Genetic of thalassemia intermediate in Kirkuk ethnic groups

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Abstract
On bases of immune-haematological and genetic markers ,the genetic variation among Kirkuk indigenous population was analyzed in this study. In a cross-sectional study of 96 patients with thalassemia intermediate were evaluated by detailed review that undertaken to define the relationships between ethnic origins, phenotype and immuno-genetic markers uniformity in relation to genetic isolation and interethnic admixture. All included patients of this study were subjected to analysis in the hereditary blood diseases centre, including (7(7.2%)) of intermarriages between different ethnic groups origin, whereas the overall consanguinity marriage rate was estimated at (89 (92.7%)) including (43(44.7%)) for first cousin marriages origin. Out of the 89 cases, 37(41.5%), 35(39.3%), and 17(19%) represent Kurdish, Arab and Turkmen ethnic groups, respectively. The distribution of thalassemia major cases within ethnic groups were relatively differs (d.f.2, P< 0.2). kurdish, (37 (41.5%)) represents the highest disease (thalassemia) sufferer group because of its relative low rate of out breeding .

Blood groups (ABO) and Rhesus (D) genetic marker show no significant differences among the triethnic sample groups (thalassemia patients) of Kirkuk with a preponderance of blood group O. No apparent relationship was found between ABO or Rhesus blood groups and the frequencies of thalassemia intermediate cases.The study showed relative genetic heterogeneity and diversity with respect to the immuno-hematological genetic markers. Further, all ethnic populations from Kirkuk were found to harbor thalassemia intermediate genetic marker.Accordingly , all ethnic populations from Kirkuk were found to harbor thalassemia intermediate genetic marker. However this study shows that ethnic groups of Kirkuk population have relative genetic heterogeneity and diversity.

Key Words: • thalassemia •ABO blood groups. Inbreeding •genetic isolation • gentic variation • reproductive isolation

Introduction
Thalassemia intermediate patients are characterized by a transfusion –independent clinical course of intermediate severity between thalsemia major and a symptomatic carriers .Since the definition of thalassemia intermediate is relative, it includes a wide range of clinically and genetically heterogeneous patients. Thalassemia is the most common, inherited single gene disorder in the world (Piomelli and Loew ., 1991) among the several hereditary hemoglobinopathies. Thalassemia is considered one of the most important genetic and public health issues in the state of Kirkuk.

Thalassemia intermediate usually are associated with dysfunction of both beta-globin genes. Clinical severity is intermediate (Hb 7-10 g/dl), and patients rarely transfusion dependent. As the frequency of thalassemia is increased by the consanguinity mating, it may be assumed that the net effect has been the creation of multiple genetic and reproductive isolates, accentuation of certain recessive alleles. However, this clinical consequence of this highly complex differentiation, leads to population heterogeneity and genetic diversity (Cao A, Galanello R.,2002).

Moreover, various evolutionary forces such as waves of people of different ethnic stocks, cultures and languages who either invaded Kirkuk or migrated to Kirkuk from different directions and contributed significantly to the present-day gene pool. These people not only settled in Kirkuk but also gradually merged and mingled with the original local populations. (http://en.wikipedia.org /wiki /Kirkuk pressures).

Ethnic origin and migrations are factors that affecting population genetics which focusing on relative distribution of genes or inherited traits (genetic markers) (Conrad DF and Hurels ME, 2007).

Hence this study aims at studying genetic marker polymorphism (hemoglobinopathies and ABO blood groups) to determine the genetic similarity of different ethnic groups of Kirkuk community ,whether these markers are expressed as clinical phenotype or not. (Risch and Merikanges, 1996; Weatherall, 1998).

Material and method
The study was conducted in the Medical Centre of Hereditary Blood Disorder, azadi hospital, Kirkuk (All patients were visiting this centre for regular follow-up and blood transfusion at fixed monthly intervals). The study was carried out during a 6-month period between October 2007 and March 2008. A total of 96 regular visitor thalassemia intermediate patients (characterized by anemia starting during the first years of life and may requiring blood transfusion therapy for survival (Minnich *et al*., 1954)were referred from all over Kirkuk to medical centre of hereditary anemia for follow-up and blood transfusion.

This study developed a cross-sectional registry to characterize the age, sex, ethnic origins and hematological features of all included thalassemia intermediate patients. Patient data were based on a medical-record review supplemented by patient interview, recorded data in patient case sheet and Laboratorial findings.

Control group
The ABO blood groups distribution of the blood donors from the Central Blood Bank in Kirkuk was used as a control groups for ABO blood groups distribution of the sample group.

Statistical analysis
Statistical analysis was performed using the SPSS 7.5 statistical software package. Continuous variables were expressed as mean ± SD. Chi square test was used to compare variables between patients and controls or between patient groups, and ($P < 0.05$) was considered statistically significant.

Results & Discussion
Ninty six patients with thalassemia intermediate were eligible for the study. Patient's data were obtained from

medical records, and not all the required data were available for some patients.

All patients (96) were belonging of three ethnic origins (Turkmen, Arab, and Kurdish) except seven patients who had a mixed ethnic back ground. Consanguineous marriage has been a historically long standing practice among the different ethnic classes of Iraq. Hereditary diseases like Thalassemia intermediate can prevail in epidemic proportions in areas characterized by high percentage of marriages between relatives (Smith, 1974) that is a common practice in the Kirkuk regions.

The overall consanguinity marriage rate was estimated at (89 (92.7%)) including (43(44.7%)) for first cousin marriages origin, While only (7(7.2%)) have inter-marriages origin between different ethnic groups. Arab versus Turkmen and Arab versus Kurdish inter-marriages were 5(71.4%) and 1(14.2%) ,respectively, whereas Kurdish group shows no out breeding.

Out of the 89 cases, 37(41.5%) , 35(39.3%), and 17(19%) represent Kurdish, Arab and Turkmen ethnic groups, respectively. But the difference was relatively significant at (d.f.2, P< 0.2)

Although the disease is prevalent mainly among Mediterranean peoples, (Leung *et al*; 2005) Countries such as Iraq display a large increase of thalassemia patients due to lack of genetic counseling and screening and breeding the people in the local population. Of the 96 of thalassemia intermediate patients who were interviewed,51 (53.1%) were male and 45(46.8) were female. A non-statistically significant difference was observed between number of male and female thalassemia patients (p= 0.07).

The mean age (mean ± standard deviation [SD]) at diagnosis of all studied cases (96) was 6.0776 ± 6.33 years (median1.0).

Actually, stable populations show more uniform distribution of ages, but in this study, age distribution of thalassemia intermediate patients among different ethnic groups shows most of sample group population was youngs; fewer people were beyond the reproductive age (compared to the age distribution of a growing population), and there were no apparent significant age distribution differences (d.f.6, P<0.05) between different ethnic groups .

Any population with many young (pre-reproductive) individuals and few people beyond reproductive age will increase because many people will enter the prime reproductive age group and few will reach the end of their lifespan. (Lee Ronald., 1994). This type of demographic momentum usually serves as an example of how population growth can be predicted from current age structure, but in the present study, the age-related profiles of sample (thalassemia intermediate patients) have been showed, that fewer people are beyond reproductive which is most likely due to death before reaching the reproductive ages or due to loss of people or due to high inflow of immigrants. Eventually, blood indices results of sample group revealed that the mean values of PCV and hemoglobin levels were 22.22±5.8 and 7.8±6.4 respectively.

Distribution of ABO blood groups

The phenotypes and genotypes of ABO blood groups, become more uniform in high degree intermingled population (Nepali GS. 1965).

Table 1: Distribution of ABO blood groups among the three different ethnic groups &the total of each blood group

Blood group	Turkmen		Arab		Kurdish		Total	
	No	%	No	%	No	%	No	%
A	7	41.1	13	37.1	11	29.7	31	34.8
B	1	5.8	10	28.5	8	21.6	19	21.3
AB	1	5.8	1	0.2	2	5.4	4	4.4
O	8	47	11	31.4	16	43.2	35	39.3
total	17	100	35	100	37	100	89	100

A part of the raw data and results of this study was performed to "penetrate the essence of the racial traits (ABO & Rh blood groups) speciation of thalassemia intermediate patients of Kirkuk populations based on the potential degree of genetic isolation and intermingling.

Phenotype frequency of the four ABO blood groups and the three corresponding allele frequencies of sample group along with data from control groups are shown in Tables 1 &2.

Table 2: Distribution of ABO blood groups among the three different control ethnic groups & the total of each blood group

Blood group	Turkmen		Arab		Kurdish		Total	
	No	%	No	%	No	%	No	%

A	236	23.1	138	21.9	38	15.2	412	21.6
B	295	28.8	117	18.6	78	31.2	490	25.7
AB	176	17.2	157	24.9	19	7.6	352	18.5
O	315	30.8	217	34.4	115	46	647	34
total	1022	100	629	100	250	100	1901	100

In the combined data of thalassemia intermediate patients ,the most frequently occurring blood group is O (39.3%), followed by A (34.8%), B (21.3%)and AB (4.4%). Rhesus blood groupings revealed that the majority of cases (93 (96.8%)) were Rh positive (Rhesus positive), but only 3 cases (3.1%) were represented as Rh negative. ". Chi square test(d.f.2,$P<0.05$) revealed that there were no significant differences between tri-ethnic groups in A,B & O blood groups.

Comparison of ABO blood groups distribution sequences within the studied tri-ethnic groups of thalassemia intermediate patients with those of the studied control group, revealed that there were significant differences (d.f.1,$P<0.05$) in AB blood group distribution only. A similar frequency distribution of the ABO blood groups of the control group has been reported in several other scheduled populations of Asian, such as, Hong Kong, China, where frequency of blood group O & B showed preponderance over that of the other blood groups. (Table 2) (http://en.wikipedia.org/wiki/Blood_type).

The most striking feature that emerged from the present study was the relative genetic isolation in almost all the genetic parameters (sero-haematological) which were studied here among Kirkuk ethnicities. This genetic isolation may be due to reproductive isolation which is a category of the mechanisms that prevent two or more populations from exchanging genes. (Wu and Davis, 1993).

The separation of the gene pools of populations, under some conditions, can lead to the genesis of distinct diversity. (National Human Genome Research Institute. 2005).

Various factors of population structure - such as population size, density, mating pattern, and micro-evolutionary forces like differential selection, migration, etc., - considerably contribute to the diversity within the population. The present analysis indicates that in addition to gene flow and selection, the genetic structure of the ethnic populations of Kirkuk is highly influenced by socio-cultural adaptation and inbreeding.

The present analysis strongly suggests that the infrastructure of these ethnic populations is highly influenced by the local inbreeding within each ethnical population.

Thus, the study suggested that the Kirkuk ethnic groups should intermarry more with each other in order to reduce the heterogeneity and the number of recessive genes alleles. However, the study also recommends public education, Population screening, genetic counseling and prenatal diagnosis as successful programs for genetic prevention.

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وراثة فقر الدم للبحر المتوسط في المجتمعات الاثنية في كركوك

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الملخص

اعتمادا على المؤشرات المناعية والدموية والجينية فان التغايرات الجينية في مجتمع كركوك قد حللت في هده الدراسة التي أجريت على ٩٦ مريض بالثلاسميا.وتمت مراجعة تنقيحية للتعرف غلى العلاقة بين المجاميع الاثنية ،والنشاءة الانموطية وتوحد المؤشرات المناعية الجينية على خلفية الانعزال الجيني والاختلاف بين المجاميع الاثنية. كل المرضى (٩٦ مريض) اخضعوا للدراسة في مركز أمراض الدم الوراثية في كركوك ،٧(٧,٢%) من المرضى كانوا نتاج لتزاوج بين أقليات مختلفة حيث كانت نسبة زواج الأقارب ٨٩(٩٢,٧%) ومن ضمنهم ٤٣(٤٤,٧%) زواج أولاد العم. من ال٨٩ مريض كان ٣٧(٤١,٥%) ، ٣٥(٣٩,٣%) ،١٧(١٩%) يمثلون اقليات الأكراد والعرب والتركمان على التوالي.وان توزيع مرضى الثلاسميا الراشد في مجموع الأقليات كان نسبيا مختلف ($d.f.2,P<0,2$).اظهر العرب أدنى نسبة ٣٧(٤١,٥%) من المرضى وذلك بسبب النسبة العالية من التزاوج خارج الأقارب.

وأظهرت الدراسة عدم وجود فروق ذات دلالة إحصائية في توزيع مجاميع الدم(ABO&Rh)مابين مختلف الأقليات في كركوك مع زيادة نسبة مجموعة الدم O على بقية المجاميع.وعدم وجود علاقة مابين مجموعات الدم وتكرار مرض الثلاسميا البالغ .

خلصت الدراسة إلى وجود نسبة من التغاير والاختلاف في المؤشرات المدروسة .علاوة على ذلك وجدت الدراسة أن جميع الأقليات تكمن مرض الثلاسميا الراشد.