Analysis of 12,517 inhabitants of a Sardinian geographic isolate reveals that predispositions to thrombocytopenia and thrombocytosis are inherited traits

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ABSTRACT

Background
Thrombocytopenia is a common finding in several diseases but almost nothing is known about the prevalence of thrombocytopenia in the general population. We examined the prevalence of thrombocytopenia and determinants of platelet count in a healthy population with a wide age range.

Design and Methods
We performed a cross-sectional study on 12,517 inhabitants of ten villages (80% of residents) in a secluded area of Sardinia (Ogliastra). Participants underwent a complete blood count evaluation and a structured questionnaire, used to collect epidemiological data.

Results
We observed a platelet count lower than 150×10^9/L in 3.2% (2.8%-3.6%) of females and 4.8% (4.3%-5.4%) of males, with a value of 3.9% (3.6%-4.3%) in the entire population. Thrombocytopenia was mild (platelet count: 100×10^9/L -150×10^9/L), asymptomatic and not associated with other cytopenias or overt disorders in most cases. Its standardized prevalence was quite different in different villages, with values ranging from 1.5% to 6.8%, and was negatively correlated with the prevalence of a mild form of thrombocytosis, which ranged from 0.9% to 4.5%. Analysis of platelet counts across classes of age revealed that platelet number decreased progressively with aging. As a consequence, thrombocytopenia was nearly absent in young people and its prevalence increased regularly during lifetime. The opposite occurred for thrombocytosis.

Conclusions
Given the high genetic differentiation among Ogliastra villages with "high" and "low" platelet counts and the substantial heritability of this quantitative trait (54%), we concluded that the propensity to present mild and transient thrombocytosis in youth and to acquire mild thrombocytopenia during aging are new genetic traits.

Key words: thrombocytopenia, thrombocytosis, genetic trait, Sardinia, geografic isolate.

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The online version of this article has a Supplementary Appendix.

Introduction

It is well known that thrombocytopenia is a common finding in several illnesses and clinical conditions. For instance, it has been shown that 46% of critically ill medical and surgical patients have a platelet count lower than 150×10^9/L,[1] and that the prevalence of thrombocytopenia is 20% in patients with systemic lupus erythematosus,[2] 37% in human immunodeficiency virus-positive drug users,[3] 18% in patients with chronic active hepatitis B, and 13% in those with chronic hepatitis C.[4]

In contrast, almost nothing is known about the prevalence of thrombocytopenia in the general population, although there is a general consensus that a low platelet count is recognized with increasing frequency in apparently healthy subjects, especially due to the measurement of platelet numbers as part of routine blood testing.[5,6] In some of these cases, further clinical investigation reveals that thrombocytopenia is secondary to an occult disease, while in others it is found that the low platelet count is inherited. When all known disorders are ruled out, subjects are usually classified as affected by immune thrombocytopenia, since no positive criteria have been identified for this disease and its diagnosis remains one of exclusion.[7]

This study takes advantage of the availability of a database including clinical, laboratory and genetic data of 12,517 subjects, resulting from a large population-based survey performed in the Ogliastra region, Sardinia. This area is characterized by genetic, demographic and environmental features which are typical of founder populations and thus ideal for studying genetic and non-genetic risk factors of common diseases because of the reduced background variability.[8,9] We addressed the issues of the prevalence of thrombocytopenia and determinants of platelet count in a healthy population with a wide age range. Although our study analyzed a specific, small geographic area, the results we obtained shed new light on some determinants of platelet count that could also operate in other populations.

Design and Methods

Study design and data collection

We analyzed data from 12,517 inhabitants of the Ogliastra region, in central eastern Sardinia, Italy (Figure 1). This mountainous area is sparsely populated with a total of 60,000 inhabitants (34 inhabitants/km^2) clustered in 23 villages. Ogliastra represents a genetic isolate since it has been geographically and socially secluded for thousands of years due to the morphology of its territory. Mitochondrial analysis traced the original population back to the Neolithic era.[10] Furthermore, several Ogliastra villages grew slowly in isolation and had little or no admixture with the others, giving rise to high endogamy (ranging from 70% to 90%) and inbreeding. As a consequence of founder effects and genetic drift, a great deal of genetic differentiation among subpopulation isolates within Ogliastra was observed.[11] Genetic diversity measures showed that these villages rank among the most genetically homogenous European populations.[12]

The data set comes from a large epidemiological survey carried out in ten villages between 2002 and 2008. The study design was cross-sectional and population-based. People living in the villages were invited to take part in the study by means of information campaigns and letters sent to every family, achieving a participation of about 80% of the resident population. The local administration in each village provided a suitably equipped site where respondents were invited to give fasting blood samples and undergo an interview, after signing informed consent.

Trained personnel administered a structured questionnaire collecting information on socio-demographic factors, lifestyle, drug consumption as well as medical and family history of many pathologies, including cancer, liver disorders, bleeding and thrombotic events. Questions about present and past illnesses were all asked following the same fixed schemes, for example, for liver disease: "Have you ever had any liver disease (e.g., hepatitis, cirrhosis)? If yes, (since) when (year or age). Any relapse (number)? Number and degree of affected relatives". The disorders were classified according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9 CM[13]). Hematologic variables, including platelet, white blood cell and red blood cell counts, mean corpuscular volume and hemoglobin concentration, were determined by a Coulter LH Hematology analyzer (Beckman-Coulter, Brea, CA, USA). Thrombocytopenia was defined as a platelet count less than 150×10^9/L, thrombocytosis as a platelet count more than 400×10^9/L, anemia as a hemoglobin concentration less than 14.0 g/dL in men and 12.3 g/dL in women and leukopenia as a white blood cell count less than 4×10^9/L.

For each participant we collected genealogical information dating back to 17th century and stored them in a relational database along with clinical and epidemiological data. To construct pedigrees we used a utility implemented in the PedNavigator software,[14] which allows the reconstruction of different types of genealogies starting from a list of individuals and setting the desired number of generations. Available data allowed us to organize the 12,517 enrolled people into 538 pedigrees (on average 4.6 generations deep) with an average family size of 37.7 individuals. Sixty-four pedigrees had more than one member with a platelet count lower than 150×10^9/L. All of them were evaluated and classified into four groups according to the degree of relationship of affected members: (i) at least three first- or second-degree thrombocytopenic relatives (high probability of a genetic disorder); (ii) two first- or second-degree affected relatives (medium probability); (iii) at least two third-degree affected relatives (low probability); (iiii) no first- to third-degree affected relatives (no probability).

The study adhered to the tenets of the Declaration of Helsinki and was approved by the review board of the institution that funded the research (Italian Ministry of Education, University and Research n°: 5571/DSPAR/2002).

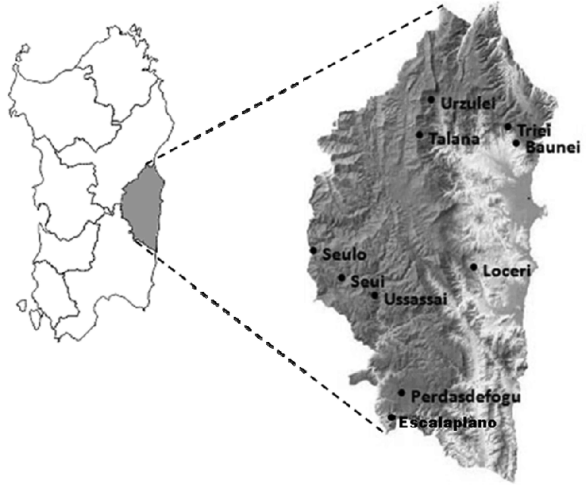

Figure 1. Ogliastra region. Geographical location of the ten villages participating in the epidemiological survey.

Statistical analysis

We explored the distribution of platelet counts in the whole sample and by village. We next computed descriptive statistics overall, by age and sex, and by village. T-tests and χ^2 tests were used to assess differences of quantitative and dichotomous traits, respectively, in men and women. Subsequently, we examined differences in platelet counts among villages by analysis of variance (ANOVA), adjusting for age and gender and using Bonferroni's correction. Confidence intervals (CI) are at the 95% confidence level. Prevalence rates of thrombocytopenia, thrombocytosis and disorders that possibly cause secondary forms of these defects were standardized by the direct method to the age and sex structure of the 2008 Italy resident population.[15] In order to identify potential dominant or recessive transmission of thrombocytopenia, we examined all the pedigrees including at least two affected individuals. Finally, to quantify the relative genetic contribution to the variation of platelet count, we carried out a heritability analysis with the variance component method.[16] This method partitions the total phenotypic variance into genetic, shared environmental, and individual-specific variances, and the heritability is simply obtained as the ratio of genetic variance to the total phenotypic variance. Since each village has a peculiar founder population and may represent a genetic sub-isolate, separate heritability estimates were obtained. STATA 9 software (StataCorp, College Station, TX, USA) was used for all the analyses except for variance component heritability analysis, which was performed using SOLAR software (Sequential Oligogenic Linkage Analysis Routine, version 4.1.0).[17]

Results

Among the 12,517 subjects, 44.3% were men and 55.7% women aged 3-105 years. Platelet count was higher in women ($P<0.0001$), and the overall prevalence of thrombocytopenia was 4.8% (95% CI, 4.3-5.4) in men and 3.2% (95% CI, 2.8-3.6) in women, whereas the prevalence of thrombocytosis was 1.5% (95% CI, 1.2-1.8) in men and 3% (95% CI, 2.6-3.5) in women. The high prevalence of anemia in our population is not surprising, since thalassemia trait is widespread in Sardinia (12%) (Table 1).

Subjects were stratified into different groups according to platelet count, and their distribution was markedly different among villages (Table 2). This finding was confirmed by ANOVA for platelet count after applying Bonferroni's correction for multiple comparisons (α=0.0011) and taking into account the effect of age and sex (Figure 2A). The standardized prevalence of thrombocytopenia in the ten villages ranged from 1.5% to 6.8%, whereas the prevalence of thrombocytosis ranged from 0.9% to 4.5% (*Online Supplementary Figure S1*). Based on these data, villages seemed to cluster into three groups: (i) Talana and Urzulei, (in northern inner Ogliastra) with the lowest platelet counts, high prevalence of thrombocytopenia and low prevalence of thrombocytosis; (ii) Seui, Seulo and Ussassai (in western Ogliastra) with opposite findings; and (iii) the remainder, located all around, with intermediate characteristics. Differences between the polar opposite groups of villages in platelet counts and in the prevalences of thrombocytopenia and thrombocytosis were statistically significant ($P<0.05$). Densities of platelet counts in the three groups of villages, even when adjusted for age and sex, give a graphical representation of all this matter (Figure 2B).

The distribution of platelet count by age and sex shows a slow, progressive decline of platelet number with aging in both males and females (Figure 3A). On average, a 10-year increase in age corresponds to a 9×10^9/L decrease in platelet count, adjusting for sex ($P<0.001$). Consequently symmetrical relationships of age with thrombocytopenia and thrombocytosis were evidenced in the overall sample (Figure 3B). A strong, negative correlation between these two abnormalities was observed (Spearman's rank correlation coefficient =-0.69, P=0.054). Similar findings were obtained when these correlations were investigated in the three groups of villages described above (Figure 3C).

We next estimated the standardized prevalence of the clinical phenotypes possibly related to platelet counts in the total sample and by village. Overall, we found that the prevalence of liver disorders was 5.5% (95% CI, 5.1-5.9), of cancer 2% (95% CI, 1.8-2.3), of bleeding events 0.8% (95% CI, 0.6-0.9) and of thrombotic events 5.8% (95% CI, 5.4-6.2). Furthermore, since the prevalence of thalassemia carriers in Sardinia is about 12%, we specifically estimated the prevalence of carriership in Ogliastra and found it to be 12.8% (95% CI, 12.2-13.3). Sporadic, significantly different prevalences of the investigated diseases among the ten villages were identified, but they were not responsible for the observed differences in the prevalence of thrombocytopenia or thrombocytosis (*data not shown*).

Heritability estimates for platelets count, adjusting for age and sex ($P<0.001$), varied from 40% (Seui) to 53%

Table 1. Characteristics[§] of the study population by sex.

	Men (5,540)	Women (6,977)
Age** (mean ± SD), years	43.8±21.4	45.7±20.9
Platelet count** $\times10^9$/L (mean ± SD)	240.5 (65.3)	260.3 (67.5)
Number of subjects with:		
thrombocytopenia**, n (%)	271 (4.9)	234 (3.3)
thrombocytosis**, n (%)	87 (1.6)	196 (2.8)
anemia**, n (%)	1401 (25.3)	1280 (18.3)
leukopenia** (%)	104 (1.9)	242 (3.5)
liver disorders, n (%)	299 (6.2)	380 (6.1)
cancer*, n (%)	95 (1.9)	162 (2.6)
bleeding events, n (%)	41 (0.8)	51 (0.8)
thrombotic events**, n (%)	358 (7.4)	360 (5.7)

[§]*data expressed as percentages are crude prevalences; *P<0.05, **P<0.0001 for t-test and χ^2 test in men and women.*

Table 2. Distribution (%) of subjects according to platelet counts ($x10^9$/L) in the whole sample and by village.

	Platelets ($x10^9$/L)<50	50-100	100-150	150-400	400-500	500-1000
Talana	0.26	0.6	6.13	92.15	0.86	0
Urzulei	0.35	0.7	5.55	92.52	0.7	0.18
Triei	0.19	0.87	4.14	92.59	1.92	0.29
Baunei	0.29	0.96	2.76	94.02	1.67	0.29
Loceri	0.28	1.13	2.73	93.61	1.97	0.28
Perdasdefogu	0.33	0.33	2.57	94.8	1.75	0.22
Escalaplano	0.23	0.53	2.52	94.05	1.83	0.84
Seui	0	0.5	1.9	94.04	3.31	0.25
Seulo	0	0.22	1.31	94.74	3.07	0.66
Ussassai	0	0.85	1.28	93.38	4.27	0.21
Overall	0.22	0.67	3.14	93.7	1.94	0.32

(Ussassai). They were not significantly different among villages, so that we also carried out a further analysis pooling together pedigrees of all the villages, obtaining a global heritability of 54% (95% CI, 49.7%-58.3%). Family environmental factors shared during cohabitation accounted for 5% of phenotypic variance.

The study of family trees is summarized in Table 3. Although thrombocytopenia affected more than one first- to third-degree relatives in several families, in none of these families did we identify a pattern of inheritance consistent with the known forms of inherited thrombocytopenia. *Online Supplementary Figure S2* shows a representative pedigree in which an autosomal dominant transmission may be suspected in one branch of the family, but this hypothesis was ruled out in other branches in which parents of thrombocytopenic subjects have normal platelet counts.

Discussion

To estimate the prevalence of thrombocytopenia for the first time in the general population, we analyzed platelet counts in 12,517 inhabitants of the Ogliastra region of Sardinia, Italy, and obtained a value of 3.9%, with males more frequently affected than females. Thrombocytopenia was not associated with other cytopenias and was mild in most cases. These data confirm the general sensation that, after the introduction of cell counters that made platelet counting a routine test, identification of patients with asymptomatic thrombocytopenia became a common event.

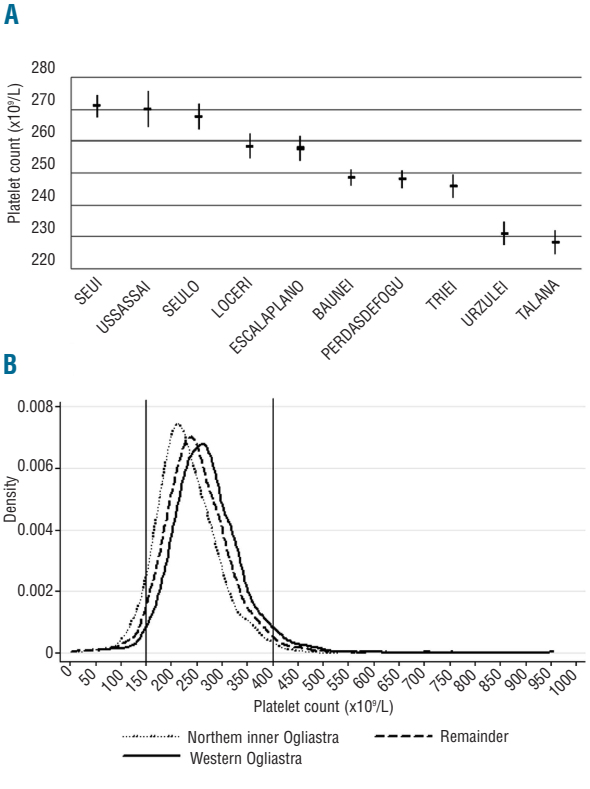

Figure 2. (A) Platelet count in Ogliastra villages. Mean values are age- and sex-adjusted by ANOVA, (95% C.I.). (A) Age- and sex-adjusted platelet count densities in Ogliastra. Relative densities are plotted grouping villages as follows: Talana and Urzulei, (northern inner Ogliastra), Seui, Seulo and Ussassai (western Ogliastra), Baunei, Loceri, Perdasdefogu, Escalaplano and Triei (remainder).

A surprising characteristic of the Ogliastra population was the great variation in the prevalence of thrombocytopenia among different villages, with values ranging from 1.5% in Seulo to 6.8% in Talana (*Online Supplementary Figure S1*). Since each of these communities represents a geographic isolate within the larger Ogliastra isolate, we first hypothesized that mutations responsible for one or more of the classical forms of inherited thrombocytopenia were differently diffused in these populations. However, the study of family trees failed to show dominant or recessive transmission of thrombocytopenia in any pedigree (*Online Supplementary Figure S2*). Moreover, the analysis of the prevalence of thrombocytopenia in different classes of age (Figure 3B) identified a direct and strong correlation between these two parameters, with only 0.8% of people younger than 18 years having a low platelet count. Since thrombocytopenia is congenital in all known inherited forms, this finding ruled out the initial hypothesis.

We next examined the possibility that differences in the prevalence of this defect derived from unequal distribution of cancer and liver disorders among different villages, since these conditions are the most frequent causes of secondary thrombocytopenia. Appropriate statistical analysis refuted this hypothesis too (*data not shown*).

Finally, a possible explanation for the uneven distribution of thrombocytopenia came from the analysis of platelet counts in single communities. This parameter was roughly normally distributed in all villages, but the curves were shifted to the left in the populations with a higher prevalence of thrombocytopenia, and to the right in those with few cases of thrombocytopenia (Figure 2B). Since the collection of blood samples took several years, we examined the possibility that seasonal variations in platelet counts were responsible for the observed differences, but we excluded this possibility (*data not shown*). Interestingly, the prevalence of thrombocytopenia was inversely related to that of thrombocytosis, which affected 7.3% of subjects younger than 18 years and 0.9% of those older than 64 years. As a whole, these data suggested that the "normal range" of platelet count was different in each village, likely influenced by genetic factors, and that the prevalence of thrombocytopenia derived from the interaction of this genetic trait with the propensity of platelet number to decline with aging: in villages with higher "normal

Table 3. Pedigrees with more than one thrombocytopenic member classified according to the degree of relationship of affected relatives.

	≥ 3 I-II degree* affected relatives	2 I-II degree* affected relatives	2 III degree* affected relatives	Total pedigrees
Talana	2	1	0	76
Urzulei	4	3	0	45
Triei	2	2	0	24
Baunei	2	4	2	117
Loceri	1	1	0	33
Perdasdefogu	0	5	0	66
Escalaplano	1	2	0	68
Seui	0	0	0	44
Seulo	0	1	0	43
Ussassai	0	0	1	22
Overall	12	19	3	538

** I, II or III degree: one, two or three meioses away, respectively.*

ranges", many young people have transient thrombocytosis and few develop thrombocytopenia with aging, while in communities with lower "normal ranges" the prevalence of thrombocytosis in youth is low and many subjects acquire thrombocytopenia during adult life.

Since it has been shown in different populations that platelet count is highly heritable,[18-20] we examined this matter in Ogliastra, confirming the datum. Notably, previous analyses on population structure through high density single nucleotide polymorphisms revealed significant genetic heterogeneity among groups of Ogliastra villages, with the largest difference being between Talana and Seulo (which also show the largest difference in mean platelet count) and the smallest difference between Baunei and Triei.[21] Furthermore, the study of the distribution of 43 serological and hematologic quantitative traits on the same cohort showed that villages clustered accordingly.[22] Northern inner Ogliastra villages differ from western ones not only from a genetic point of view, but also as far as platelet count is concerned. Altogether these data further support the idea that the propensity to present transient thrombocytosis in youth and to acquire thrombocytopenia with aging are genetically transmitted in the communities analyzed.

Further investigation is required to ascertain whether this conclusion also applies to populations other than those living in Ogliastra, but some evidence in the literature seems to support this hypothesis, at least concerning thrombocytopenia. Several years ago, a wide variation of "normal" platelet counts was identified in volunteers of different ethnic origins, such that it was concluded that platelet counts well below 150×10^9/L may be observed in healthy subjects of African and Afro-Caribbean origin.[23] This finding was subsequently confirmed by other researchers in a healthy Ugandan population.[24] Interestingly, platelet counts were significantly lower in adults older than 24 years than among younger people. Moreover, a recent study further supported the possibility that mild thrombocytopenia does not necessarily imply an underlying illness. After monitoring 191 healthy Italian adults with incidentally discovered platelet counts between 100×10^9/L and 150×10^9/L for 64 months, it was concluded that most of them did not develop either a platelet count lower than 100×10^9/L or any other disorder.[25]

Thus, the present investigation corroborates the conclusions of previous studies and suggests that some subjects inherit a predisposition to develop mild, "idiopathic" thrombocytopenia during adult life. At this point, an important question is whether this type of thrombocytopenia should be considered a new form of inherited thrombocytopenia with a very low penetrance and late onset, or whether it represents the lower extreme of the normal range of platelet count. The best way to answer this question is to verify whether affected subjects have a clinical phenotype related to their subnormal platelet counts. We, therefore, searched for a relationship between bleeding and thrombocytopenia in the whole population, and concluded that no association existed. Moreover, we found a similar prevalence of hemorrhages in people with platelet counts between 50×10^9/L and 150×10^9/L (1.3%) and those with platelet counts between 150×10^9/L and 400×10^9/L (0.8%). At variance, bleeding events occurred more frequently (3.7%) in the few subjects with platelet counts lower than 50×10^9/L. On this basis, it seems reasonable to conclude that the mild thrombocytopenia affecting adults in the Ogliastra area should not be considered an illness.

As for thrombocytopenia, the prevalence of thrombocytosis in general population has never been reported in literature. Thus our study provided the first estimate. The 2.3% prevalence we estimated looks surprisingly high, but thrombocytosis was very mild in the vast majority of cases, with only 0.3% of subjects having a platelet count above 500×10^9/L and none having a count more than 1000×10^9/L. We have no data to identify for sure the origin of high platelet counts in Ogliastra villages, but the declining prevalence of this abnormality with age seems to exclude myeloproliferative disorders. Since the frequency of thrombocytosis was significantly different in different villages and was negatively related to that of thrombocytopenia, the previous discussion on thrombocytopenia also applies to thrombocytosis and suggests that the predisposition to this defect was inherited. Whether genetic factors alone were sufficient to produce platelet counts higher than normal or whether additional causes, such

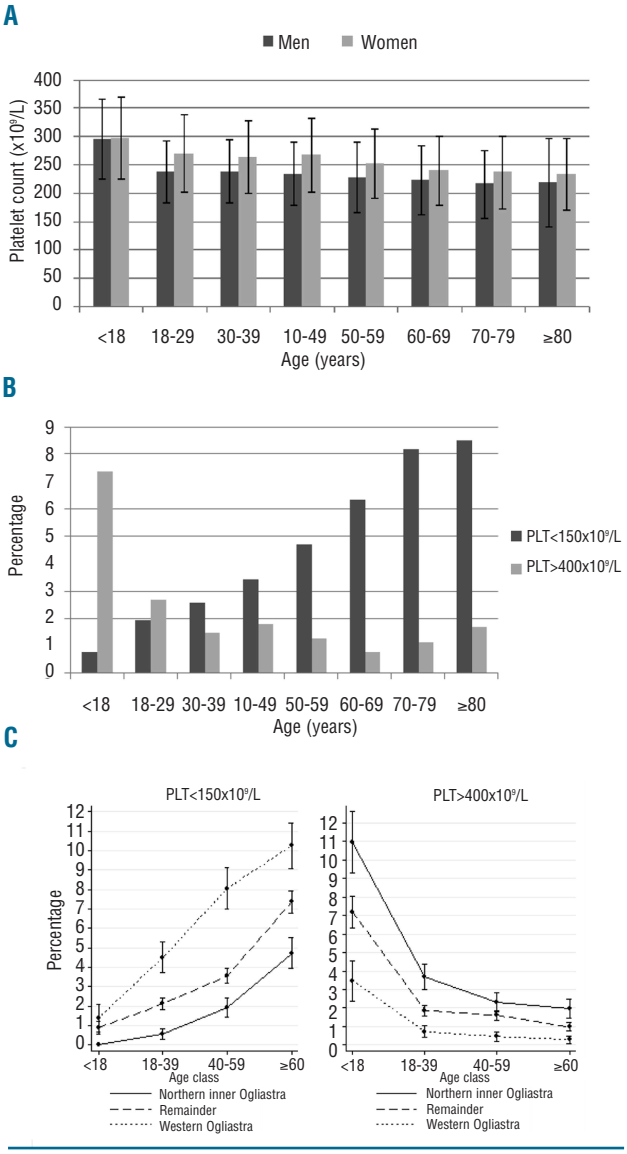

Figure 3. (A) **Platelet count by age and sex. Mean platelet count, with 1 SD, in the overall sample.** (B) **Relationship of thrombocytopenia and thrombocytosis with age. Sex-adjusted age-specific prevalence of thrombocytopenia and thrombocytosis in the overall sample.** (C) **Relationship of thrombocytopenia and thrombocytosis with age by groups of villages. Proportions along with standard errors, are plotted grouping villages as follows: Talana and Urzulei, (northern inner Ogliastra), Seui, Seulo and Ussassai (western Ogliastra), Baunei, Loceri, Perdasdefogu, Escalaplano and Triei (remainder).**

as inflammatory disorders, were required to uncover this propensity is unknown to us, since the Ogliastra database does not include parameters for answering this question. As for thrombocytopenia, it is also important to decide whether thrombocytosis is associated with a clinical phenotype. The observation that thrombotic events were no more frequent in populations with a higher prevalence of thrombocytosis seems to indicate the benign nature of this defect. The finding that none of the 107 subjects with thrombocytosis younger than 18 years developed thrombosis further supports this conclusion. Thus, the mild and transient thrombocytosis affecting young Ogliastra people should not be considered an illness, but rather the highest part of the normal range of platelet count in this population.

From a practical point of view, the results of our study show that an acquired, mild thrombocytopenia does not necessarily indicate the presence of an underlying disorder. Thus, after exclusion of causes of secondary thrombocytopenia and demonstration that thrombocytopenia remains stable over time, affected subjects can be reassured that, in all probability, they are healthy and will not develop severe thrombocytopenia or suffer from bleeding events in the future.

Similar considerations also apply to young subjects with mild thrombocytosis and no signs of myeloproliferative disorders or any other illness: they do not risk thrombosis and, in all probability, their platelet count will return within the normal range in the future.

In other words, the usual normal range of platelet counts is too narrow for the Ogliastra population and exposes people to the risk of being investigated for illnesses that they do not have. Further research is required to ascertain whether the same concept also applies to populations other than the one which we investigated. In this case, considering the possibility that a mild deviation from the normal range of platelet count derives from the genetic background rather than from an illness will become a general recommendation.

In conclusion, analysis of platelet counts in the Ogliastra isolates provided the first estimate of the prevalence of thrombocytopenia and thrombocytosis in a general population, confirmed that platelet count is a highly heritable trait and revealed that platelet number declines with aging. Moreover, it revealed that the propensity to present platelet counts slightly higher than 400×10^9/L or lower than 150×10^9/L is a new genetic trait.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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