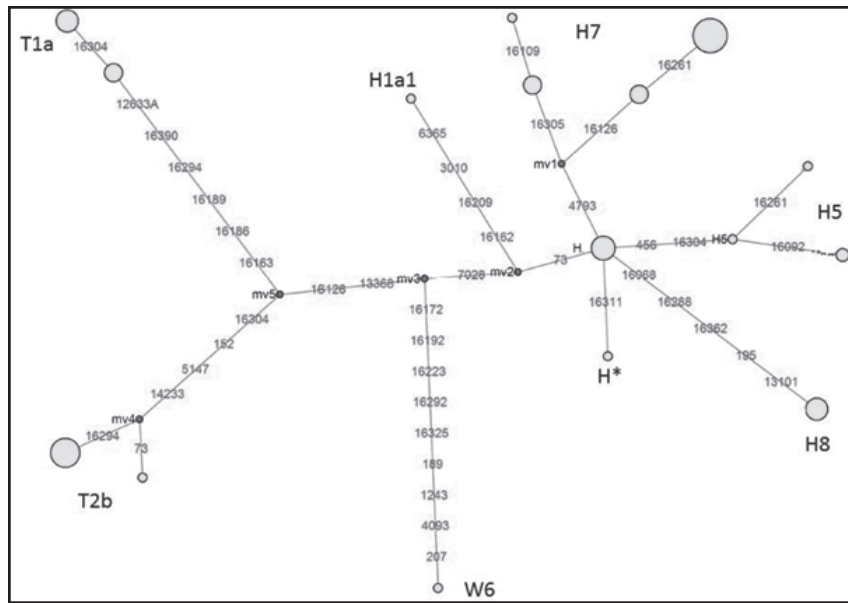


Fig. 5. Reduced-Median-Joining phylogenetic network of mtDNA haplotypes gathered by high-resolution analysis in the population of the island of Susak. Circle sizes are proportional to the haplotype frequency in the sample.



Fig. 6. PCA plot based on frequencies of (sub)haplogroups in 10 island populations and 1 continental population.

more reduced genetic variability, in line with previously published results on the maternal heritage of this island population¹⁶.

The PC plot, as a visual representation of the detected mtDNA frequencies on Susak, demonstrated the significant genetic distance of Susak from all other Croatian islands. The first principal component divides the Kvarner islands of the Croatian Littoral (Krk, Cres and Rab) from the Dalmatian islands (Brač, Hvar, Korčula, Vis, Lastovo, Mljet), together with Susak. On the other hand, the second principal component divides Susak strongly

from all other subpopulations, putting him in the outlying position (Figure 6).

An interesting example to mention is another genetic outlier, that shows striking similarities with Susak. It is the island Tristan de Cunha²⁴ – the most remote inhabited archipelago in the world, from the volcanic group of islands in the South Atlantic Ocean. It has only 3 km² suitable for settlement and agriculture, the soil has volcanic geological features, a well-documented genealogy that dates back to the first permanent settlement in the early 19th century has been recorded and only 7 surnames are present on the is-

land. The current population of 278 individuals is thought to have descended from 15 ancestors, seven females and eight males who arrived on the island at various times between 1816 and 1908. A study conducted by Soodyall et al.²⁵ in 1997 analyzed the maternal heritage of the Tristan de Cunha islanders and the results showed that their present-day mtDNA pool can be traced to five female ancestors – five founder mtDNA lineages. However, these data identified inconsistencies in the number of mtDNA types and the written records. Although the historical documents mentioned two sister pairs among the founding females, mtDNA data suggested only one pair of sisters. The subsequent Y chromosome data gave additional support to the previous mtDNA results, demonstrating that DNA is a powerful archival source that can be used to test oral traditions of a population²⁶. The demographic, historic and genetic similarities of these two islands are quite surprising and have, as such, already been described in an early paper called „Tristan de Cunha and Susak” in 1964²⁴.

Conclusion

This paper presents a review of the 50-year long anthropological and epidemiological research of the population of Susak – the most remote genetic isolate of the Croatian Littoral and even Croatia in general. Its specific features have put the island in the focus of diverse research during the last five decades and we have presented here, for the first time, its maternal genetic diversity as a continuation of this extensive work. The study confirmed the island's high level of isolation and reduced genetic diversity. At the present, the native community of Susak is

vanishing and is reduced to a small number of elderly and disabled inhabitants that refuse to leave the island. Once they are gone, their traditional community will disappear, together with other reproductively isolated autochthonous Croatia subpopulations. That is why information about their microevolution, degree of isolation and genetic structure and specificity present a valuable contribution. It would be of even greater scientific interest to further explore this extraordinary and unique community in subsequent population genetic and biomedical studies.

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UDALJENI IZOLAT HRVATSKOG PRIMORJA – 50 GODINA ISTRAŽIVANJA OTOKA SUSKA S NOVIM SPOZNAJAMA O NJEGOVOJ GENETIČKOJ RAZNOLIKOSTI

SAŽETAK

Ovaj rad donosi prikaz pedesetogodišnjih antropoloških i epidemioloških istraživanja populacije otoka Suska. Otok Susak je primjer ekstremnog genetičkog izolata s vrlo niskom stopom raznolikosti i vrlo visokim stupnjem srođivanja zbog prakse izrazite endogamije. Zbog svojih je specifičnih obilježja bio u fokusu raznih istraživanja u posljednjih pola stoljeća, a u ovoj studiji se još daje dodatni, novi uvid u majčinsko genetičko nasljeđe Suska. U tu je svrhu analizirana raznolikost haplogrupa mitohondrijske DNK (mtDNK) na temelju SNP-ova kontrolne i kodirajuće regije mtDNK na uzorku od 64 nesrodnih stanovnika otoka Suska. Samo tri osnovne haplogrupe su utvrđene na otoku – H, T i jedan pripadnik haplogrupe W, te mali broj haplotipova i odsutnost određenih tipičnih europskih haplogrupa (J, K, V, U, X). Analiza haplotipova utvrdila je pet mogućih osnivačkih linija od ukupno 16 različitih haplotipova. S obzirom na analizu genetičke raznolikosti, otok Susak zauzima drugu najnižu poziciju među genetičkim izolatima u Hrvatskoj, što je također u skladu s raznolikošću mtDNA na otoku. Populacija otoka Suska i njemu sličnih izolata će u bliskoj budućnosti najvjerojatnije nestati pa stoga ove rezultate smatramo dragocjenim doprinosom daljnjim populacijsko-genetičkim i epidemiološkim istraživanjima.