Iranian J Publ Health, Vol. 42, No. 9, Sep 2013, pp. 1007-1015

Original Article

Identification of Mutation of Glucose-6-Phosphate Dehydrogenase (G6PD) in Iran: Meta- analysis Study

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(Received 24 Feb 2013; accepted 11 Jun 2013)

Abstract

Background: Glucose-6-phosphate dehydrogenase is one of the most common genetic deficiencies, which approximately 400 million people in the world suffer from. According to authors' initial search, numerous studies have been carried out in Iran regarding molecular variants of this enzyme. Thus, this meta-analysis presented a reliable estimation about prevalence of different types of molecular mutations of G6PD Enzyme in Iran.

Methods: Keywords "glucose 6 phosphate dehydrogenase or G6PD, Mediterranean or Chatham or Cosenza and mutation, Iran or Iranian and their Persian equivalents" were searched in different databases. Moreover, reference list of the published studies were examined to increase sensitivity and to select more studies. After studying titles and abstracts of retrieved articles, excluding the repeated and unrelated ones, and evaluating quality of articles, documents were selected. Data was analyzed using STATA.

Results: After performing systematic review, 22 papers were entered this meta-analysis and 1698 subjects were examined concerning G6PD molecular mutation. In this meta-analysis, prevalence of Mediterranean mutation, Chatham mutation and Cosenza mutation in Iran was estimated 78.2%, 9.1% and 0.5% respectively.

Conclusions: This meta-analysis showed that in spite of prevalence of different types of G6PD molecular mutations in center, north, north-west and west of Iran, the most common molecular mutations in people with G6PD deficiency in Iran, like other Mediterranean countries and countries around Persian Gulf, were Mediterranean mutation, Chatham mutation and Cosenza mutation. It is also recommended that future studies may focus on races and regions which haven't been taken into consideration up to now.

Keywords: G6PD, Mediterranean, Chatham, Cosenza, Mutation, Iran

Introduction

G6PD (Glucose-6-phosphate dehydrogenase) is one of the most important body enzymes which exists in different cells like red blood cells (1-2). G6PD deficiency is one of the most prevalent genetic deficiencies, which approximately 400 million people in the world suffer from. G6PD deficiency can result in problems such as mental retardation, renal failure, infant jaundice, liver dis-

eases and chronic anemia. Children or adults with this deficiency will experience severe life-threatening hemolytic attacks in a case they use some materials including Anti-malaria drugs, oxidative materials or fava bean (1-4).

G6PD deficiency varies in terms of variation and spread (3). Approximately, 7.5% of people around the world carry one or two deficient G6PD genes (1). In studies carried out in this regard, prevalence of G6PD deficiency in Pakistan, UAE, Saudi Arabia, Kuwait, Bahrain, Oman, Egypt and Iran was 2-8, 11, 2-26, 19, 21, 27, 1 and 11.5% respectively(4, 5). Also, its prevalence varies in different areas of Iran. For example, its prevalence was 3.2 in 2501 screened infants in Esfahan (centre of Iran) (6) and 2.1% in Zanjan (Center and North West of Iran) (7).

Previous researches on prevalence of G6PD molecular variants reveals that Mediterranean, Chatham and Cosenza mutations are the most common mutations in Iran with the highest frequency attributable to Mediterranean mutation (1). Prevalence of Mediterranean and Chatham mutation were 86.4 and 9.71% respectively in Gilan (5, 8). Moreover, Mediterranean mutation prevalence was reported 91.2% and 66.2% in Kurdish (West of Iran) (9) and Mazandaran (North of Iran) (5, 8).

Preliminary electronic search in addition to researchers professional experiences reflect the fact that several studies have been carried out on determining molecular mutation of G6PD and each of them has reported different level of these mutations. However, researchers are still using similar designs and methodology which impose huge financial and non-financial burden; if we can present a more convincing and acceptable estimation from the results of previous studies, a new strategy and process may be used in future research.

One of the most important research methods which help us prepare the best estimation for prevalence of a factor in society is a systematic review and meta-analysis. Although meta-analysis was just used, in the past, in clinical work-measuring studies, it is now used to combine results of descriptive-analytical studies for various phenomena.

Since no meta-analysis has been done to combine results of prevalence of different types of molecular mutations in people with G6PD deficiency in Iran, we decided to present a reliable estimation of prevalence of different types of molecular mutations of G6PD enzyme through extracting and collecting all available reports, documents and studies using systematic review methods, combining their results using meta-analysis and concerning limitations and considerations related to heterogeneity.

Methods

Study design

The present research is a systematic review and meta-analysis to determine prevalence of molecular mutations of G6PD enzyme in Iran relying on document review

Search strategy

To find studies published electronically between 1990 and 10/11/2012, articles published in foreign and domestic journals in Persian databases of "SID, Iranmedex, Magiran, Medlib and Irandoc" and English databases of "PubMed, Google Scholar and WHO Site" were used. The search process was implemented using Persian and English keywords including glucose 6 phosphate dehydrogenase or G6PD, Mediterranean and mutation, Chatham, Cosenza, Iran or Iranian, names of provinces of Iran and conjunctions "and" and "or" and their Persian equivalents. Moreover, reference list of these studies was reviewed for more sensitivity and selection of more relevant studies which we could not access through databases. Research evaluation was done randomly by one of the researchers; it was shown that no study was excluded. Meanwhile, to access findings of unpublished studies, we corresponded with experts and experienced people in this field; unfortunately, no unpublished study was found.

Study selection

Full text or summary of all articles, documents and reports obtained from our research were extracted. After studying titles, repeated papers were

excluded. It is worth mentioning that to avoid publication bias, findings were examined by researchers to recognize and exclude repetitive studies. Then, articles were carefully studied by researchers and the relevant articles were selected and irrelevant ones were excluded.

Quality evaluation

After the relevant studies were determined in terms of title and content, STROBE checklist containing question on: "molecular analysis of different mutations, research objectives, studied subjects, presentation of findings suitably and presentation of results based on objectives" was applied to evaluate quality of documents. Every question had one score and any paper which obtained four scores entered to meta-analysis. Since we did not want to enter the score of "study quality" as an independent variable in meta-regression model, we ignored questions like "carrying out a research by a well-known university or organization, carrying out a research by an expert or experienced person and publication of an article in a well-known journal with high impact factor, etc."

Extracting data

Data was extracted by researchers in terms of "article title, corresponding author, research year, sample size, research place, prevalence of Mediterranean, Chatham and Cosenza molecular mutations, and type of molecular analysis used in every study" and data entered Excel program.

Study inclusion criteria

All studies which have reported the prevalence of G6PD molecular mutation in Iran and also achieved the minimum quality score were included in the study.

Study exclusion criteria

In the first hand, some irrelevant studies were excluded after their titles, abstracts and full texts were studied. Then quality of the remaining papers was evaluated against the STROBE checklist; accordingly those that achieved scores less than four (out of six) were also excluded.

Analysis

To analyze data, Stata Software was used. Standard error of prevalence of G6PD molecular mutations was calculated in every study according to binomial distribution formula. Finally, Cochran's test was used to determine heterogeneity index among studies. According to heterogeneity results (with Meta command in meta-analysis), random effects model was used to estimate prevalence of G6PD molecular mutation in Iran. Finally, meta-regression method was used to study the effects of variables which were determined as probable sources of heterogeneity in studies. Point estimation of G6PD molecular mutations prevalence with confidence interval of 95% was calculated in forest plots; in this plot, square size showed weight of every study and lines in its both sides showed confidence interval of 95% (Fig. 1-3).

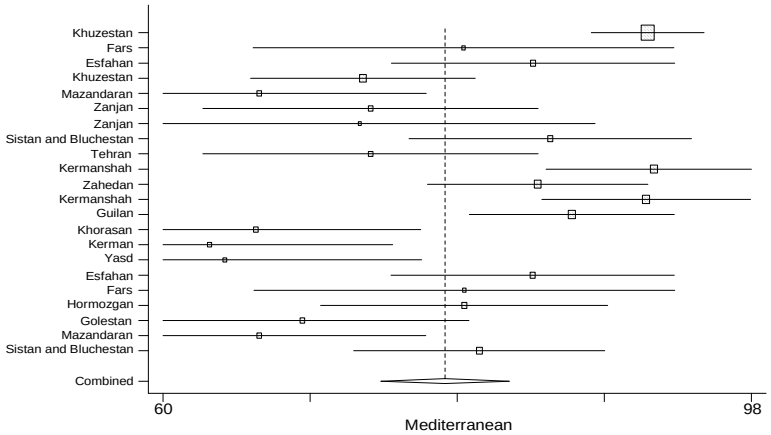

Fig. 1: Difference the estimated prevalence of Mutation of Mediterranean in each study and overall. This chart shows that the range in prevalence of Mutation of Mediterranean is 68.04-90.7 (Based on analysis Bayes)

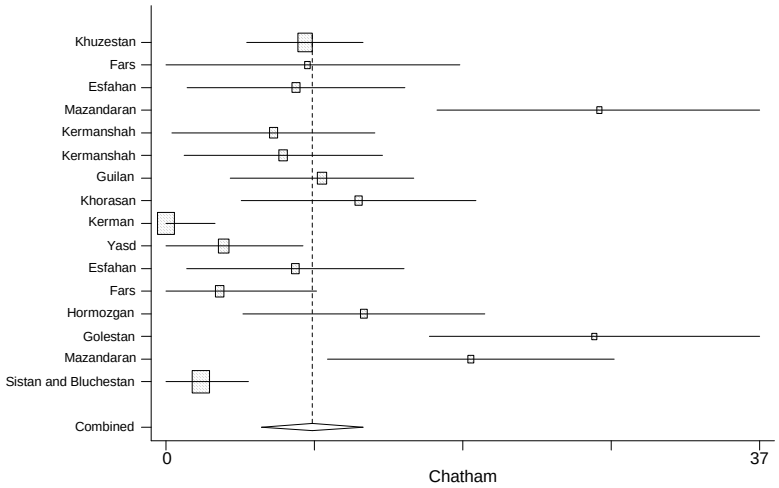

Fig. 2: Difference the estimated prevalence of Mutation of Chatham in each study and overall. This chart shows that the range in prevalence of Mutation of Chatham is 0.7-18.6 (Based on analysis Bayes)

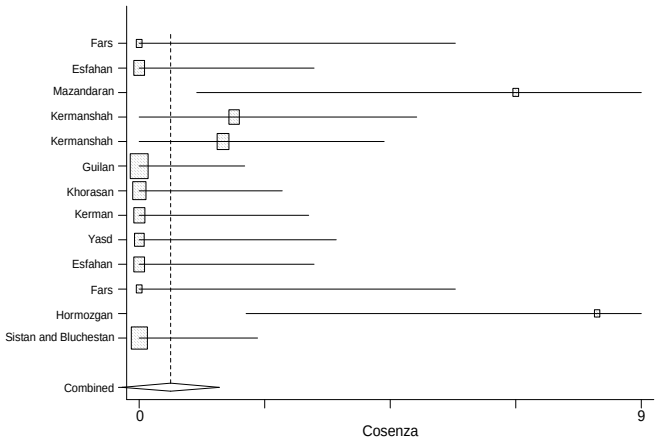

Fig. 3: Difference the estimated prevalence of Mutation of Cosenza in each study and overall. This chart shows that the range in prevalence of Mutation of Cosenza is 0.52-0.62 (Based on analysis Bayes)

Results

Using relevant keywords and "or" operator, the maximum sensitivity was ensured for selecting articles and documents (No. of articles selected in the first step: 1648). Then using "and" operator and increasing the specificity of the study, 388 relevant articles were selected and their abstracts were studied, as a result, 294 articles were selected. Of them, 197 ones were repeated due to database overlap and thus were excluded. After full text of the remaining articles was reviewed, 72 articles were excluded because they weren't related to objectives of this meta-analysis. All 23 remaining articles, whose qualities were evaluated using a checklist, achieved the minimum score of entering this meta-analysis; however, results of two articles were excluded due to repetition of findings and cross publication bias (double publishing in two different journals). Moreover, one more article was added after searching the references of the articles (Fig. 4).

Twenty two papers (5,8-24) reported the prevalence of G6PD Mediterranean molecular mutation in various regions of Iran, and 1698 subjects were examined; this sample size varied from 33 subjects in Mortazavi's study (15) to 231 subjects in Ghaderi Gandman's study (10) (average: 77.2 and mean:66 samples in every study). Among these studies, prevalence of Mediterranean mutation varied from 63% in Noori Delooli's study (20) to 91.7% in Mozafari's study (17). Prevalence of Mediterranean mutation in Iran was 78.2 (74.1-82.3) according to random effect model (Table 1). The variable "place" entered meta-regression model as a heterogeneity probable factor; it was shown that place caused heterogeneity in different studies (coefficient=2, P=0.0001). Totally 1233 subjects were examined in 16 studies which reviewed the prevalence of Chatham molecular mutation.

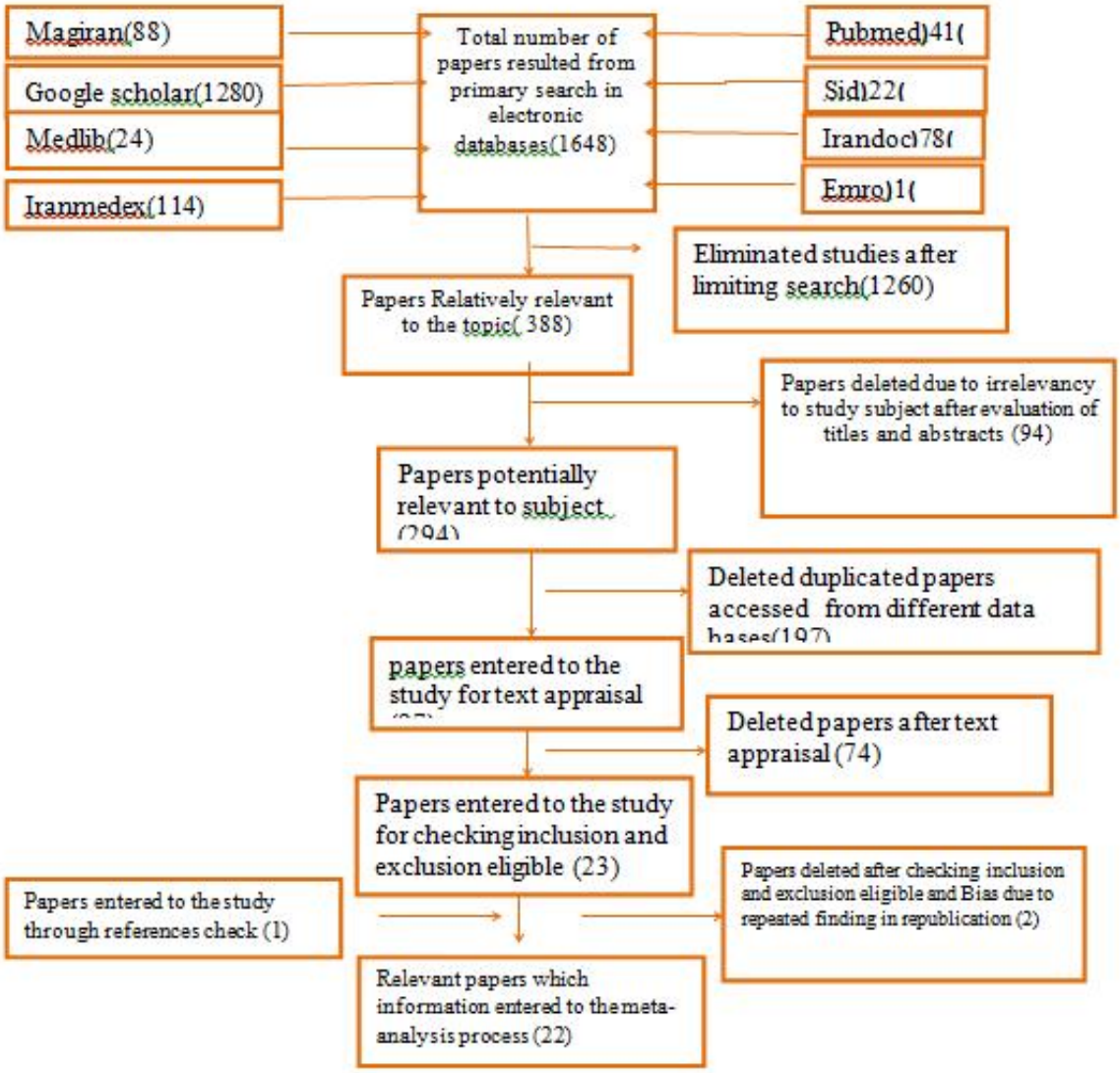

Fig. 4: Papers search and review flowchart

Sample size in different studies varied from 34 samples in Hashemi Gorji's study (11) to 231 samples in Ghaderi Ganomi's study (10). Among different studies carried out in this regard, prevalence of Chatham mutation varied from 0% in Noori Dalooli's study (20) to 27% in Masbanmani's study (13). Moreover, provenance of Chatham molecular mutation in Iran in this meta-analysis was 9.1 (5.9-12.3) (Table 1). It is worth mentioning that the variable "place" had no role in heterogeneity in different studies according to meta-regression model (coefficient=-0.2, *P*=0.7).

Total sample size of 857 subjects was tested in 13 studies that reviewed prevalence of Cosenza molecular mutation. Sample size which entered this meta-analysis varied from 34 subjects (21) to 103 subjects (19). Prevalence of Cosenza molecular mutation varied from 0% in Khorasan, Kerman, Fars, Esfahan, Yazd, Gilan and Sistan and Baloiuchestan to 8.2% in Hormozgan. In this met-analysis, prevalence of Cosenza molecular

mutation in Iran was 0.5 (-0.3-1.4) according to fixed effect model (Table 1).

All samples entered this meta-analysis were analyzed using PCR-RFLP method, except Mesbahnamin's in which Cosenza (1376 G → C) was carried out using combination of SSCP, DNA sequence analysis and Bsu36 I restriction enzyme digestion of PCR-amplified exons 11–13.

Table1: Description of the studies included in the meta-analysis

Authors	Year of publication	Sit of study	Molecular Mutation type					
			Mediterranean		Chatham		Cosenza	
			Sample size	Prevalence	Sample size	Prevalence	Sample size	Prevalence
Ghaderigandomani(10)	2011	Khuzestan	231	91.3	231	8.66	-	-
Hashemigorji(11)	2009	Fars	34	79.4	34	8.8	34	0
Hashemigorji (11)	2009	Esfahan	62	83.9	62	8.1	62	0
Kazeminezhad(12)	2009	Khuzestan	144	72.91	-	-	-	-
Mesbannamin (13)	2002	Mazandaran	74	66.21	74	27	74	6.75
Mortazavi(14)	2002	Tehran	64	73.4	-	-	-	-
Mortazavi(15)	2006	Zanjan	33	72.7	-	-	-	-
Mortazavi(16)	2010	Sistan and Bluchestan	59	85	-	-	-	-
Mortazavi(16)	2010	Tehran	64	73.4	-	-	-	-
Mozafari(17)	2009	Kermanshah	60	91.7	60	6.7	60	1.7
Nakhaee(18)	2012	Sistan and Bluchestan	101	84.2	-	-	-	-
Rahimi(9)	2006	Kermanshah	68	91.2	68	7.3	68	1.5
Nooridaloii (19)	2003	Guilan	103	86.4	103	9.71	103	0
Nooridaloii (5)	2006	Khorasan	76	66	76	12	76	0
Nooridaloii (20)	2008	Kerman	64	63	64	0	64	0
Nooridaloii (20)	2008	Yasd	55	64	55	3.6	55	0
Nooridaloii (21)	2009	Esfahan	62	83.87	62	8.06	62	0
Nooridaloii (21)	2009	Fars	34	79.46	34	3.34	34	0
Nooridaloii (22)	2006	Hormozgan	73	79.45	73	12.33	73	8.21
Nooridaloii (23)	2004	Golestan	71	69	71	26.7	-	-
Nooridaloii (8)	2007	Mazandaran	74	66.2	74	19	-	-
Nooridaloii (24)	2005	Sistan and Bluchestan	92	80.42	92	2.17	92	0
Combined based on random or fixed method			1698	78.2(74.1-82.3)	1233	9.1(5.9-12.3)	857	0.5(-0.3-1.4)
	Heterogeneity test	Q		103.8		73.3		12.4
		p		0.0001		0.0001		0.4

Discussion

This meta-analysis which was carried out with a systematic strategy, presented an estimation of prevalence of different types of G6PD molecular mutations in Iran. Mediterranean, Chatham ،Cosenza and G6PD A mutations were the studied mutations in Iran, whereas, in some studies the

molecular mutations were unknown. Prevalence of Mediterranean, Chatham، and Cosenza molecular mutations in people with G6PD deficiency was estimated 78.2%, 9.1% and 0.5 percent respectively. Additionally, none of the studies which investigated G6PD A in people with G6PD deficiency, confirmed the prevalence of this mutation.

Mediterranean mutation is a point mutation in nucleotide No. 563 of G6PD gene and changes Cytosine base to Thymine base (C563T) in exon No. 6 of gene (encoding area). This movement causes phenylalanine amino acid to replace serine amino acid in G6PD protein in place No. 188. Mediterranean mutation is the second common abnormality and is mainly associated with favism (1, 11). The highest prevalence of Mediterranean mutation is found in Kermanshah and Khoozestan and other provinces of Iran have also reported high prevalence; whereas the lowest frequency was reported in Kerman (63%) (12, 17, 20). Its prevalence in neighboring countries like Saudi Arabia, Oman, Turkey, India, UAE and Pakistan is 80, 74, 77, 60.4, 55.5 and 76% respectively. Its prevalence is also high in countries on the Mediterranean coast like Spain, Italy and Greece (1, 3-5, 10, 11); it can be said that its prevalence is similar in Iran, in neighboring countries and in countries on the Mediterranean coast (according to results of this meta-analysis).

Chatham mutation is the second most common mutation (after Mediterranean mutation) in some provinces of Iran (9). Its variety is as a result of a single-base mutation in exon No. 9 of G6PD gene. This mutation is because of substitution of Guanine base for Adenine base in Nucleotide No. 1003 (G 1003 A). This mutation is the cause of class II of G6PD deficiency which creates one of the most severe G6PD deficiency types and severe hemolytic anomia although it has less than10% of normal enzymes (1, 9). Different provinces reported different frequencies of Chatham mutation prevalence (10-20). The highest frequency was reported in north of Iran (Mazandaran and Golestan: 27 and 26.7% respectively) (13). These figures are equal to the highest frequency in the world and are similar to its prevalence in Italy. Prevalence of Chatham mutation in Japan, Spain, Oman, Indonesia, Kuwait, Jordan, and Brazil is 2, 2, 10, 7.1, 7.1, 8.82 and 0.66% respectively that according to the present meta-analysis, prevalence of this mutation in Iran is higher than its prevalence in the mentioned countries (1, 25-28).

Cosenza mutation is due to substitution of Guanine base for cytosine in Nucleotide 1376 G-C cDNA G6PD which changes Arginine Amino Acid in position 459 to Proline (Arg 459 Pro). This type was first recognized in Italy and its phenotype is associated with severe enzyme deficiency (1, 9). Prevalence of this molecular mutation was low in this meta-analysis. It was high in Hormozgan and Mazandaran (8.21 and 6.75% respectively) (8, 22). Most provinces of Iran which examined this mutation in people with G6PD deficiency, reported zero mutation. However, Cosenza mutation has been reported in eastern Mediterranean countries and Mediterranean countries, especially Italy.

Prevalence of G6PD A^- an African originated mutation was zero in different parts of Iran according to a study which examined 857 patients with G6PD deficiency across different areas of Iran (9); however, its prevalence is high in different parts of the world. For example, it is high in Algeria, Africa and South Africa. Even in Kuwait, its mutation is higher than Mediterranean mutation (1, 9, 27).

Non-access to some unpublished reports and studies may be the probable limitation of this meta-analysis. Nevertheless, according to authors of articles entered this meta-analysis and to references of these articles, the first research published in Iran regarding different types of molecular mutations in people with G6PD deficiency was in 2002; owing to rapid publication of articles electronically, it is almost impossible to miss a relevant article in this regard.

Since type of mutation remained unknown in some samples examined in different studies, more molecular studies must be carried out to recognize all mutations in Iranian population. Moreover, all studies focused on 43% of Iran provinces which have high prevalence of G6PD deficiency. Thus, owing to racial and ethnic variety in different parts of Iran, further research must be carried out on

ethnicities, races and regions which haven't been taken into consideration.

Conclusion

This meta-analysis showed that in spite of prevalence of different types of G6PD molecular mutations in center, north, north-west and south of Iran due to various ethnicities like Kurds in west, Arabs and Fars people in southwest and south, Balouch people in southeast and other populations in north of Iran as well as prevalence of malaria in the past and even now (in different studies, a direct relationship was reported between G6PD deficiency and prevalence of Malaria), the most common molecular mutations in people with G6PD deficiency in Iran are Mediterranean, Chatham and Cosenza types accordingly (like most countries on Persian Gulf and Mediterranean countries).

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors declare that there is no conflict of interest.

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