HIGH ALTITUDE ADAPTATION

PHYSIOLOGICAL ADAPTABILITY, THYROID FUNCTION,BODY COMPOSITION AND GENETIC VARIABILITY IN CENTRAL ASIA HIGH ALTITUDE POPULATIONS.

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RESUMEN: Adaptabilidad Fisiológica, Función Tiroidea, Composición Corporal y Variabilidad Genética en Poblaciones de Altura de Asia Central

Se recogió datos sobre adaptabilidad fisiológica a la altura, función tiroidea, composición corporal y variaciones genéticas, durante el programa CAHAP (Central Asia High Altitude People). Se estudió a más de 400 varones sanos de cuatro poblaciones diferentes: una muestra de la aldea Sary Tash, Kirghiz, 3200 m (HA); una muestra de Talas, Kirghiz, 900 m; una muestra de Kazakh, valle de Keghen, monta_as de Tien Shan, 2100 m (MA); y una población de baja altura (LA), Uighur, 600 m. En este artículo se examinan veinte variables fisiológicas y somatométricas. Los valores de hemoglobina y eritrocitos son significativamente mayores en las muestras de monta_a que en las de baja altura. Las variaciones en los volúmenes pulmonares son controversiales. No se observó diferencias significativas en los indicadores de función tiroidea (T4 libre y hormona estimulante de la tiroides) entre el grupo HA Kirghiz y el grupo LA Kirghiz. Los resultados sugieren la presencia de adaptaciones fisiológicas a la hipoxia hipobárica en el grupo HA Kirghiz así como en el grupo MA Kazakh. La menor adiposidad de los del grupo MA Kazakh comparada con la del grupo La Uighur para relacionarse con el estrés asociado a al ambiente de altura asi como al estilo de vida. El agua corporal total y el agua extracelular, que se predijeron por los métodos de dilución y de impedancia bioeléctrica, mostraron alta correlación, sugiriendo la posibilidad de del uso confiable de las fórmulas predictivas desarrolladas en sujetos caucásicos. Se analizó los sistemas de grupos sanguineos, las isozimas y los polimorfismos de proteinas séricas con métodos multivariantes. Los mapas genéticos obtenidos usando el análisis de componente principal muestran la centralidad de los Uighurs, Kazakhs y Kirghiz dentro de la amplia variabilidad genética de las poblaciones asiáticas, en concordancia con su centralidad geográfica y la historia compleja del poblamiento de la región.

Palabras claves: Altura, Asia Central, Kirghiz, Kazakh, Uighur, Fisiología, Tiroides, Composición corporal, Antropometría, Variabilidad genética.

RÉSUMÉ: Adaptabilité physiologique, fonction de la thyroïde, composition corporelle et variabilité génétique des populations de haute altitude d'Asie Centrale.

Des données sur l'adaptabilité physiologique à la haute altitude, la fonction de la thyroïde, la composition corporelle et la variabilité génétique ont été recueillies au cours du programme de recherche CAHAP (Central Asia High Altitude People). L'étude a porté sur des sujets sains de sexe masculin, appartenant à 4 populations différentes : un échantillon Kirhgiz de haute altitude (HA) du village de Sary Tash, Pamir (3 200 m); un échantillon de référence Kirghiz de Talas (900 m); un échantillon Kazakh de moyenne altitude (MA) de la vallée de Keghen (montagnes du Tien Shan, 2 100 m) et une population Uighur de basse altitude (LA) (600 m).

Dans cette étude ont été examinées vingt variables physiologiques et somatométriques. Dans les échantillons de montagnes les valeurs d'hémoglobine et d'érythrocytes sont nettement supérieures à celles des échantillons de basse altitude. Les variations de volumes pulmonaires sont controversables. On n'a pas observé de différences significatives dans les indicateurs de la fonction thyroïdienne (T4 libre et hormone stimulante de la thyroïde) entre le groupe Kirghiz HA et le groupe Kirghiz LA. Les résultats suggèrent la présence d'adaptations physiologiques à l'hypoxie hypobare dans le groupe Kirghiz HA, ainsi que dans le groupe Kazakh MA.

Il semblerait que l'adiposité moindre des sujets du groupe Kazakh MA en comparaison avec ceux du groupe Uighur LA soit à mettre en relation avec le stress associé à l'environnement montagneux, aussi bien qu'avec le style de vie. L'eau corporelle totale et l'eau extracellulaire, prédites par les méthodes de

dilution et d'impédance biolélectrique ont montré une forte corrélation, suggérant la possibilité de l'emploi confiable des formules prédictives développées chez les sujets caucasiens.

Les systèmes de groupes sanguins, les isozymes et les polymorphismes de protéines sériques ont été analysés par des méthodes multivariantes. Les cartes génétiques obtenues par analyse du composant principal montrent la position centrale des Uighurs, des Kazakh et des Kirghiz au sein de l'ample variabilité génétique des populations asiatiques, en accord avec leur position géographique centrale et l'histoire complexe du peuplement de la région.

Mots-clés : Haute altitude, Asie Centrale, Kirghiz, Kazakh, Uighur, Physiologie, Thyroïde, Composition corporelle, Anthropométrie, Variabilité génétique.

SUMMARY: Data on physiological adaptability to high altitude, thyroid function, body composition and genetic variations were collected during the CAHAP (Central Asia High Altitude People) research program. More than 400 healthy adult males from four different populations were studied: a high altitude (HA) Kirghiz sample of the Sary Tash village in Pamir (3200 m); a reference Kirghiz sample from Talas (900 m); a middle altitude (MA) Kazakh sample from the Keghen valley (Tien Shan mountains, 2100 m) and a lowland (LA) Uighur population (600 m).

Twenty physiological and somatometric characters are examined in the present report. There are significantly higher values of hemoglobin and erythrocytes in the mountain samples than in the lowland ones. The variations in lung volumes are controversial. No significant differences in thyroid function indicators (free T4 hormone and thyroid stimulating hormone) were noted between HA Kirghiz and LA Kirghiz. Results suggest the presence of physiological adaptations to hypobaric hypoxia in HA Kirghiz as well as in MA Kazakhs.

The lower adiposity in MA Kazakhs than in the LA Uighurs seems to be related to stress connected to the mountain environment as well as to the lifestyle. Total body water and extracellular body water, predicted by the dilution and bioelectric impedance methods, are highly correlated, suggesting the possibility of the reliable use of predictive formulae developed on Caucasian subjects.

Blood group systems, isozymes and serum protein polymorphisms were analyzed with multivariate methods. The genetic maps obtained using Principal Component analysis show the centrality of Uighurs, Kazakhs and Kirghiz within the wide genetic variability of Asian populations, in agreement with their geographic centrality and the complex history of the peopling of the region.

Keywords: high altitude; Central Asia; Kirghiz; Kazakh; Uighur; physiology; thyroid; body composition; anthropometry; genetic variability.

INTRODUCTION

The study of human adaptability to high altitude (HA) in Central Asia populations is an interesting field of research. In fact, there is little information on this topic in the international literature in comparison with the data available for other HA populations, such as Andean Aymaras and Quechuas, Ethiopian Ahmara, and Tibetans, Han, Bothia and Sherpas in the Tibeto-Himalayan region.

Although some studies have been promoted by the Kirghiz Institute of Cardiology in Bishkek and by the Institute of Anthropology of the Moscow State University, many aspects of the biology of HA peoples of Tien Shan and Pamir are still unexplored. Moreover, the results of these studies have been published mainly in Soviet or former Soviet national journals. An interesting, but certainly not recent, general review of HA adaptation in the Pamir and Tien Shan mountains was published in "The biology of HA peoples" (Baker ed.) (1978) by Mirrakhimov, who briefly summarized the results of several studies performed by his research group and by many other Soviet investigators. In the same IBP volume, Frisancho (1978) discussed data on the growth of children in the Tien Shan mountains collected by Psyzuk et al. (1967) and by Miklasheveskaya et al. (1972). Miklasheveskaya et al. (1979) published a review of their studies of HA human growth in "Physiological and morphological adaptation and evolution" edited by Stini.

Subsequently, numerous papers have been published but mainly in Russian (Mirrakhimov, 1972, 1978; Mirrakhimov et al., 1981, 1985, 1987, 1988; Mirrakhimov and Ibraimov, 1982; Ibraimov and Mirrakhimov, 1979; Ibraimov et al. 1990; Aitbaevet alP, 1992; Aldashev et al., 1989; Aliev et al., 1993; Daniiarov et al., 1982, 1992; Episkoposyan et al., 1994; Khmelnitskii et al., 1991; Reshetnikova et al., 1991,1994; Tulebekov et al., 1977). In 1983 an interesting new edition of the 1977 "Adaptive reactions in human populations" (edited by Alexeeva) was published, which also contains an overview of HA adaptation studies. Unfortunately, the data reported is not always useful for comparative studies on account of the peculiar topics investigated and the different methods of data collection and analysis.

The CAHAP (Central Asia High Altitude People) research program has been promoted in collaboration with the Laboratory of Anthropology of the Academy of Science of Kazakhstan. The aim of the project is the collection and analysis of new anthropological and genetic data in HA Central Asia populations in order to have results directly comparable with the information already present in the international literature on other HA peoples and in particular with the original information collected in the Peruvian Andes with the same methods and instruments (Tarazona-Santos et al., present issue). The main objectives of the CAHAP Program are

the study of human adaptability to HiA, body composition, nutrition and genetic variability in Kazakhs of the Tien Shan mountains and in Kirghiz from Pamir. Two Italo-Kazakh expeditions were carried out in 1993 in Kazakhstan and 1994 in Kirghizstan in order to collect new information on these topios.

In the present communication we would like to describe our experimental design, to synthesize the obtained results and to give some preliminary indications regarding further analyses currently in progress.

MATERIAL AND METHODS

Kirghiz, Kazakhs and Uighurs are Turkich-speaking (Altaic linguistic family) populations that settled in the Pamir and Tien Shan mountain ranges during the last 4-5 centuries. From an anthropological point of view they have been defined as TurkoMongolic populations (Alexseev and Gochman, 1983).

In the present research, the high altitude (HA) Kirghiz population of the Sary Tash village in Pamir (3200 m) is compared with a lowland (LA) Kirghiz reference sample from Talas (900 m). To detect possible gradients of human adaptability, data were also collected on middle altitude (MA) Kazakhs from the Keghen valley (Tien Shan mountains, 2100 m) and in a lowland (LA) Uighur population from the Pendjim village (600 m), in Kazakhstan.

Sary Tash is a HA village a few kilometers from the border with Tajikistan, in the heart of the Pamir mountains. The local population numbers around 1500 and is largely concentrated in the village or scattered in outlying areas. It is extremely isolated, especially during the long winter months when it is cut off by snow. Hygiene is primitive and food supplies are scarce: there is no sewer system or water mains. The local economy, based on grazing sheep and goats or raising yaks and horses moved to the mountain pastures during the summer, offers bare survival. Only a small amount of food is imported.

The village of Talas is in the most northerly section of Kirghizstan, along the trade routes to Kazakhstan and Uzbekistan, important since ancient times (The Silk Route). The health and hygiene situation is fair and the local economy, based on farming and cattle raising, ensures complete and abundant food supplies. Numerous bazaars and local markets provide good product distribution.

The Keghen valley is on a high plain a few kilometers from the northern slopes of the Tien Shan range. Although isolated, especially during the winter months, it is a rather hospital place for human settlements. The local economy is mainly based on grazing sheep, goats and horses but also on farming.

The village of Pendjim is in the most eastern section of Kazakhstan, only 18 km from the boundary with China. It is inhabited mostly by Uighurs, who emigrated from the Xing-Chang (Chinese Uighur autonomous region) in recent decades. The local economy is based on farming and cattle raising while some bazaars provide products from China and from the rest of Kazakhstan.

After a preliminary medical analysis, more than 400 fully healthy subjects were studied. They were unrelated adult males, native to the study area. In particular, data were collected during the summer of 1993 from 123 Kazakhs from the Keghen valley and 80 Uighurs from the Pendjim village, while in the summer of 1994, 114 Kirghiz from the Sary Tash village and 91 Kirghiz from the Talas plains were examined.

The following physiometric, anthropometric and genetic variables, selected from the wider information collected during the CAHAP expeditions, are investigated in the present report:

1. ***Adaptability to high altitude.*** Forced Expiratory Volume (FEV) and Forced Expiratory Volume in one second (FEV1) were assessed with a Vitalograph Alpha spirograph, while hematological parameters (hemoglobin, erythrocytes and haematocrit) were measured with an Emo-Flash photometer (Menarini, Florence, Italy). The main somatometric characters involved in adaptability to HA were measured according to the Anthropometric Standardization Reference Manual of Lohman et al. (1988). Thyroid function by concentration analysis of free T4 hormone (FT4) and thyroid stimulating hormone (TSH) was studied in relation to hypoxia and to phenylthiocarbamide (PTC) taste sensitivity (by the Harris and Kalmus method, 1950).

2. ***Body composition.*** Eleven anthropometric variables related to body composition and in particular to adiposity (skinfolds) were measured following Lohman et al. (1988). Total body water (TBW) and extracellular water (ECW) were assessed by D2O and NaBr dilution, respectively. Fat patterning was analyzed by multiple frequency

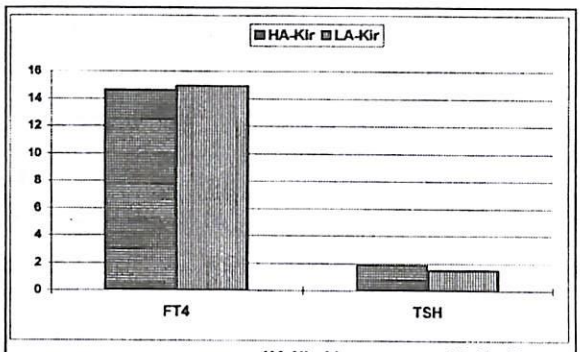
bioelectrical impedance (Human IM Scan tetrapolar impedance plethysmograph, Dietosystem, Milan, Italy).

3. ***Genetic variability***. The distribution of more than 20 "classic" genetic markers and of several mt-DNA (d-loop region) and n-DNA polymorphisms (microsatellites) was examined. In particular, a multivariate analysis of the distribution of blood group systems (ABO, Rh, MNSs, Kell, P, Duffy, Kidd and Diego) is presented in this survey.

RESULTS AND DISCUSSION

1. Adaptability to high altitude

There were no significant differences in thyroid function indicators (FT4 and TSH) between HA Kirghiz and LA Kirghiz (Figure 1). Moreover, no relationships were observed between the PTC Taste Sensitivity distribution and the thyroid function (Facchini et al., 1997).



	HA-Kirghiz			LA-Kirghiz		
	N	Mean	S.D.	N	Mean	S.D.
FT4 (pg/mL)	78	14,6	2,17	70	14,90	2,72
TSH (mIU/mL)	78	1,82	1,11	70	1,49	0,92

Fig.1 Free T4 hormone (FT4) and thyroid stimulating hormone (TSH) values in high (HA) and low (LA) altitude Kirghiz. Differences are not statistically significant.

The discussion of the relations between the hypoxic environment and thyroid function i s interesting because the topicbis still controversial and few is the available data . Many studies have supported the idea that acute, but also chronic (Ramirez et al., 1995), exposure to HA could produce a marked elevation of plasma T3 and T4, while having no influence on (Sawhney et al., 1991) or causing a reduction of (Basu et al., 1995) Thyroid Stimulating Hormone (TSH). More in general, many authors have observed that HA hypoxia could induce an increase in thyroid function (Chakraborty et al. 1987). Nevertheless, studies on animals reported by Frisancho (1993) show that HA exposure leads to reduced thyroid function, perhaps related to a deficient secretion of TSH or a decreased requirement for T4 (and hence a concomitant reduction of hormone synthesis). Also Gambert (1991) supports this last hypothesis and notes that HA populations in the Andes, whose diets are deficient in iodine, have less goiters than people with similar diets living at lower altitude. This should imply that there is an altitude-related increase in T4 sensitivity and thus a decreased requirement for T4.

Finally, during acclimatation to hypoxia, several investigators have reported initial increases in serum T4 and T3 concentrations at HA, followed by decreases toward normal with continued exposure, while TSH levels were normal (Blume, 1984; Ward et al., 1989).

As regards Central Asia, studies carried out in the former USSR (Tien Shan and Pamir Mountains) have shown that healthy local HA populations have a hypofunction of the thyroid gland (Miklashevskaya et al., 1979). Our data are consistent with these observations, suggesting a slightly decreased or normal function of the thyroid gland in HA environments.

In conclusion, studies on humans in acute hypoxia have suggested a temporary increased thyroid function whereas those on humans and animals in chronic hypoxia have indicated decreased or normal function of the thyroid gland. Nevertheless it should be considered that there are two complicating factors in the interpretation of thyroid response to HA: a deficiency of iodine typical of the mountain habitat and the general influence of a cold environment on thyroid function.

As argued by Heat and Williams (1995), both these variables are much easier to control in experimental animals that in humans. In addition, in the study of acute exposure to HA, several experiments have been performed on a limited number of subjects (soldiers or mountain-climbers) but not on large samples (Chakraborty et al. 1987; Blume, 1984; Mordes et al. 1983). There are probablytwo or more different adaptive physiological responses to hypoxia based on the type of exposure (acute or chronic).

Although data analysis of the hematological and pulmonary variations is still in progress, most of the observed values indicate significant physiological adaptive responses to hypoxia both in the MA and HA samples.

In particular, the hematological parameters appear to be altitude-sensitive also at 2100 m. and then they increase at 3200 m. While MA Kazakhs and HA Kirghiz have higher hematological values than

LA Uighurs and LA Kirghiz, no differences were found between MA Kazakhs and HA Kirghiz (Figure 2). The values seem consistent with those reported in the review by Mirrakhimov (1978).

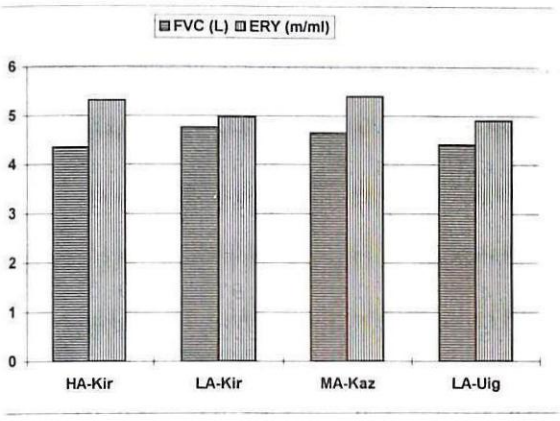


Fig.2 Forced Vital Capacity (FVC) and number of Red Cells (ERY) in the 4 samples: High Altitude Kirghiz (Sary Tash, 3200 m) and Low Altitude Kirghiz (Talas, 900 m), Middle Altitude Kazakhs (Keghen valley, 2100 m) and Low Altitude Uighurs (Pendjim, 600 m). For ERY and FVC the differences are significant ($p<0.001$).

Lung volumes are higher in MA Kazakhs than in LA Uighurs, while the two groups are similar in somatic and chest dimensions. The comparison between HA Kirghiz, LA Kirghiz and MA Kazakhs is complicated by the effects of nutritional stresses in the HA Kirghiz population. HA Kirghiz in fact exhibit lower somatic and chest dimensions than the LA Kirghiz and MA Kazak samples which are characterized by a proper nutrition and a favorable environment (Figure 3). Lung volumes are also lower in HA Kirghiz than in LA Kirghiz and MA Kazakhs (Figure 2).

2. Body composition

The LA Uighurs have higher values than MA Kazakhs for all the characters related to body composition (Table 1). The lower adiposity in MA Kazakhs than in the LA Uighurs seems to be related to stress connected to the environment as well as to the lifestyle (Facchini et al., in press). The data on the HA Kirghiz and LA Kirghiz are still being analyzed, but a clear decrease in adiposity is present in the mountain sample, confirming the effects of the unfavorable HA environment. In fact, the body composition analysis reveals different fat patternings in relation to the different nutritional environments and climatic stresses (hypobaric hypoxia, cold, etc.).

TBW and ECW were assessed in a subsample of 28 MA Kazakhs both by D2O and NaBr dilution, respectively, and by multiple frequency bioelectrical impedance (BI) at 1 and 100 kHz, respectively; formulae developed on a sample of Caucasian subjects with a hydration status similar to that of the study population were applied. TBW and ECW predicted by the two methods are highly correlated and not significantly different. These results suggest that the selected predictive formulae developed on Caucasian subjects may provide a precise and accurate assessment of ECW and TBW in Turko-Mongolic populations (Battistini et al., 1995)

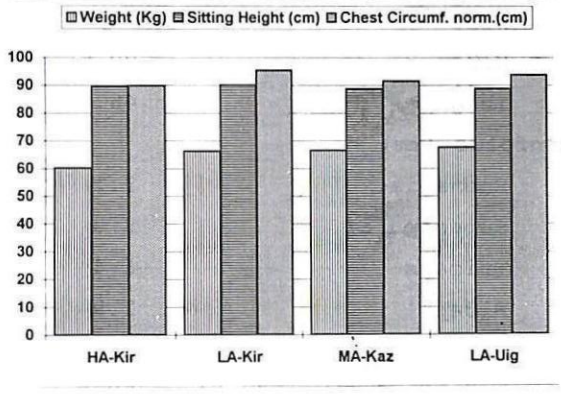


Fig.3 Selected anthropometric variations in the 4 samples: High Altitude Kirghiz (Sary Tash, 3200 m) and Low Altitude Kirghiz (Talas, 900 m), Middle Altitude Kazakhs (Keghen valley, 2100 m) and Low Altitude Uighurs (Pendjim, 600 m). For Sitting Height ($p<0.05$), Chest Circumference ($p<0.05$) and Weight ($p<0.001$) the differences are significant.

3. Genetic variability

The results for the distribution of more than 20 blood group systems, isozymes and serum protein polymorphisms are among the first available for Central Asia. The PTC Taste Sensitivity polymorphism was also tested: in agreement with other data on Kirghiz populations (Ibraimov and Mirrakhimov, 1979; Mirrakhimov and Ibraimov, 1982), a higher PTC Non-Taster frequency was found in HA Kirghiz than in LA Kirghiz (Facchini et al., 1997).

As regards blood group distribution, the samples were typed for the AB O, Rh, MNSs, Kell, P, Duffy, Kidd and Diego systems (Pettener et al., 1996). As an example, Fig. 4 shows the genetic relationships among 31 Asian populations based on the ABO, Rh, Kell and MNSs systems, the most widely studied blood groups.

Tab. 1 Fat patterning variations in Middle Altitude (MA) Kazakhs (2.100 m.) and lowland (LA) Uighurs (600 m.).

	MA-Kazaks (N=122)		LA-Uighurs (N=79)		ANOVA	
	Mean	S.D.	Mean	S.D.	F	p
Age (yr)	32.4	8.7	33.2	12.6		
Height (cm)	169.0	6.4	168.9	5.5	0.02	0.87
Weight (kg)	66.5	8.7	67.6	11.0	0.59	0.45
Body Mass Index (KG/CM2)	23.3	2.6	23.7	3.7	0.94	0.33
Circunferences (cm)						
Upper arm	27.4	2.3	28.4	3.0	7.97	>0.01
Waist	78.5	6.9	81.6	10.3	33.21	>0.01
Hip	90.5	5.6	92.8	6.4	14.46	>0.01
Thigh	46.3	3.2	48.1	3.9	12.92	>0.01
Skinfolds (mm)						
Supraliac	9.1	3.5	12.7	5.9	24.61	>0.01
Subscapular	8.5	2.9	11.5	4.7	31.43	>0.01
Triceps	6.4	2.4	7.6	3.3	6.85	>0.01
Biceps	2.9	0.8	4.2	1.6	66.26	>0.01
Calf	4.6	1.1	6.8	2.4	66.86	>0.01
Arm muscle area (cm2)	50.0	6.9	54.3	9.4	9.25	>0.01
Arm Fat Area (Cm2)	8.5	3.5	10.7	5.3	12.11	>0.01
Ratios (mm;cm)						
Sub. Sk./Tric.sk	1.38	0.29	1.59	0.45	14.5	>0.01
Sup. Sk./Tric.sk	1.46	0.41	1.70	.047	13.6	>0.01
Sub. Sk./Calf sk	1.99	0.64	1.90	0.66	0.7	0.42
Tric. Sk./Calf sk	1.39	0.37	1.14	0.34	18.1	>0.01
Waist/Hip	0.87	0.04	0.88	0.06	2.0	0.16
Waist/Thigh	0.17	0.01	0.17	0.01	0.0	0.92

The first principal component (38.1 % of total variation) describes a regular east to west cline. Caucasoid groups present negative values starting from Turkic, Near East and European averages, while Mongoloids show a tendency to positive values. Along the second component a wide variation is shown by Mongoloid groups in comparison with the narrow range that characterizes Caucasoids. The position of the populations suggests a south to north gradient. On the whole the two components account for 60.3 % of the total variation and give patterns of genetic affinity congruent with the geographic map of Asia. Within this genetic map the four Central Asia samples cluster in the center of the graph at the boundaries between the Caucasoid and Mongoloid groups. The two Kirghiz samples exhibit different trends, the population from the plain being closer to Caucasoids. This is probably related to its more western geographic position and its location along the ancient Silk Route. It is also interesting to note the central position along the first axis of the Himalayan and Tibetan Central Asia mountain populations, which according to geography cluster with negative values for the second axis.

Multivariate analysis shows genetic affinity among Uighurs, Kazakhs and Kirghiz. The new data indicate that the patterns of genetic variability should not affect the reliability of the interpopulation comparisons performed in the present study. Moreover, the four samples present an intermediate position between the major groups of Caucasoids and Mongoloids. The detected genetic centrality of Uighurs, Kazakhs and Kirghiz

is in agreement with their geographic centrality and the complex history of the peopling of the region.

The present results are being confirmed by the assessment of further blood group systems, red cell enzyme polymorphisms and serum proteins. The analysis of several mtDNA (d-loop region) and N-DNA (microsatellites) polymorphisms will allow a complete survey of the genetic composition of the Kazakhs, Kirghiz and Uighurs from Central Asia.

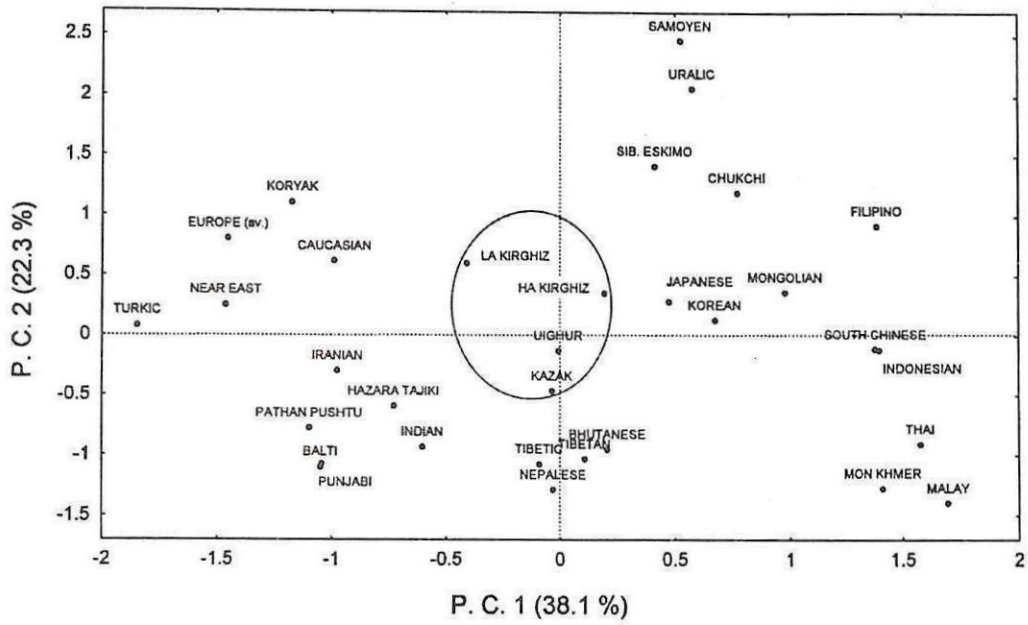


Fig.4 Principal component analysis of genetic variability in selected Asian populations based on blood group systems

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