Mendelian Diseases and Conditions in Croatian Island Populations: Historic Records and New Insights

Vanja Saftić[1], Diana Rudan[2], Lina Zgaga[3]

[1]Department of Pediatrics, Osijek University School of Medicine, Croatia
[2]Department of Internal Medicine, Holy Ghost General Hospital, Zagreb, Croatia
[3]Department of Medical Statistics, Epidemiology, and Medical Informatics, Andrija Štampar School of Public Health, Zagreb University School of Medicine, Croatia

> **Correspondence to:**

Diana Rudan
Department of Internal Medicine
General Hospital "Holy Ghost"
Ulica Sveti Duh 64
10000 Zagreb, Croatia
irudan@hotmail.com

Among Croatian islands, there are several which are known for unusual autochthonous diseases and specific medical conditions that result from the reproductive isolation and specific population genetic structure. These populations are characterized by high degree of genetic isolation, consanguinity, and inbreeding. The reported diseases include Mal de Meleda on Mljet island, hereditary dwarfism on Krk island, familial learning disability on Susak island, familial ovarian cancer on Lastovo island, and several other rare diseases and conditions inherited in Mendelian fashion. We present a historical perspective on how these conditions were first described, interpreted, and assessed. We reviewed the information obtained through genetic research in the past several years, when the genetic etiology of some of these conditions was explained. The disease gene causing Mal de Meleda was first localized at 8q chromosome, and mutations in the ARS (component B) gene encoding SLURP-1 (secreted mammalian Ly-6/uPAR-related protein 1) protein were identified subsequently. The genetic etiology of dwarfism on the island of Krk is explained by a mutation in the PROP1 gene, responsible for the short stature. The search for mutations underlying other monogenic diseases in Croatian islands is under way.

Unusual autochthonous diseases and specific medical conditions on Croatian islands result from the reproductive isolation and specific genetic structure of their populations, characterized by high degree of genetic isolation, consanguinity, and inbreeding. In this review, we present historical perspective on how these conditions were first described, interpreted, and assessed.

Mal de Meleda – Mljet Disease (Island of Mljet)

It was named after Croatian island of Mljet, previously called Meleda, where the first cases were reported by Stulli (1-4). According to Schnyder et al (5,6), the disease originated on the island of Mljet between 1397 and 1808, when the island was used by the Dubrovnik Republic for quarantining people suffering from plague and leprosy (7). This resulted in reproductive isolation and high consanguinity, which increased the frequency of homozygous genotypes on the island and thus increased the incidence of Mal de Meleda (8). Among the island population, it was historically thought that Mal de Meleda arises as a contact dermatitis with an unknown endemic plant on the island (6).

History and genetic epidemiology of Mal de Meleda

It was recently revealed that the disease is not exclusively found on Mljet island. In the past two decades, several sporadic cases have also been reported in Italy (9), Tunisia (10), western region of Saudi-Arabia (11), and United Arab Emirates (12). A recent analysis showed that Croatian and Algerian families with the disease share the common haplotype that presents the same mutation in both populations (13). This is consistent with a genetic epidemiological view that a causal mutation originated on Mljet at least 800 years ago, and was then spread by sailors through trade routes of the medieval Dubrovnik Republic.

The trading routes of the Dubrovnik Republic went toward the Middle East and Northern Africa, as the Republic of Venice ruled the Northern Adriatic Sea. This explains the sporadic cases of the disease in the Middle East and northern Africa (14).

An alternative hypothesis is that the mutation responsible for Mal de Meleda could be much older and more widespread. However, other sporadic cases of recessive palmoplantar keratoderma were reported in Sweden (15,16), Japan (17), and a Chinese family in Taiwan (18), but their clinical presentation was milder than in original Mal de Meleda and some of the usual signs were absent. This implies possible founder mutations in other genes involved in the same genetic pathway. Recently, two new mutations and four ancestral haplotypes were observed in 69 patients from the countries of the Mediterranean basin, whereas an additional haplotype was found in the German and Scottish patients (19), which supports the view that the disease could have a possible etiological complexity and allelic heterogeneity.

Features of disease

The first changes in keratinization of the skin become clinically manifest several months after birth, typically affecting palms and soles, with the characteristic skin thickening (Table 1). A diffuse palmoplantar keratosis is the most prominent feature, which at first presents as yellowish, smooth skin on palms and soles. Eventually, painful fissures develop, which do not necessari-

Table 1. Features of the Mal de Meleda*

Autosomal recessive inheritance
Onset at birth or in early infancy
Characteristic glove-like and sock-like hyperkeratosis with sharp margination
Occasional hyperkeratotic plaques on elbows, knees. or corner of the mouth
Marked hyperhidrosis, maceration, and malodor
Slow progression without remissions
Ortohyperkeratosis, hypergranulosis, and acanthosis on histological examination, with no signs of epidermal or spongiotic atypia
Increased amount of tonofibrils and keratohyalin granules on electron microscopy

*Source: references **8** and **11**.

ly correspond to creases of the skin. Hyperkeratosis extends to the sides and the dorsa of the feet and hands, and interdigital spaces are macerated, with a sharp delineation from healthy skin. An intense hyperhidrosis produces unpleasant fetid smell which is present only in the affected areas of the skin (8).

Contractures of variable severity due to hyperkeratosis are usually present on the fifth finger, and they are associated with bilateral brachytelephalangia in the majority of cases. Other symptoms and signs are less common and they may involve papulous keratoses, hyperkeratotic changes similar to lichenification, perioral erythema, and a cystic osteolysis and acroosteolysis of the wrist and tarsal bones and phalanges (20). Typically, orthohyperkeratosis, hypergranulosis, and acanthosis are observed on histological examination, with no signs of epidermal or spongiotic atypia (5,20). Electron microscopy shows increased amount of tonofibrils and keratohyalin granules (20). Symptoms progress very slowly and there are no indications that life expectancy among the affected is reduced (21,22).

New insights into genetic etiology

The first attempt to understand the possible genetic etiology of the disease was undertaken by Šalamon et al (23), who analyzed MN, Ss, and Kk erythrocyte antigen polymorphisms in 9 patients with Mal de Meleda on the island of Mljet. They merely attempted to demonstrate the increased homozygosity in the patients in comparison with control population, to show that the disease may be caused in some way by increased consanguinity. However, their results were inconclusive due to a very small sample and a small number of analyzed genetic markers.

An analysis of the pedigrees of 12 cases living on the island of Mljet showed that the disease had an autosomal recessive inheritance pattern (8). Based on the knowledge of pedigree structure, an analysis of two large consanguineous families from Algeria, which included 10 affect-

ed individuals, localized a disease gene to chromosome 8qter (24). The maximum two-point lod score for D8S1751 was found in this study, and it amounted to 8.21, which was the first positional cloning of the gene region. An analysis of 5 affected individuals originating from the island of Mljet confirmed the segment of homozygosity in the same region, implying a founder effect (25). A subsequent study on 12 individuals from Mljet further confirmed the findings (8).

Subsequent pooled genetic analysis of 12 Algerian kindred and 7 Croatian families with a denser set of genetic markers identified the mutations in the ARS (component B) gene encoding a protein SLURP-1 (secreted mammalian Ly-6/uPAR-related protein 1) (26). SLURP-1 belongs to the Ly-6/uPAR receptor superfamily and secreted proteins, which are known to participate in signal transduction, immune cell activation, and cellular adhesion. SLURP-1 shows a high degree of structural similarity with the three fingers motif of snake neurotoxins, which suggests its interaction with the neuronal acetylcholine receptors. SLURP-1 potentiates human alpha 7 nicotinic acetylcholine receptors present in keratinocytes (27). Therefore, SLURP-1 is likely to be a secreted epidermal neuromodulator that influences both epidermal homeostasis and inhibition of tumor necrosis factor (TNF)-alpha release by macrophages during wound healing. Such roles would explain hyperproliferative and inflammatory clinical phenotype in Mal de Meleda (27).

There is a number of clinically similar phenotypes, which can now all be easily distinguished from Mal de Meleda based on genetic mutations involved. Papillon-Lefevre syndrom, also recessive palmoplantar keratosis, has a candidate genetic region on the chromosome 11q14, and subsequent genetic analyses identified the mutations in the gene encoding cathepsin C (8,28-30). Another recessive palmoplantar keratoderma, characterized by additional cardiac symptoms such as cardiomegaly and ventricu-

lar tachycardia, and found in 4 families from the island of Naxos, Greece, is due to a mutation in plakoglobin (31,32). Vohwinkel's syndrome differs from Mal de Meleda by an autosomal dominant inheritance and mutations identified on the GJB2 gene, which encodes the gap junction connexin26 (Cx26) (33,34).

Hereditary dwarfism (island of Krk)

History and genetic epidemiology of "Hanhart's Dwarfs" from Krk island

The first report on hereditary dwarfism on the Island of Krk was written by Jauregg in 1906 (35). He termed the condition "coastal maritime cretinism", implying iodine deficiency as the possible cause. It was soon realized, however, that dwarfs originate only from two adjacent villages, Bašćanska Draga and Jurandvor, while no cases were seen anywhere else on the island. The first cases of dwarfism, two brothers born in 1864 and 1869, were detected in Bašćanska Draga. Two more cases were born in 1877 and 1880 in Jurandvor. Since then, 23 dwarfs have descended from the two villages (36,37). This pattern attracted Swiss geneticist Hanhart (38), who termed the condition "heredodegenerative genitodystrophic nanism". The systematic study of the condition was then performed by Vojska in 1938 (39). A group from the Rijeka School of Medicine, Croatia, reinitiated the studies of the cases in the 1970s and published their results recently (37,40,41).

The two villages where the condition occurred, Bašćanska Draga and Jurandvor, have a small, highly inbred population. The total population of the villages in 1973 amounted to 459 and 164 inhabitants, respectively, and the share of autochthonous inhabitants was 95.4% and 89.0%, respectively (40). Twice removed parental consanguinity was 11.9% and 22.0%, respectively (41). Consanguineous marriages were pronouncedly common in the past. The mo-

tivation for this phenomenon was preservation of the land within a family (40,41). A total of 53 children lived in the two villages at the time of 1991 Census, totaling only 11.4% in the population (37). The percentage of people older than 65 years was 40.6% (compared to 12%-14% in the general Croatian population), which makes this population markedly old and regressive. The average number of members of a household was extremely low, 1.6 in Jurandvor and 2.1 in Bašćanska Draga. Most men were laborers and agriculture workers, and most women were housewives. Illiteracy was very rare and found at the prevalence of less than 5% and only in the oldest age group (37,40).

Features of the condition

The population of both villages seems to have a large share of relatively short people in comparison with the other 9 villages from the islands of Rab, Vis, Lastovo, and Mljet (Figure 1) (42). More than two thirds (68%) of women were shorter than 159 cm, and 14% of women were shorter than 150 cm. Most women (54%) were between 150 and 159 cm. Most men were between 170 and 179 cm (49%). Eight percent of men were shorter than 159 cm. An increase in height could be noted in younger age groups, corresponding to the general trend (40).
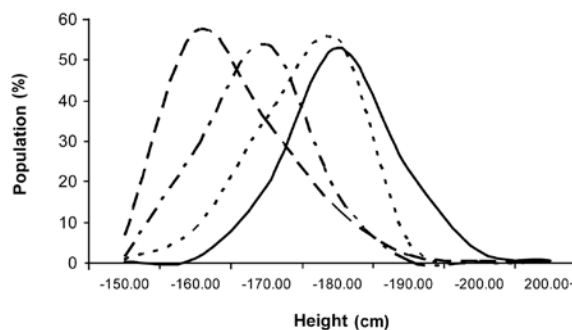

Figure 1. Effect of PROP-1 mutation on height in Jurandvor/Bašćanska Draga (V11) population isolate in comparison to other investigated population isolates: Rab, Banjol, Barbat, Supetarska Draga, Lopar, Mljet, Lastovo, Vis, Komiža, and Susak (V1-V10; ref. 42). Dotted line – men from V11, full line – men from other villages, dashed line – women from V11, dashed-dotted line – women from other villages.

In the 1970s, when the research was conducted, there were 8 dwarfs in the population of the two villages. Dwarfs were found in six different families, three of which had a positive family history of nanism. The youngest dwarf was 17 years old and the oldest was 82. It seems that the condition does not influence the life expectancy of the affected. Socio-economic conditions in which the dwarfs lived differed greatly. Researchers found a brother and sister from Baščanska Draga living in very poor conditions, suffering from mental retardation, and arthritic changes that impaired their mobility (41).

In 1974, all 73 children from both villages underwent auxological examination, with the purpose of exploring hereditary dwarfism. Height below the 10th percentile was found in 13 children, 4 of which showed growth retardation (3rd percentile or lower). Of those 13 children, 10 were revisited 2 years later. The retardation of growth was still present in 4 of these children (41). After this, the growth hormone curve was established, and a lack of somatotropin was determined to be the cause of retardation of growth in two of the four children. One of these children came from a family with known history of hereditary dwarfism (40,41). All other clinical and biochemical tests were normal for their age (40).

New insights into genetic etiology

The genetic etiology of the condition was revealed in 1999, when it was shown that a mutation in a candidate gene PROP1 is responsible for the short stature of the dwarfs from the Krk island (43). Similarly, familial dwarfism in a highly consanguineous family, where PROP1 was also responsible for the condition, was recently observed in Tunisia (44). Generally, dwarfism can be caused by isolated growth hormone deficiency or multiple pituitary hormone deficiency (MPHD) (43). When found in more than one member of the same family, it can show autosomal dominant, autosomal recessive, or X-linked modes of inheritance. Studies also suggested that familial MPHD dwarfism constituted a genetically and pathogenetically highly heterogenous group (45).

Genetic studies carried out in recent years showed that multiple pituitary hormone deficiency can be caused by mutations in at least three pituitary transcription factors: POU1F1 (formerly called PIT1), PROP1, or HESX1 (46). Mutations in POU1F1 result in a total deficiency of growth hormone and prolactin, and a variable deficiency of thyroid stimulating hormone. Mutations in PROP1 lead to the aforementioned deficiencies coupled with additional deficiencies of gonadotrophins and variable deficiency of ACTH (47). Gene PROP1 (termed "Prophet of Pit-1") is necessary for POU1F1 expression (47,48). The most common mutational hot spot in PROP1 mutations is the 2-bp deletion, 296delGA (A301G302del) (48,49).

Learning Disability (Island of Susak)

History and genetic epidemiology of learning disability on Susak

The small island of Susak is a unique example of extreme isolation and inbreeding. Founded by only two families of settlers, the island's population rose to 300 in the year of 1771, then to 1111 in 1880, 1427 in 1900, and 1876 in 1945 (50). After the World War II, a most of the population emigrated, and the current population is estimated to be less than 300 inhabitants. However, almost entire emigration from the island moved to Hoboken, New Jersey, USA, where they still live in a "closed" community, marrying each other (51). Therefore, the population of Susak and its emigration in Hoboken represent an outstanding example of genetically very homogenous group, separated some half a century ago and living in different environmental setting which, although limited in size, could be a suit-

able model for studies of genetic vs environmental impacts on human health (52).

While studying consanguinity, the researchers were able to reconstruct 374 genealogies, which covered the entire island population, most of the emigration, and usually four (in some cases up to six) generations of ancestors. The family trees showed many cases of consanguinity, indicating that the island population is extremely inbred. There were only seven different surnames among almost 1400 inhabitants, with a couple of "dominant" surnames present in the vast majority of population (50,52). A basic analysis of blood polymorphisms was performed through analysis of frequency distribution of blood groups. In a sample of 200 inhabitants, the frequencies were the following: 0 – 46%; A – 49%; B – 4%; AB – 1%; In a subsample of 50 inhabitants, the frequency of positive Rhesus factor was 86%, and negative 14% (50). These data are significantly different from those found in the surrounding populations, with a low proportion of blood group B and high proportion of blood group A in comparison with neighboring Croatian, Slovenian, and Italian populations (14).

A systematic medical check-up was performed on the entire island population (50,51). Among 346 children examined in 1957, multiple congenital anomalies were present in 25 cases, clustering in 12 families, and a detailed description of each particular case, along with the results of examination in siblings was presented (50). Special attention was also given to psychiatric disorders, presumably common on the island. Among the entire population (some 1400 at the time), there were 129 persons fulfilling the criteria for some psychiatric diagnosis: 57 cases of oligophrenia, 33 cases of senile dementia, 21 cases of psychoses, 16 cases of schizophrenia, and 2 other undefined cases (50). In many of those cases, there had been striking evidence of familial clustering of the diseases, with learning disability being a common feature in most of them (14,50).

Features of the condition

The prevalence of learning disability was determined in Susak and 9 other isolate villages on 5 different Croatian islands as control populations: Gornji Humac (Brač island), Gdinj and Svirče (Hvar island), and Pupnat, Čara, Račišće, Lumbarda, and Smokvica (Korčula island) (53). Learning disability was defined as the inability to attend the public school system. As the elementary schools (grade 1-8) in the place of the study are both public and compulsory, the assessment of child's ability to attend the school is performed at the age of six, based on a combination of IQ score measurement and behavioral assessment. The assessment is based on standard set of tests, as required by Croatian Ministry of Science, Education, and Sports (54). These tests include: perception test, test of point linkage, general knowledge test, drawing test, and numerical test; intelligence test based on drawing a human image; Bender Gestalt test; and Raven's progressive colored matrices (54). Data on the individuals unable to attend school were retrieved from local general practitioners and were considered to be complete. The prevalence of learning disability was calculated as the proportion of individuals unable to attend school in the total population of each village (as of January 2001). Ethical approval for this study was obtained from the Ethics Committee of the Zagreb University School of Medicine, Zagreb, Croatia (54). It was shown that the prevalence of learning disability in Susak was 2.5%, ie, at least 5 times higher than expected in the general Croatian population, with familial clustering of the cases (54).

New insights into genetic etiology

One of the most frequently documented and repeated findings in human biology is the association between consanguinity and cognitive dysfunction and learning disability (54). The genetics of human cognition is still in its early development, but it is likely to be a highly com-

plex and multifactorially determined polygenic human trait. In some way, increased individual genome-wide homozygosity reduces the biological potential of cognition in all human populations, and the specific mechanisms are still to be revealed. The investigations of genetic diversity on Susak based on microsatellite DNA markers, as compared to the same markers in smaller samples of other populations, revealed that the average heterozygosity and allelic diversity in Susak are considerably smaller (54), and that Susak island represents an extreme example of reduced genetic diversity in global terms (Table 2). In some way, this places its population at a greater risk of cognitive dysfunction in comparison to general Croatian population.

Table 2. Comparison of Susak gene diversity based on autosomal microsatellite markers, with corresponding published gene diversities from isolates or outbred populations

| | Diversity (N alleles)* | | | |
| | Susak | Yakut | Danes | Japanese |
Marker	2N = 142	2N = 102	2N = 118	2N = 100
D7S484	0.809 (7)	0.819 (8)	0.684 (6)	0.781 (7)
D8S260	0.79 (8)	0.829 (9)	0.803 (9)	0.807 (9)
D7S517	0.79 (9)	0.801 (7)	0.833 (10)	0.763 (7)
D8S258	0.57 (4)	0.676 (4)	0.746 (7)	0.657 (5)
D7S669	0.78 (8)	0.778 (8)	0.771 (10)	0.798 (9)
D8S272	0.474 (8)	0.807 (9)	0.757 (10)	0.819 (8)
D7S510	0.74 (6)	0.668 (7)	0.778 (10)	0.802 (8)
D7S640	0.842 (15)	0.869 (16)	0.872 (17)	0.889 (20)
D7S513	0.82 (13)	0.815 (13)	0.836 (14)	0.899 (15)
D8S514	0.703 (6)	0.762 (6)	0.656 (7)	0.712 (8)
D7S516	0.785 (5)	0.697 (7)	0.704 (6)	0.695 (6)

*Source: references 51 and 52. The data for Yakut, Danes, and Japanese populations are from *http://info.med.yale.edu/genetics/kkidd/contents.html.*

Familial Ovarian Cancer (Island of Lastovo)

History and genetic epidemiology of ovarian cancer on Lastovo island

Rudan (55) investigated the incidence of cancer in isolate island populations of the Eastern Adriatic. The number of cancer cases on five islands (Brač, Hvar, Korčula, Vis, and Lastovo) over the 20-year period (1971 to 1990) has been extracted from the Croatian Cancer Registry. The population of coastal Dalmatia, characterized by

similar environmental factors but quite different population genetic structure, represented a control population of over 800000. The leading hypothesis was that, if there were genes or gene complexes (especially with recessive inheritance) responsible for genetic susceptibility to certain types of cancer, the incidence of those cancer types should be greater in reproductively isolated island populations than in the control population, due to increased manifestation of such genes/gene complexes caused by founder effect and inbreeding (14,55).

The most striking finding in these analyses was a 7-fold increase in the incidence of ovarian cancer in Lastovo in comparison to the general population (42.4 vs 6.3 per 100000, $P<0.001$). Further analysis showed a strong familial clustering, represented as dramatically greater average kinship between the ancestors of the diseased in comparison to the average kinship of the entire island's population (Figure 2).
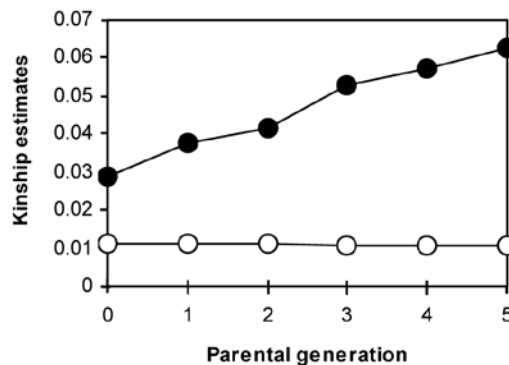

Figure 2. Kinship estimates of ovarian cancer cases (closed circles) and of the remaining population of the island of Lastovo (open circles) and in five generation of their ancestors; all differences were statistically significant at the level $P<0.05$ (56).

Features of disease

The disease affects mainly younger women on the island (up to 45 years of age), and shows familial clustering, which further supports the primarily genetic etiology. Histologically, the disease does not differ from the ovarian cancer cases seen in the general population (55,56).

New insights into genetic etiology

As the prognosis of the disease is rather poor, and epidemiological analysis covered the period from 1971-1990, there were no cases or specimens left for further studies. However, it is highly likely that a mutation in a gene similar to BRCA1 is present in the island, possibly a novel and unique variant, with a very high lifetime penetrance. A genetic screening program of the candidate genes is planned among the women in the island to detect early those at increased lifetime risk of ovarian cancer (55,56).

Other Mendelian diseases and conditions (Islands of Krk, Pag, Silba, and Lastovo)

A number of other monogenic diseases and conditions have been described on Croatian islands. Table 3 lists the evidence for those conditions, and also for extremely rare mutations that were observed in unusually high frequencies in specific Croatian island isolates. Prevalence of albinism and progressive spastic quadriplegia is much higher in the island of Krk than in the general Croatian population (36). Familial congenital hip dislocation was present in unusually high frequencies at the island of Lastovo (57), while increased incidence of glucose-6-phosphate dehydrogenase deficiency was encountered on Vis island (58).

Apart from disease-causing mutations, there are many examples in the literature on very un-

usual and extremely rare genetic variants present in Croatian island populations. Those include deleted/triplicated alpha-globin gene in a massive pedigree from a genetically isolated community on the island of Silba (59), and PGM1*W3 phosphoglucomutase-1 variant on the island of Olib (60). Other extremely unusual findings include a reported high frequency of mtDNA haplogroup F (61) and Y-chromosome haplogroup P* in some small and isolated settlements of Hvar island, which are typical of far East and almost absent in Europe (62).

Conclusion

This review highlighted the fact that in highly structured population ("metapopulation") in which its small components remain isolated, there is a very high chance that through founder effect, genetic drift, and subsequent inbreeding, there will be many extremely rare genetic variants brought to unusually high frequencies and revealing its phenotypic effect at the level of specific subpopulations. Although these mutations are extremely rare in outbred, general population, and therefore have no effect on the total disease burden, the understanding of their effect on the phenotype could be of great general interest. These extremely rare mutations of large effect can reveal entirely new and unknown molecular and metabolic pathways from genes via expression profiles to proteomics, metabolomics, and eventually phenotype (63). Such understanding could provide new targets for development of drugs and novel therapeutic approaches, which are currently in short supply (64). Therefore, isolated human populations can be of great value in finding such new and unusual genetic variants, which would not be possible in general population (65).

Table 3. Overview of the evidence of extremely rare mutations present in unusually high frequencies in specific Croatian island isolates

Type of research	Island	Reference
Reports on Mendelian diseases:		
albinism	Krk	36
progressive spastic quadriplegia	Krk	36
familial congenital hip dislocation	Lastovo	57
G6PD deficiency	Vis	58
Reports of high population frequencies of extremely rare genetic variants:		
deleted/triplicated alpha-globin gene	Silba	59
PGM1*W3 phosphoglucomutase-1 variant	Olib	60
mtDNA haplogroup F	Hvar	61
Y-chromosome haplogroup P*	Hvar	62

of the Republic of Croatia (No. 0108330). There are no conflicts of interest related to this manuscript.

References

1   Stulli L. On a skin variety [in Italian]. Antologia di Firenze. 1826; fasc: 71-2.

2   Bosnjakovic S. A report on the so-called "Mljet disease" ("Mal de Meleda") [in German]. Acta Derm Venereol. 1938;19:88-122.

3   Fatovic-Ferencic S, Holubar K. Mal de Meleda: from legend to reality. Dermatology. 2001;203:7-13. Medline:11549792

4   Fatovic-Ferencic S, Holubar K. The portrait and paper of a forgotten hero – Luca Stulli (1772-1828) and the Mal de Meleda of yesteryear: a 175-year anniversary. J Invest Dermatol. 2001;116:198-9. Medline:11168819

5   Schnyder UW, Franceschetti AT, Ceszarovic B, Segedin J. Autochthonous Meleda disease [in French]. Ann Dermatol Syphiligr (Paris). 1969;96:517-30. Medline:5367495

6   Schnyder UW, Franceschetti AT, Cezarovic B, Segedin J. Mljet disease (Mal de Meleda) [in Croatian]. Lijec Vjesn. 1970;92:747-56. Medline:5206842

7   Salamon T, Cezarovic B, Nardelli-Kovacic M, Schnyder UW. The Meleda disease – an acroerythrokeratodermy [in German]. Z Hautkr. 1981;52:580-6.

8   Bakija-Konsuo A, Basta-Juzbasic A, Rudan I, Situm M, Nardelli-Kovacic M, Levanat S, et al. Mal de Meleda: genetic haplotype analysis and clinicopathological findings in cases originating from the island of Mljet (Meleda), Croatia. Dermatology. 2002;205:32-9. Medline:12145432

9   Brambilla L, Pigatto PD, Boneschi V, Altomare GF, Finzi AF. Unusual cases of Meleda keratoderma treated with aromatic retinoid etretinate. Dermatologica. 1984;168:283-6. Medline:6235136

10 Zahaf A, Charfi C, Baklouti A, Jarraya C. Palmoplantar keratoses type Meleda [in French]. Sem Hop Paris. 1987;63:1043-6.

11 Lestringant GG, Halawani NA, Zagzouk F. Mal de Meleda. Int J Dermatol. 1989;28:277-8. Medline:2524451

12 Lestringant GG, Frossard PM, Adeghate E, Qayed KI. Mal de Meleda: a report of four cases from the United Arab Emirates. Pediatr Dermatol. 1997;14:186-91. Medline:9192409

13 Fischer J, Bouadjar B, Heilig R, Huber M, Lefevre C, Jobard F, et al. Mutations in the gene encoding SLURP-1 in Mal de Meleda. Hum Mol Genet. 2001;10:875-80. Medline:11285253

14 Rudan I, Campbell H, Rudan P. Genetic epidemiological studies of eastern Adriatic island isolates, Croatia: objective and strategies. Coll Antropol. 1999;23:531-46. Medline:10646227

15 Gamborg Nielsen P. Two different clinical and genetic forms of hereditary palmoplantar keratoderma in the northernmost county of Sweden. Clin Genet. 1985;28:361-6. Medline:2935332

16 Kastl I, Anton-Lamprecht I, Gamborg Nielsen P. Hereditary palmoplantar keratosis of the Gamborg Nielsen type. Clinical and ultrastructural characteristics of a new type of autosomal recessive palmoplantar keratosis. Arch Dermatol Res. 1990;282:363-70. Medline:2260881

17 Nagashima M. Palmoplantar keratoses. In: Miura O, Ochiai K, editors. Clinics and genetics. Vol. 9. Inheritance of dermatological and urological diseases. Tokyo: Igaku – Shoin Publishers; 1977. p. 23-7.

18 Jee SH, Lee YY, Wu YC, Lu YC, Pan CC. Report of a family with mal de Meleda in Taiwan: a clinical, histopathological and immunological study. Dermatologica. 1985;171:30-7. Medline:3161759

19 Marrakchi S, Audebert S, Bouadjar B, Has C, Lefevre C, Munro C, et al. Novel mutations in the gene encoding secreted lymphocyte antigen-6/urokinase-type plasminogen activator receptor-related protein-1 (SLURP-1) and description of five ancestral haplotypes in patients with Mal de Meleda. J Invest Dermatol. 2003;120:351-5. Medline:12603845

20 Frenk E, Guggisberg D, Mevorah B, Hohl D. Meleda disease: report of two cases investigated by electron microscopy. Dermatology. 1996;193:358-61. Medline:8993971

21 Kogoj F. Mljet disease ("Mal de Meleda") [in German]. Acta Derm Venereol. 1934;15:264-99.

22 Kogoj F. Mljet disease [in Croatian]. Zagreb: JAZU; 1963.

23 Salamon T, Hadziselimovic R, Hajdic G. The MNSs and Kk blood group systems in the disease of Mljet (mal de Meleda). Dermatology. 1994;188:78-9. Medline:8305767

24 Fischer J, Bouadjar B, Heilig R, Fizames C, Prud'homme JF, Weissenbach J. Genetic linkage of Meleda disease to chromosome 8qter. Eur J Hum Genet. 1998;6:542-7. Medline:9887370

25 Patel H, Nardelli M, Fenn T, Houlston R, Coonar A, Patton MA, et al. Homozygosity at chromosome 8qter in individuals affected by mal de Meleda (Meleda disease) originating from the island of Meleda. Br J Dermatol. 2001;144:731-4. Medline:11298530

26 Fischer J, Bouadjar B, Heilig R, Huber M, Lefevre C, Jobard F, et al. Mutations in the gene encoding SLURP-1 in Mal de Meleda. Hum Mol Genet. 2001;10:875-80. Medline:11285253

27 Chimienti F, Hogg RC, Plantard L, Lehmann C, Brakch N, Fischer J, et al. Identification of SLURP-1 as an epidermal neuromodulator explains the clinical phenotype of Mal de Meleda. Hum Mol Genet. 2003;12:3017-24. Medline:14506129

28 Fischer J, Blanchet-Bardon C, Prud'homme JF, Pavek S, Steijlen PM, Dubertret L, et al. Mapping of Papillon-Lefevre syndrome to the chromosome 11q14 region. Eur J Hum Genet. 1997;5:156-60. Medline:9272739

29 Toomes C, James J, Wood AJ, Wu CL, McCormick D, Lench N. Loss-of-function mutations in the cathepsin C gene result in periodontal disease and palmoplantar keratosis. Nat Genet. 1999;23:421-4. Medline:10581027

30 Nakano A, Nomura K, Nakano H, Ono Y, LaForgia S, Pulkkinen L, et al. Papillon-Lefevre syndrome: mutations and polymorphisms in the cathepsin C gene. J Invest Dermatol. 2001;116:339-43. Medline:11180012

31 Coonar AS, Protonotarios N, Tsatsopoulou A, Needham EW, Houlston RS, Cliff S, et al. Gene for arrhythmogenic right ventricular cardiomyopathy with diffuse nonepidermolytic palmoplantar keratoderma and woolly hair (Naxos disease) maps to 17q21. Circulation. 1998;97:2049-58. Medline:9610536

32 McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet. 2000;355:2119-24. Medline:10902626

33 Maestrini E, Korge BP, Ocana-Sierra J, Calzolari E, Cambiaghi S, Scudder PM. A missense mutation in connexin26, D66H, causes mutilating keratoderma with sensorineural deafness (Vohwinkel's syndrome) in three unrelated families. Hum Mol Genet. 1999;8:1237-43. Medline:10369869

34 Solis RR, Diven DG, Trizna Z. Vohwinkel's syndrome in three generations. J Am Acad Dermatol. 2001;44 2Suppl: 376-8. Medline:11174420

35 Jauregg VW. "Little people" from the island of Krk [in German]. Wien Klin Wochenschr. 1906;43:1273-9.

36 Zergollern L. A follow-up on Hanhart's dwarfs of Krk. Birth Defects Orig Artic Ser. 1971;7:28-32. Medline:5173178

37 Kopajtic B, Dujmovic M, Kolacio Z, Kogoj-Bakic V. Enclaves of hereditary dwarfism on the island of Krk, Croatia. Coll Antropol. 1995;19:365-71.

38 Hanhart E. Krk island disease [in German]. Arch Julius Klaus Stift Vererbungsforsch Sozialanthropol Rassenhyg. 1925;1:181-9.

39 Vojska V. A report on the so-called small people from Krk [in German]. Archiven den Rassen-Geselschaft in Biologie. 1941;34:433-52.

40 Rajh-Gustincic M, Kopajtic B. Auxological examination of children in the region of hereditary nanism on Krk [in Croatian]. Medicina (Acta Facultatis Medicinae Fluminensis). 1978;15 Suppl 2:25-32.

41 Kopajtic B, Kogoj-Bakic V, Kolacio Z, Brozovic Z. Social and health status of inhabitants of the villages Jurandvor and Baščanska Draga on the island of Krk [In Croatian]. Medicina (Acta Facultatis Medicinae Fluminensis). 1978;15 Suppl 1:33-40.

42 Rudan I, Biloglav Z, Carothers AD, Wright AF, Campbell H. Strategy for mapping quantitative trait loci (QTL) using human metapopulations. Croat Med J. 2006;47:532-42. Medline: 16909450

43 Krzisnik C, Kolacio Z, Battelino T, Brown M, Parks JS, Laron Z. The "little people" of the island of Krk – revisited. Etiology of hypopituitarism revealed. J Endocr Genet. 1999; 1:9-19.

44 Reynaud R, Chadli-Chaieb M, Vallette-Kasic S, Barlier A, Sarles J, Pellegrini-Bouiller I, et al. A familial form of congenital hypopituitarism due to a PROP1 mutation in a large kindred: phenotypic and in vitro functional studies. J Clin Endocrinol Metab. 2004;89:5779-86. Medline: 15531542

45 Dattani MT. Novel insights into the aetiology and pathogenesis of hypopituitarism. Horm Res. 2004;62 Suppl 3:1-13. Medline:15539793

46 Rainbow LA, Rees SA, Shaikh MG, Shaw NJ, Cole T, Barrett TG, et al. Mutation analysis of POUF-1, PROP-1 and HESX-1 show low frequency of mutations in children with sporadic forms of combined pituitary hormone deficiency and septo-optic dysplasia. Clin Endocrinol (Oxf). 2005;62:163-8. Medline:15670191

47 Sornson MW, Wu W, Dasen JS, Flynn SE, Norman DJ, O'Connell SM, et al. Pituitary lineage determination by the Prophet of Pit-1 homeodomain factor defective in Ames dwarfism. Nature. 1996;384:327-33. Medline:8934515

48 Wu W, Cogan JD, Pfaffle RW, Dasen JS, Frisch H, O'Connell SM, et al. Mutations in PROP1 cause familial combined pituitary hormone deficiency. Nat Genet. 1998;18:147-9. Medline:9462743

49 Lee JK, Zhu YS, Cordero JJ, Cai LQ, Labour I, Herrera C, et al. Long-term growth hormone therapy in adulthood results in significant linear growth in siblings with a PROP-1 gene mutation. J Clin Endocrinol Metab. 2004;89:4850-6. Medline:15472175

50 Cvjetanovic B, Guberina P, Mirkovic M, Mohorovicic A, editors. Susak Island [in Croatian]. Zagreb: JAZU; 1957.

51 Rudan I, Stevanovic R, Vitart V, Vuletic G, Sibbett L, Vuletic S, et al. Lost in transition – the island of Susak (1951-2001). Coll Antropol. 2004;28:403-21. Medline:15636100

52 Bohacek N. Tristan da Cunha and Susak [in Serbian]. Lijec Vjesn. 1964;86:1412-6. Medline:5893114

53 Rudan I, Rudan D, Campbell H, Biloglav Z, Urek R, Padovan M, et al. Inbreeding and learning disability in Croatian island isolates. Coll Antropol. 2002;26:421-8. Medline:12528265

54 Croatian Ministry of Health and Croatian Ministry of Education and Culture: Regulations on enrolling the children in elementary schools [in Croatian]. Narodne novine. 1991;13:425-7.

55 Rudan I. Inbreeding and cancer incidence in human isolates. Hum Biol. 1999;71:173-87. Medline:10222641

56 Rudan I. Ancestral kinship and cancer in Lastovo island, Croatia. Hum Biol. 2001;73:871-84. Medline:11804202

57 Maricevic A. Incidence of congenital hip dislocation in Lastovo 1885-1993 [in Croatian]. Lijec Vjesn. 1995;117:126-9. Medline:8600324

58 Markic J, Krzelj V, Markotic A, Marusic E, Stricevic L, Zanchi J, et al. High incidence of glucose-6-phosphate dehydrogenase deficiency in Croatian island isolate: example from Vis island, Croatia. Croat Med J. 2006;47:566-70. Medline: 16909453

59 Turcinov D, Krishnamoorthy R, Janicijevic B, Markovic I, Mustac M, Lapoumeroulie C, et al. Anthropogenetical analysis of abnormal human alpha-globin gene cluster arrangement on chromosome 16. Coll Antropol. 2000;24: 295-302. Medline:11216396

60 Borot N, Arnaud J, Rudan P, Chaventre A, Sevin J. Phosphoglucomutase-1 subtypes in two populations in Adriatic islands: presence of PGM1*W3 (PGM1*7+) allele. Hum Hered. 1991;41:309-15. Medline:1838099

61 Tolk HV, Barac L, Pericic M, Klaric IM, Janicijevic B, Campbell H, et al. The evidence of mtDNA haplogroup F in a European population and its ethnohistoric implications. Eur J Hum Genet. 2001;9:717-23. Medline:11571562

62 Barac L, Pericic M, Klaric IM, Rootsi S, Janicijevic B, Kivisild T, et al. Y chromosomal heritage of Croatian population and its island isolates. Eur J Hum Genet. 2003;11:535-42. Medline:12825075

63 Gamulin S. Impact of molecular medicine on pathophysiology, medical practice, and medical education. Croat Med J. 2003;44:374-85. Medline:12950140

64 Campbell H, Rudan I. Interpretation of genetic association studies in complex disease. Pharmacogenomics J. 2002;2: 349-60. Medline:12629506

65 Wright AF, Carothers AD, Pirastu M. Population choice in mapping genes for complex diseases. Nat Genet. 1999;23: 397-404. Medline:10581024