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Extreme founder effect associated with hyperglycemia and hyperlipidemia on the island of NIAS/Indonesia

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ABSTRACT

The island of Nias/Indonesia shows an extremely reduced genetic diversity indicating a strong founder effect. As a consequence, the prevalence of some disease genes should significantly differ among populations depending on the gene pool passed on to the founder population and their successive expansion as it has already been documented for several monogenic diseases. Results of the current study based on routine laboratory blood examination give rise to the notion that this might also hold true for polygenic disorders. We observed very high prevalence of hyperglycemia (non-fasting glucose above 200 mg/dL in 14 % Nias population compared to 1.5 % in the population of the neighboring island of Sumatra) accompanied by hypertriglyceridemia, high non-HDL-cholesterol, and low HDL-cholesterol levels. These findings suggest that the Nias population may be disproportionally affected by prediabetes and type 2 diabetes mellitus. By contrast, laboratory parameters potentially indicative of other polygenic disorders such as total plasma cholesterol, electrolytes, creatinine, urea, and uric acid were comparable between the inhabitants of Nias and Sumatra islands. To our knowledge this is the first study suggesting that the extremely strong genetic bottleneck seen in the Nias population translates into the widespread metabolic disease with potentially deleterious influence on public health.

1. Introduction

Our previous studies revealed extremely reduced Y-chromosome and, to a lesser extent, mitochondrial DNA diversity on the West-Indonesian Island of Nias, suggesting a strong bottleneck or founder effect [1–3]. Oral tradition also indicates that the population of Nias goes back to a few ancestors (founders) who arrived on the island around 800 years BP and apparently displaced the ancestral population [4–6]. This time scale is independently supported by both the archaeological evidence from deposits in the cave Tögi Ndrawa showing a continuous occupation from at least 12 000 years to a stop 850 years ago [7] and genetic data using a “molecular clock” approach [3,8]. Based on the drastically reduced genetic diversity of the Nias population, the molecular clock estimates that this extreme bottleneck effect dates back about 800 years [3].

The extremely reduced genetic diversity of the Nias population is likely to have serious public health implications. The prevalence of some disease genes may differ significantly between populations depending on the gene pool passed on to the founder population and their successive expansion. For example, some diseases that are very rare on the neighboring island of Sumatra might be common on Nias, and conversely, diseases that are rare on Nias could occur more frequently on Sumatra (Fig. 1). One would also expect some diseases remaining endemic to Nias that is restricted solely to this island – a scenario similar to the well-documented Finnish disease heritage ([9] Finnish Disease Heritage Database, www.findis.org).

Actually, four examples of monogenic diseases endemic to Nias have been documented: first, a novel homozygous autosomal recessive mutation in the *B3GAT3* (c.419C > T [p.(Pro140Leu)]) gene, causing skeletal dysplasia, identified by analysing a consanguineous Niassian family [10]; second, highly elevated prevalence of oculocutaneous albinism type 1 (*OCA1*) in the Nias population with a novel homozygous mutation in the tyrosinase gene (c.701C > T) [11]; third, X-linked form of familial gout common in a clan in South Nias, which was as yet not

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Fig. 1. Geographic location of islands of Nias and Sumatra (Indonesia) - Red dot: City of Medan, capital of Sumatra (source: https://d-maps.com/carte.php?num_car=28852&lang=de). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

associated with a mutation in one of the so far known X-linked genes associated with this disease (hypoxanthine-guanine phophoribosyl-transferase (HPRT) or phosphoribosyl-pyrophosphate synthetase (PRPS1)) [12]; fourth, in the south of Nias a large family with an autosomal dominant form of polydactyly through three generations has been identified (Kennerknecht et al., unpublished data). On the other hand, the prevalence rate of prosopagnosia or face blindness, a highly selective impairment in individual recognition of faces and suggestive of autosomal dominant inheritance, is in the same range on Nias as in the rest of the world [13].

In contrast to these Mendelian disorders, no systematic study of the prevalence of polygenic diseases in the Nias population has been conducted so far. Patients attending the hospital *Rumah Sakit Umum Daerah* (RSUD) in Gunungsitoli appear to be frequently affected by diabetes mellitus type 2, elevated cholesterol levels, nephrolithiasis, and hypertension. Therefore, in the present study selected laboratory parameters potentially reflecting common polygenic diseases were determined in routinely collected blood serum in the cohort of Nias natives and compared with subjects from the neighboring island of Sumatra.

2. Material and methods

Study subjects and sample collection - This study was performed as a part of the project approved by the Nias Government through the Nias Health Office, Nias Heritage Foundation (YPN) (Reference 443/3898/P2P) and by the Ethics Committee of the Westphalian-Lippe Chamber of Physicians and the University of Münster, Germany (Reference 3Kenn1). The samples were taken from the residual material with no further use for diagnostic purposes, were immediately anonymized, and the backtracking was irreversibly capped. Consequently, the ethical counseling/permission was not mandatory for this study (Reference 2023-428-f-N, the Ethics Committee of the Westphalian-Lippe Chamber of Physicians and the University of Münster). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Over 500 sera obtained during routine diagnostic procedures at Hospital *Rumah Sakit Umum Daerah* (RSUD) Gunungsitoli, Indonesia were randomly collected. The quality of the material was checked, and potentially hemolytic sera were excluded from further analysis. Finally, a total of 441 samples was assessed. For the control group, 201 randomly selected non-haemolytic sera collected from the Hospital *Rumah Sakit Harapan*, Medan/Sumatra, Indonesia, were selected for further examination. The material was aliquoted (1.0 mL) and stored initially at −20 °C and later at −70 °C until analysis.

Laboratory analysis - Clinical laboratory parameters were analysed in a routine hospital laboratory (Central Laboratory Facility, University Hospital Münster, Germany) using commercially available assays. Except for serum lipoprotein profile, all analyses were done on the automated laboratory analyser (Siemens Advia 1800) using photometric assays for cholesterol, triglycerides, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C), glucose, and blood urea nitrogen (urea-N) colorimetric assays for creatinine and uric acid, and indirect potentiometry for sodium and potassium. Non-HDL-cholesterol (non-HDL-C) was calculated as a difference between total and HDL-C. For all quantitative assays used, the daily monitored precision and accuracy were below 3.2 % and 3.7 %, respectively. The analytical quality was constantly surveyed according to regulations of the German Chamber of Physicians and the laboratory took part in the external quality assessment schemes.

Statistical analysis - For the analysis of clinical laboratory parameters, an exploratory statistic was performed using the MedCalc Statistical Software version 19.1.3 (MedCalc Software bvba, Ostend, Belgium). The distribution of variables was assessed for normality using Shapiro-Wilk test. Non-normally distributed parameters were analysed after logarithmic transformation. Parametric Student t-test (2-sided) or Welch-test, or non-parametric Mann-Whitney *U* test were used for comparison of means. Chi-square test was used for comparison of distributions. Data are shown as arithmetic mean ± standard deviation (SD) for normally distributed parameters and median ± interquartile range (IQR) for non-normally distributed parameters.

3. Results

The population of Nias studied here included over 500 randomly selected subjects admitted to the Hospital *Rumah Sakit Umum Daerah (RSUD)* in Gunungsitoli. Based on the absence of signs of haemolysis, serum samples obtained from 441 subjects aged 45.1 ± 16.3 (53 % males and 47 % females) were selected for further laboratory studies. Body mass index (BMI) and blood pressure data were not available in the studied population. For the control group, leftover serum samples obtained from randomly chosen 201 patients aged 47.5 ± 13.0 (48 % males and 52 % females) admitted to the Hospital *Rumah Sakit Harapan* in Medan, the capital of the island of Sumatra/Indonesia, were analysed in the laboratory in parallel with samples from individuals from Nias.

To assess disease phenotypes in the Nias population, basic clinical laboratory parameters reflecting common metabolic disorders were examined. As shown in Table 1 and Fig. 2, Nias probands were characterized by substantially elevated serum concentrations of glucose and triglycerides compared with the control population from Sumatra. Of

Table 1
Clinical laboratory parameters in Nias and control (Sumatra) populations.

	Nias population	Control population
	n = 441	n = 201
Total cholesterol (mg/dL)	171.7 ± 53.6	168.1 ± 30.9
Triglycerides (mg/dL)	156 ± 106	106 ± 59[a,b]
Creatinin (mg/dL)	1.0 ± 0.5	0.8 ± 0.4[a,b]
Urea-N (mg/dL)	14.0 ± 9.0	12.0 ± 5.0[a,b]
Uric acid (mg/dL)	5.4 ± 2.6	5.6 ± 2.1
Non-fasting glucose (mg/dL)	104 ± 75	84 ± 23[a,b]
Sodium (mmol/L)	143 ± 6	143 ± 5
Potassium (mmol/L)	4.0 ± 0.7	4.3 ± 0.6

Data represent mean ± SD or median ± IQR.
[a] $p < 0.001$ (Student t-test or Welch-test).
[b] $p < 0.001$ (Mann-Whitney *U* test).

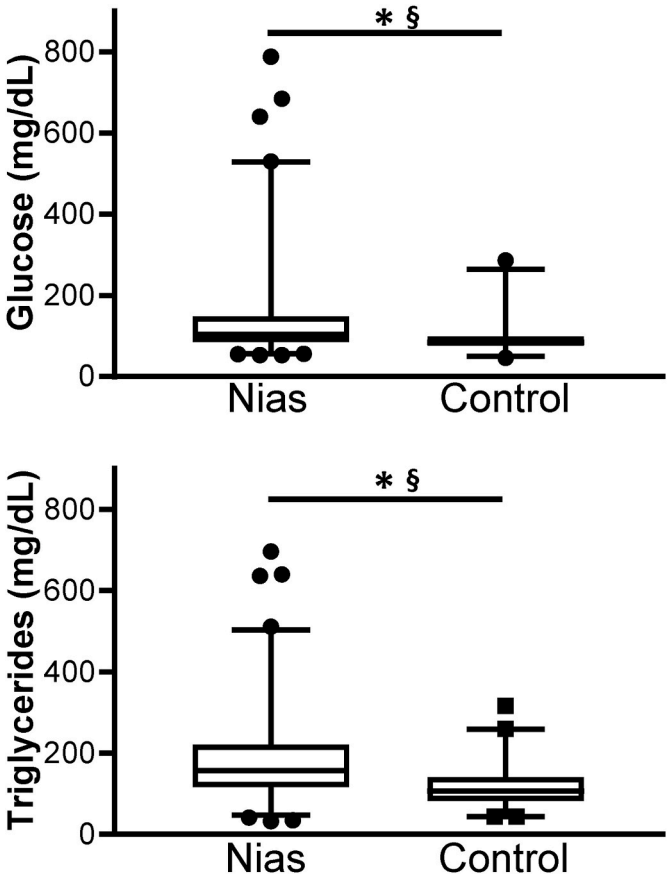

Fig. 2. Distribution of glucose and triglycerides in the Nias and control populations – Non-fasting glucose and triglycerides were determined in 441 and 201 probands in the Nias and control populations, respectively. Box-Whisker plots show the medians, quartiles, and 1st or 99th percentiles for both parameters in the two studied groups. * - $p < 0.001$ (Student t-test or Welch-test), § - $p < 0.001$ (Mann-Whitney *U* test).

the 441 Nias samples tested, 65 samples (14 %), were found to have non-fasting plasma glucose levels exceeding 200 mg/dL indicative of overt diabetes mellitus whereas only 3 of 201 samples (1.5 %, $\chi^2 = 27.8$, $p < 0.001$) in the control population had similarly increased glucose concentrations. Similarly, 187 samples from the Nias population (41 %) but only 17 samples from the control population (8.5 %, $\chi^2 = 73.2$, $p < 0.001$) had triglyceride levels above 175 mg/dL indicating non-fasting hypertriglyceridemia. To further characterize the dyslipidemic phenotype in the Nias patients, we determined LDL- and HDL-C and calculated non-HDL-C in 28 Nias probands with the highest triglyceride levels (>300 mg/dL). In these probands low HDL-C (21.2 ± 10.1 mg/dL) and high non-HDL-C (214 ± 51.8 mg/dL), but normal LDL-C (104.2 ± 37.5 mg/dL) were observed. In addition, slightly but significantly elevated serum levels of parameters reflecting impaired renal function (creatinine and urea-N) were observed in the Nias probands as compared to controls (Table 1). In contrast, both populations showed no significant differences in serum levels of total cholesterol, uric acid, sodium, and potassium (Table 1).

4. Discussion

The extreme population bottleneck observed on the island of Nias is likely to profoundly influence the occurrence of clinical genetic diseases encountered among the islanders. While prevalence rates for certain disorders seem to be of the same order of magnitude as in neighboring islands and/or mainland Southeast Asia, significantly higher or lower frequencies may be expected for others. Because very common diseases are more easily recorded than rare ones, there will be a bias in favour of diseases with a high prevalence rate and/or those the identification of which is easy such as the autosomal recessive oculocutaneous albinism type 1 (OCA1) [11] with a 10-fold higher prevalence rate on Nias. Since the most common diseases worldwide are polygenic, they are good candidates to demonstrate the influence of a genetic bottleneck. Although no systematic studies of the disease prevalence on Nias were conducted to date, local physicians repeatedly raised the suspicion that that hyperglycemia, hypercholesterolemia, or hypertension are more common on Nias than on Sumatra.

In the present study based solely on routine blood parameters, we document for the first time an increased prevalence of hyperglycemia in the Nias population. Actually, no less than 14 % of individuals in Nias had a non-fasting plasma glucose concentration higher than 200 mg/dL, which is tantamount to overt diabetes mellitus, whereas the corresponding percentage in the Sumatra population was only 1.5 %, which is close to previous estimates of the diabetes prevalence in Indonesia [14,15]. Hyperglycemia in the Nias cohort was associated with hypertriglyceridemia, low HDL-cholesterol and high non-HDL-C, but normal LDL-cholesterol levels - a phenotypic constellation typical of the type 2 diabetes mellitus or prediabetic state arising as a consequence of insulin resistance. While the metabolic phenotype seen in the Niassian population argue against the notion that monogenic forms of diabetes (Maturity Onset Diabetes Mellitus, MODY), which are generally not accompanied by overt dyslipidemia, contribute to the high prevalence of hyperglycemia in the Nias cohort, this possibility cannot be entirely dismissed. At all events, our results suggest that the Nias population is disproportionally affected by diabetes or prediabetes. In contrast, we found no evidence of a higher prevalence of other common mono- or polygenic disorders such as hypercholesterolemia in this population. Based on the electrolyte determination we could also exclude certain forms of hypertension such as Liddle disease. Although laboratory parameters reflecting renal function (creatinine, urea) were significantly higher in the Nias than in the Sumatra population, the differences were marginal, clinically irrelevant, and fell within the respective reference ranges. In our view, it is unlikely that these differences genuinely reflect a higher prevalence of renal disorders or a specific (endemic) Nias kidney disease. Notwithstanding, an X-linked form of gout is found on Nias, but almost restricted to one clan in the south [12].

Several important limitations of the present study must be acknowledged. First, control over the preanalytical conditions of the present study was limited because of the still inadequate health infrastructure in Nias. Although this could have some influence on the results in the Nias group, it should be emphasized that except for glucose, all laboratory parameters investigated in the present study are characterized by high stability not only in plasma but also in whole blood. With regard to glucose, increasing the time period before centrifugation of serum samples is likely to decrease rather than increase the concentration and, therefore, is unlikely to contribute to the higher incidence of hyperglycemia encountered among the Nias inhabitants. Second, the sampling procedure adopted in this study rise question, how well do the selected blood samples represent the general population of Nias. While the sampling bias obviously cannot be excluded, we would like to point out that the Rumah Sakit Umum Daerah (RSUD) hospital, where sera were collected, is a general medical institution serving the whole island population and dealing with most common diseases rather than special and rear pathologies. We believe that this at least to certain extend extenuate the potential sampling bias and that the selected blood samples fairly well represent the whole Nias population. Third, because of regulatory obstacles, we were unable to assemble a sex- and age-matched control group from healthy inhabitants of Sumatra and instead resorted to left-over samples from randomly selected patients, which were similarly to Nias samples obtained from a hospital laboratory. Although this procedure could potentially bias the control group, the median values of all laboratory parameters obtained in this group, except for blood glucose, were within their respective reference

intervals, indicating that it can reasonably serve as a proxy for the normal Sumatra population.

In conclusion, the present study documents for the first time the high prevalence of a highly abnormal metabolic phenotype corresponding to diabetes mellitus and/or a prediabetic state among the inhabitants of the island of Nias. The prevalence of some diseases can significantly differ between populations, depending on the gene pool of the founder population and its successive expansion. Considering our previous findings showing an extreme genetic bottleneck in the Nias population, our current results call for further investigation in this population with the aim of delineating this phenotype at the molecular level. In addition to improving public health care, this could also help to further determine the origin and dispersal of the remote Niassian population.

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Author contribution statement

I.K. conceived and planned the study, collected samples, interpreted the data, and wrote the manuscript. J.M.H. conceived the study and collected samples, M.F. performed the analysis and interpreted the data, J.-R.N. performed the analysis, interpreted the data, and wrote the manuscript.

Data availability statement

Data will be made available upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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