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Genetic Counseling for Families with Sporadic Intellectual Disability in North of Iran: A Retrospective Study

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Abstract

Background: Intellectual Disability (ID) is a heterogeneous disorder, in which at least 600 genes participate. The present study aimed to identify the effect of genetic counseling and consanguinity marriage in Iranian families with sporadic mental disability.

Materials and Methods:
In this retrospective cross-sectional study, we examined 151 families with a sporadic mental disability referred for genetic consultation to the Welfare Center of Sari city, North of Iran.

Results: About 41.05% (n=62) of the cases were consanguinity marriage. In this study, other diseases were also observed with ID. The following four types of consultations were also reviewed, most of which were Diagnostic Counseling (DC) (60%). According to the inheritance pattern analysis, the share of non-hereditary cases was higher compared to the share of hereditary and unknown cases. The results of the present study showed a significant difference between consanguinity marriages and potential genetic etiology ID (P=0.012). Besides, there was no significant difference between other groups.

Conclusion: In this study, we highlighted the importance of genetic counseling and found that consanguinity marriage was a key factor in the development of the disease in our society. Therefore, given the high cost of genetic tests and socio-economic problems, it is wise to include genetic counseling to prevent many diseases such as mental disability before birth.

Key Words: Consanguinity marriage, Genetic counseling; Intellectual disability, Sporadic

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1- INTRODUCTION

Intelligence is a set of reasoning, planning, problem-solving, thinking, understanding complex issues, fast learning, and learning from experience. Intellectual Disability (ID) is an advanced neurological disorder, in which these three main characteristics: cognitive impairment, adaptive functioning, and the onset of growth (1). According to the ID definition, a neurological disorder is defined as a significant deficit in cognitive functioning and adaptation beginning before 18 years old and is confirmed by a diagnostic method with an Intelligence Quotient (IQ) of less than 70.1. Since this disorder is highly heterogeneous, there is no single inheritance pattern, therefore, it is considered as the dominant autosomal and recessive and X-linked disorder (2). The ID affects Approximately 1 to 3% of the world's population suffers from the ID (3).

Its intensity varies from mild to severe. The ID can occur in several ways and at different ages among pediatrics. There are several origins of this disorder: genetic disorders, environmental causes, brain injury, brain disorders, nutrition deficiencies, and metabolic errors among infants (4). The origins of the ID include genetic abnormalities, environmental, prenatal, and postnatal environmental factors. Various genes with different inherited states contribute to the pathogenesis of ID and are known as heterogeneous genetic disorders (5).

Genetic origins are very heterogeneous, so far more than 600 ID-related genes have been identified (6). Although environmental causes of ID are still important, for example, fetal alcohol syndrome and congenital viral infection, it has been found that genetic factors play a more significant role to contribute to the disease (7). In general, a specific genetic cause is more likely to be involved in severe and syndromic forms compared to the mild and non-syndromic forms. However, the diagnostic method is similar among ID categories. The law of disability of the findings of the examination is crucial in resolving whether the disorder is syndrome or non-syndrome (8). Symptoms of the underlying syndrome include abnormal growth patterns, facial or peripheral dysphoric, skin and hair abnormalities, neurological symptoms, hepatosplenomegaly, and skeletal changes (4). Suspected ID may develop during infancy, although children of less than 5 years old are usually affected worldwide. ID could be more easily diagnosed at 5 years old when the cognitive abilities become more stable. Children with ID may have a history of delaying talking, sitting, crawling, or walking (9).

Receiving and diagnosing using the brain MRI is recommended if there are microcephaly, macrocephaly, seizure, or neurological symptoms. Testing and diagnosis using the two specific genetic testing technologies: Chromosome MicroArray (CMA), and Next-Generation DNA Sequencing (NGS. Chromosome Micro Arrays, fragile X testing, and urinary metabolic screening should be carried out on all children with ID).

It is worth noting that children with ID are more likely suffer from other diseases, including cataracts, visual and hearing impairments, congenital heart disease, constipation, obesity, and sleep disorders, which may lead to additional referrals, such complications side effects not only affect overall performance and quality of life but can also increase challenging behaviors. Metabolic disorders are an important cause in the identification and their diagnosis is very crucial since they are often progressive and may require specific treatment. Besides, most of them are autosomal recessive, so the risk of recurrence is high (4). Consanguineous marriages are an important factor in the transmission of mental disability in children from families with ID history.

This is a social issue, primarily. Consanguineous marriages are common worldwide as in Iran. The culture and practice of marriage are different according to geography in this country. Iran is a country with a relatively high rate of consanguineous marriages (40%). In the urban area, there is also a high heterogeneous rate that the large genetic sample population has been neglected, trying to discover genes involves in Autosomal Recessive Intellectual Disability (ARID) in the country (10, 11).

Chromosomal abnormalities such as Down's syndrome along with fragile X syndromes include up to 15% of ID cases. Overall, 8% of total ID and 11.5% of all ARID genes have been identified in several studies conducted on the Iranian population (12). The purpose of this study was to investigate the role of consanguinity marriages and genetic counseling in the birth of mentally handicapped children, as well as the role of genetic counseling in preventing this disorder.

2- MATERIALS AND METHODS

2-1. Study Design and Sample Population

In this retrospective study, we examined 151 families of patients with a sporadic mental disability, who referred to welfare centers in Sari city, Mazandaran province of Iran, and had complete available files.

2-2. Methods

Baseline checklists were designed to gather patients' information from files, including sex, age, family history of ID, type of consanguinity marriage, genetic counseling, and patterns of inheritance, referral time, other disease or syndrome, and the results of genetic tests.

2-3. Laboratory Tests and Measurements

Two categories of genetic testing were used to identify the cause of the disease including molecular and cytogenetic tests.

2-4. Intervention

To determine the type of inheritance pattern, the pedigrees were evaluated for hereditary, non-hereditary, and unknown cases. Afterward, it was evaluated for syndromic or non-syndromic characteristics. Primarily, individuals with ID were examined using their karyotypes to determine the contribution of numerical/structural chromosome abnormalities. Afterward, to identify gene mutations, different molecular methods such as DNA sequencing and MLPA were applied. For non-syndromic ID, we examined karyotypes like the syndromic patients and then, primarily. DNA sequencing was applied as syndromic patients. We also followed up patients for other disorders rather than mental handicaps because mental disability is usually associated with other disorders as well.

2-5. Ethical Consideration

All required ethical issues including the principle of confidentiality and informed consent were included in this study and were approved by the ethics committee of Mazandaran University of Medical Sciences. In this study, parents of the subjects were informed about the aim of the study and also the written consent was taken from them.

2-6. Inclusion and Exclusion Criteria

In this study, the families with one child who were suffered from the confirmed ID after diagnostic, psychological procedures such as IQ tests and other cognitive tests were included. Loss of data from the initial assessment, withdrawal of the child's family from the examination, the child's mortality, was also the exclusion criteria of the present study,

2-7. Data Analyses

The results of this study including demographic and clinical features of the patients were analyzed using SPSS V.22 (SPSS Inc., Chicago, IL, USA). To describe the data, descriptive statistics and Chi-square tests were applied. Kolmogorov-Smirnov test was employed to assess the normal distribution. Mann-Whitney U and Chi-square tests were used to analyze the data and a P-value < 0.05 was considered as statistically significant.

3- RESULT

In this study, 151 families with Sporadic ID patients from *Mazandaran* province were studied. The type of marriage was examined, primarily. Approximately, 41% of the patients had consanguinity marriages (**Figure. 1**).

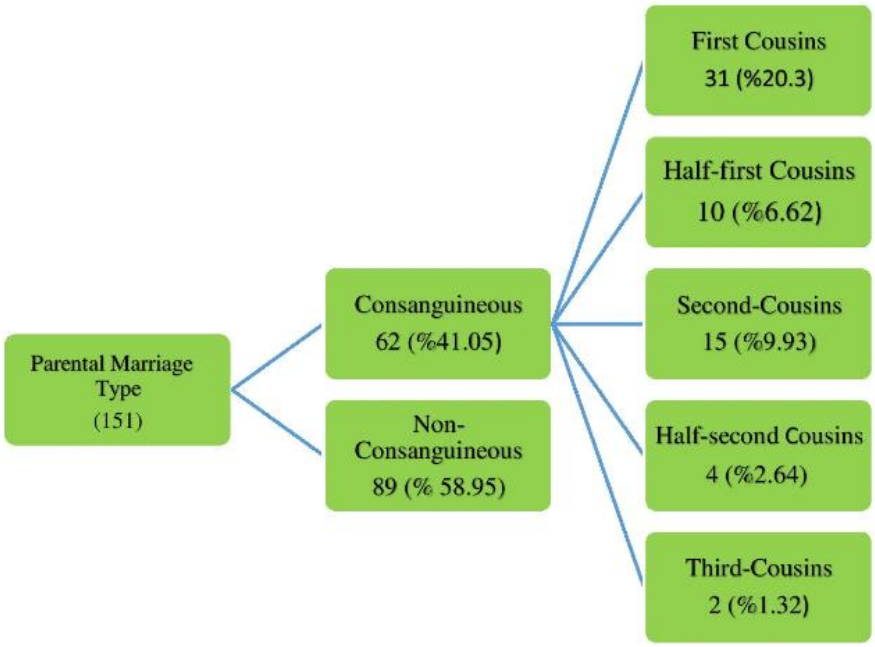

Fig.1: The types of family relationships in consanguineous marriages in this study and number of individuals and their percentage are presented in each box.

Besides, we examined the type of counseling for these 151 individuals, of whom 90 (60%) received DC (Diagnostic Counseling), 42 (28%) PCC (Pre-Conception Counseling) counseling, 7 (5%) DPC (During Pregnancy Counseling), and 10 (7%) PMC (Pre-Marriage Counseling) (**Figure. 2**). Since the ID is associated with other disorders, about 30% of patients have a physical disability, 21% have developmental delays, and 15% have microcephaly and other problems as shown in **Figure. 3**. In this study, the results showed that there is a significant relationship between consanguinity marriage and etiology of the disease ($p=0.012$) ($P<0.05$), and there was no significant relationship between other variables.

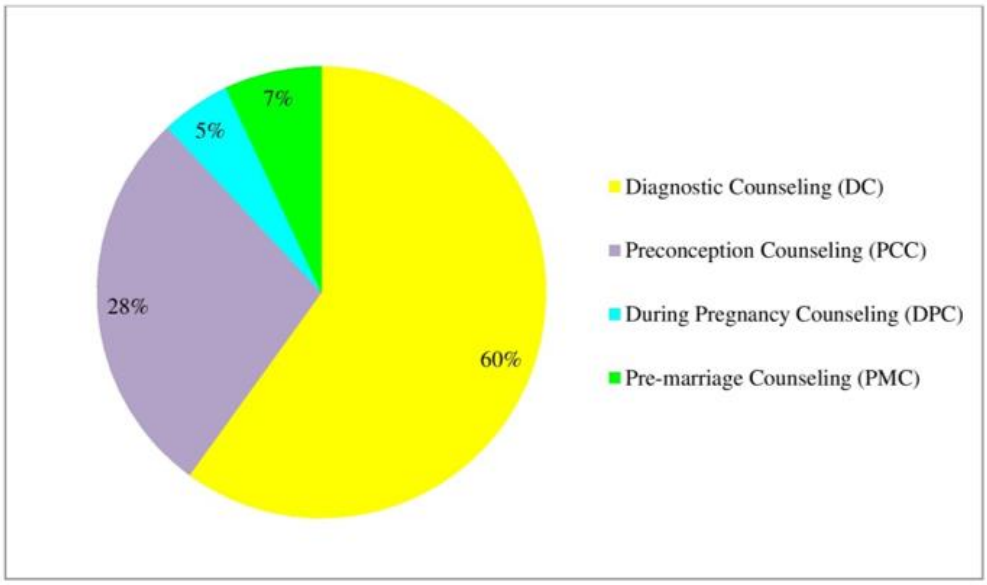

Fig. 2: Distribution of families according to times of referral for Genetic counseling in this study.

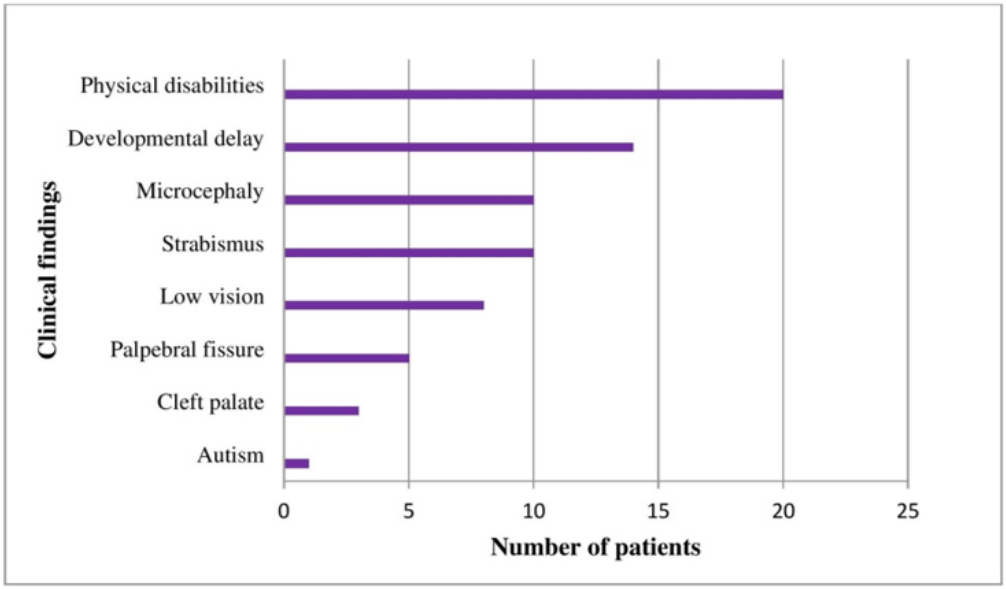

Fig .3: Summary of clinical finding of the Individuals with syndromic ID in this project.

The incidence of this disorder between the two genders was 74% and 25% among the boy and girl adolescents under 18 years old, respectively (**Table.1**). Finally, several genes for diseases associated with ID are listed in **Table. 2**. According to the results of the present study, the number of syndromic and non-syndromic patients was approximately the same (**Figure.4**). The following were etiologically assessed and found that the share of non-hereditary cases was greater compared to the share of hereditary and unknown cases (**Figure. 5**). These patients were evaluated for karyotype results, and we concluded that the proportion of structural chromosome abnormalities was greater compared to the proportion of other chromosome abnormalities (**Table. 3**).

Table-1: Baseline characteristics of participants in families with sporadic ID in our study (n=151).

Variables	Gender			P-value
	Male, number (%)	Female, number (%)	Total, number (%)	
Age (year)				
≤ 6	30(19.8%)	10(6.7%)	40(26.6%)	0.8
6-12	35(23.3%)	8(5.3%)	43(28.4%)	0.81
12-18	33(21.8%)	14(9.3%)	47(31.1%)	0.82
≥18	15(9.9%)	6(3.9%)	21(13.9%)	0.9
Mean (year)	11.81	12.97	12.022	
Standard deviation	5.968	6.184	6.071	
Mode	5	5	5	

Table-2: ID disease genes mutated in families genes and their location, function and related diseases.

Family ID	Gene	Function	Locus	Disease	OMIM*
001	PDYN	Opioid peptide activity	20p13	Spinocerebellar ataxia	131340
002	PTPRQ	Phosphatase activity	12q21.31	Deafness(AR*,AD*)	603317
003	COQ8A	Kinase activity	1q42.13	Cerebellar ataxia (AR)	606980
004	NAGLU	Hydrolase activity	17q21.2	Mucopolysaccharidosis	609701
005	STAG1	Chromatin binding	3q22.3	Mental retardation (AD)	604358
006	LYST	Protein binding	1q42.3	Chediak-higashi syndrome	606897
007	NAA10	Catalytic activity	Xq28	Ogden syndrome	300013
008	ARMC2	Positive regulator of hedgehog	2q37.1	Joubert syndrome	617612
009	LAMA2	Signaling receptor binding	6q22.33	Muscular dystrophy	156225
010	WDR62	Protein binding	19q13.12	Microcephaly	613583
011	PUF60	DNA binding protein	8q24.3	Verheij syndrome	604819
012	CCDC	Protein binding	19q13.32	3-M syndrome 3	614145
013	ATP1A2	ATP binding	1q23.2	Familial hemiplegic migraine	182340
014	CHRND	Ion channel activity	2q37.1	Multiple pterygium syndrome	100720

* OMIM: Online Mendelian Inheritance in Man, AD: Autosomal Dominant, AR: Autosomal recessive.

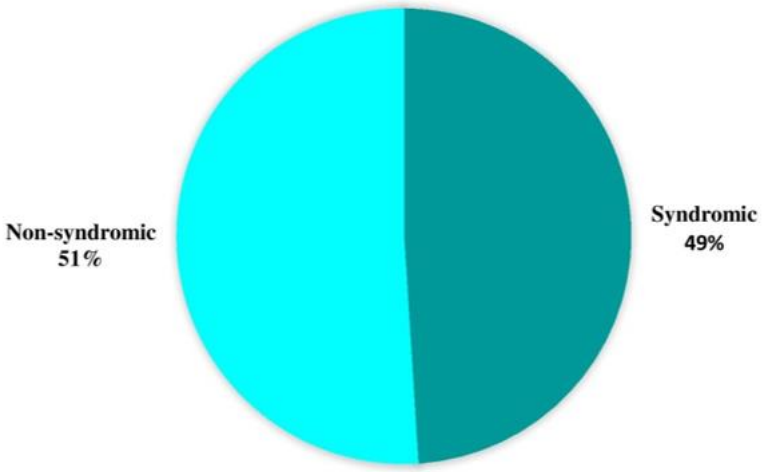

Fig. 4: Distribution of subjects according to type of syndromic and non-syndromic cases.

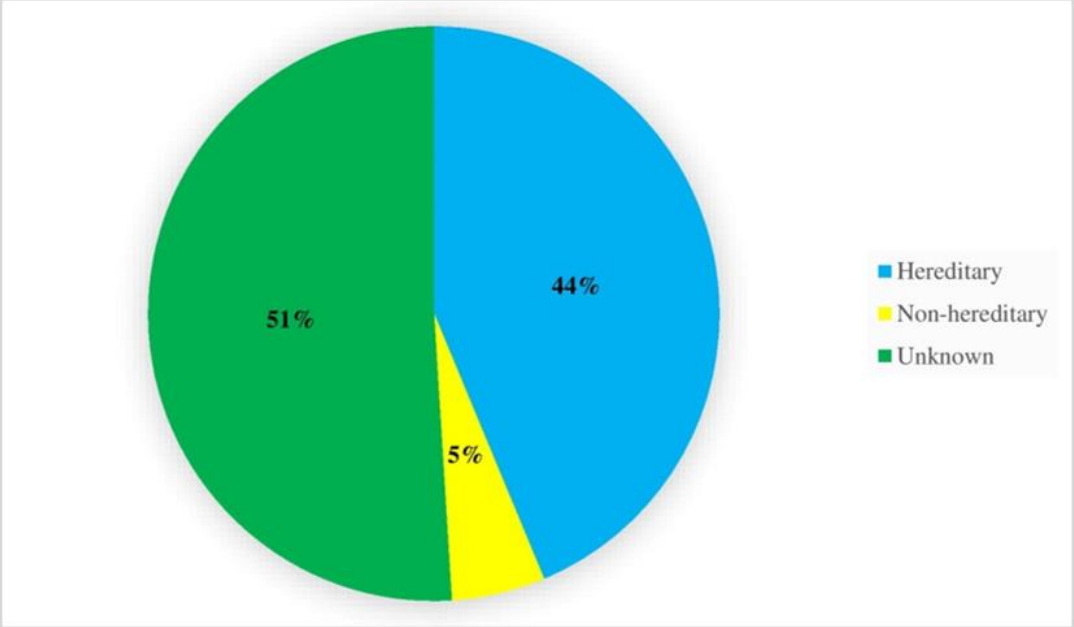

Fig. 5: Overall classification of patients according to their etiology.

Table-3: Cytogenetic findings in patients with intellectual disability.

Karyotypes	Number of patients
Numerical abnormalities	
47, XY,+21	2
49, XXXXY	1
Structural abnormalities	
46,X,fra(X) (q27.3)	2
46, XX,rob(14;21)(q10;q10)+21	1
46,XY,rec(10)dup(10p)inv(10)(p11.2q26.3)	1
46,XY,inv(9)(p11q12) mat,t(22:11)(q13.1;q25)pat	1

4- DISCUSSION

In this study, we showed that families with one ID child indicate referral to genetic counseling and also consanguineous marriage is one of the major reasons of this disorder among affected families. In the present study, which was performed on families with sporadic ID who had referred to genetic counseling welfare centers in Sari, about 41.05% of the marriages were consanguineous. The results of the present cannot be generalized to society but can indicate the importance of this issue in the province and the whole country. Besides, ID is a serious genetic heterogeneity disorder and it puts massive economic pressure on the family, community, and health system. The inheritance pattern has a different autosomal dominant, recessive, and sex-linked patterns (3,13-16). Most of the genes discovered in Iran by exome sequencing techniques revealed the Autosomal Recessive Inheritance

Disability (mainly ARID). Indicators such as the high rate of consanguinity marriages, ethnicity, religious beliefs, and geographical location of Iran increase this disease as well as other rare recessive genetic disorders among these families. Because of the various causes of this disorder, there are two types of syndromic and non–syndromic forms, as previously described (17). Exome sequencing is a more appropriate choice for detecting the desired gene mutation in non-syndromic form. But in patients with the syndromes, finding the desired mutation is determined using simpler techniques (13,14,17).

It seems that one of the effective ways to prevent an ID birth and other genetic disorders in our society is to consult with a genetic specialist. In this way, using the careful examination of the history, drawing the pedigree, and obtaining the type of inheritance pattern, one can make the necessary suggestions to prevent the recurrent childbirth with the same disease. Genetic counseling is a health service that provides information and supports people with genetic disorders who either are at risk or may be at risk (18, 19).

Nowadays, chromosomal aberrations are a common cause of ID. Chromosomal abnormalities in ID can be numerical or structural. In the present study, the routine cytogenetic analysis was also carried out on 140 ID cases, which revealed that 5.7 % of all patients had an abnormal karyotype, 3.57% had structural chromosomal abnormalities, and 2.14% had numerical aneuploidies, which emphasize that structural disorders of the autosomes are the most common type of chromosomal aneuploidies among sporadic IDs in the North of Iran. However, there were no statistically significant differences between the results of the present study and the published reports in Turkey, Saudi Arabia, and Morocco. It worth noting that, these studies are almost identical to our study methodologically (20-22). According to our findings, approximately 41% of patients were from consanguinity marriages, and also the autosomal recessive inheritance was more frequent among the sporadic patients. Therefore, this should be considered in every genetic counseling with consanguine families in the future (12). According to the results of the present study, the prevalence of cousin marriage among parents with ID children were consistent with the findings of the Nemati et al. (18). In this study, we found that out of 151 patients, 90 (60%) were from diagnostic counseling type, which is important for genetic counseling.

Genetic counseling aims to provide information and support to families at risk of having genetic disorders or currently have members with congenital defects or genetic disorders. Clinical genetics deals with the diagnosis and management of medical, social, and psychological aspects of hereditary diseases. As the unique feature of a genetic disease is its tendency to relapse within families, the unique aspect of genetic counseling is its focus not only on the primary patient but also on the patient's family. The results of the present study confirm that genetic counseling plays an important role in preventing neurodevelopmental disorders like mental disability. Moreover, mental disability is associated with other disorders of autism and physical disability (18, 23, 24).

4-1. Study Limitations

The limitations of the study were that we could not provide precise statistics on the prevalence and incidence of consanguineous marriage since the participant referring to genetic counseling welfare centers in Sari was not representative of all the families with sporadic ID in the society and also small sample size can be considered as the limitation of this study.

5- CONCLUSION

Genetic counseling has been identified as one of the major contributors to the prevention of congenital diseases. Genetic counseling has an important effect on deciding important issues such as spouse selection and fertility. Genetic counseling also creates many ethical problems for professionals. Therefore, professionals should be familiar with ethical issues and the health system must prioritize treatment, and authorities must provide effective and positive ways to reduce costs and equitable access. The ethical process of these consultations would have a significant impact on couples' decision-making. Using a comprehensive program to prevent the birth of disabled children has a professional commitment to the principle of equity in the distribution of medical law resources rooted in the culture of some ethnic and social groups. As a first step, society must be fully aware of its incompatibilities and arrests so that it can act consciously. As a religion that focuses on worldly affairs and thinking, it does not encourage family marriages. In some cases, this is banned. It is suggested that these diseases must be reduced using public health efforts to reduce marriage rates. Alternatively, with prenatal counseling and a history check of the disease, given the high cost of sequencing, we hope the genetic counseling role-play well.

6- ACKNOWLEDGMENTS

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7- CONFLICT OF INTEREST: None.

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