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Prenatal Screening Using QF-PCR and Karyotyping with an Evaluation of Short Tandem Repeats Markers in the Iranian Population

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ABSTRACT

Background: Quantitative fluorescent Polymerase Chain Reaction (QF-PCR) has been widely used by laboratories as a rapid, low-cost, and convenient test compared to conventional karyotyping for detecting the most common aneuploidies for prenatal diagnosis. Although the latter has been considered the gold standard for detection, the debate to use QF-PCR or both methods together continues.

Methods: We screened the results of QF-PCR and karyotyping to compare their detection rate for the most common aneuploidies. In addition, we aimed to investigate the most informative markers in the Iranian population for aneuploidies.

Results: We screened 741 pregnant women's amniotic fluid samples with nuchal translucency (NT) ≥ 2.5 for two years, during which QF-PCR and karyotyping were performed to compare the results. Also, we did a statistical assessment of samples for heterozygosity of 25 short tandem repeats (STR) markers in the Iranian population, which can be applied to find the most informative markers based on the population for each chromosome analyzed in the QF-PCR test.

Conclusion: QF-PCR could be used as a stand-alone test to reduce the workload and time-consuming of karyotyping, but using both of them could lead us to the most reliable results.

Introduction

Prenatal diagnosis is routinely offered to all women who are at high risk for aneuploidies.[1] Aneuploidy is the occurrence of chromosome numerical aberration, which typically results in trisomy (presence of one or more extra chromosomes) or monosomy (loss of a chromosome). It is known that aneuploidy is the leading cause of congenital abnormalities and abortion.[2] Nowadays, prenatal screening for fetal aneuploidy is a common practice in most countries, including Iran, and has been clinically available for nearly four decades in the most developed ones. Advanced maternal age, family history, fetal ultrasound markers (soft markers), and positive biochemical markers are considered risk factors for performing screening tests for chromosomes 21, 18, 13, and sex chromosomes (X and Y).[3] Before the screening, at-risk couples have been counseled to choose between invasive methods, including chronic villus sampling (CVS) or amniocentesis, and non-invasive prenatal testing (NIPT), which uses cell-free DNA in maternal plasma.[4] Cytogenetic karyotype testing enables the visual diagnosis of chromosomal abnormalities such as full chromosome aneuploidies, structural abnormalities, polyploidy, and mosaicism. Both QF-PCR and fluorescence in situ hybridization (FISH) provide a rapid prenatal diagnosis of chromosome aneuploidy, and FISH is a valuable adjunctive test for diagnosing mosaicism.[5] For the QF-PCR technique is used amniotic fluid (AF) or CVS directly and does not require cell culture as traditional cytogenetic methods.[6] Some benefits of this technique include high throughput, low labor-intensive protocol, and higher robustness than other methods such as FISH and karyotyping, which are also cheaper than the others.[7] This method could detect aneuploidy for all chromosomes and triploidy by recognizing Short Tandem Repeats (STR). STRs or microsatellites frequently source DNA variations with two to six pairs of nucleotide repeats. They make up 3% of the total genome. As they are highly polymorphic, these markers vary between populations. Therefore, a study is required based on the heterogeneity of STR markers in that particular population.

Several studies compared the accuracy of karyotyping and QF-PCR in the Iranian population. Rostami et al., compared Prenatal Screening for Aneuploidies using QF-PCR and Karyotyping in the Iranian population. Using QF-PCR alone, they were able to detect abnormalities in 98.59% of all cases; however, the karyotyping results increased the detection rate to 99.85% of the cases.[8] In 2019, Masoudzadeh and Teimourian made a statistical comparison between karyotyping and QF-PCR for prenatal diagnosis. They observed chromosomal rearrangements and mosaicisms not detected by QF-PCR but detected by karyotyping. However, maternal cell contamination made the karyotyping fail but not the QF-PCR.[1]

According to the World Health Organization, birth defects affect 4-8% of births worldwide, and their incidence varies between different countries.[9] The prevalence of chromosomal abnormalities in Yazd is about 0.05%. Many studies have investigated amniocentesis and abortion treatment in Yazd and showed a relatively high rate of abortion.[10-13] in a previous study, we examined high-risk mothers and the diagnostic value of prenatal screening tests in Yazd. The causes of amniocentesis included old age (45.9%), positive results of Down syndrome screening (23%), high NT ultrasound (4.9%), and pathological results of anomaly scan sonography (3.8%).[14] To date, the gold standard for prenatal diagnosis is karyotyping. However, the current disadvantage of conventional karyotyping is the prolonged time (about two weeks) to get the results, which is very long for patients and pregnant women of gestational age. Consequently, there has been an urgent need for a high-precision and high-speed test to minimize patient anxiety and decrease the results interval. In this paper,

we used the combination of karyotyping and QF-PCR for STR markers to detect aneuploidy.

Materials and Methods

Sampling: The current investigation involved sampling and analyzing 741 pregnant women's AF and whole blood with a gestational age between 15 and 22 weeks between 2018 and 2020. They were selected due to referral to Dr. Mazaheri Medical Genetic Laboratory in Yazd because of the risk of fetal chromosomal abnormalities. Exclusion criteria were women who used the CVS sample due to their young gestational age and women with high blood pressure during pregnancy, pre-eclampsia, and systematic diseases due to impaired maternal serum markers. A protocol used for analysis in this study is shown in Figure 1. This protocol is part of the standard genetic testing services at Dr. Mazaheri Medical Genetic Laboratory. Typically, 20 ml of AF from pregnant women are taken by a perinatologist; 2.5-2 ml of the sample is isolated for QF-PCR, and the remainder is evaluated for fetal karyotyping.

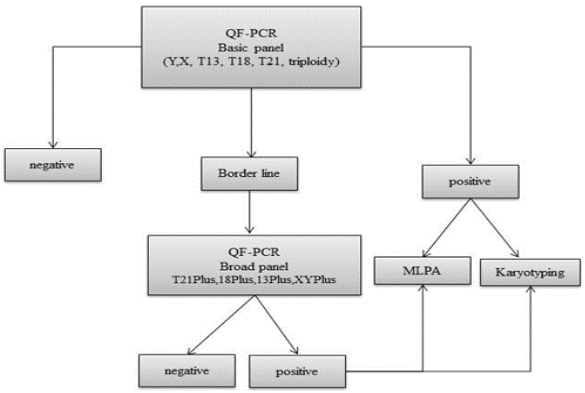

Figure 1. Genetic analysis protocol of amniocentesis candidate mothers

Multiplex QF-PCR: Numerical anomalies of chromosomes 13, 18, 21, X, and Y were analyzed by QF-PCR to determine the number of copy markers mentioned. According to the instructions, DNA was first extracted from uncultured AF cells using the Amplisens Moscow Russia kit. Then the quantity and quality of the extracted DNAs were evaluated using a spectrophotometer. Moreover, the extracted DNAs were amplified using the Geneproof omniplex QF kit with 25 diagnostic markers and multiplex QF-PCR in a vial, according to Figure 2.

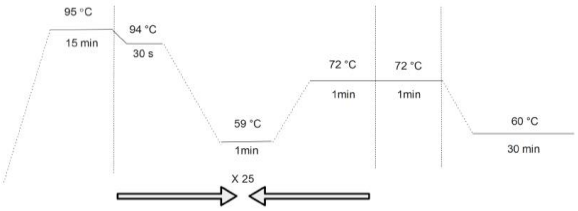

Figure 2. Thermocycler methodology

Here, 25 probes are used based on STRs on chromosomes 13, 18, 21, X, and Y. The markers employed are D21S1432, D21S1411, D21S1435, D21S1437, D21S1412, and D21S11 for chromosome 21, D18S51, D18S391, D18S1002, D18S535, and D18S386 for chromosome 18, D13S742‹D13S628‹D13S258‹D13S631And DS13S305 for chromosome 13, AMXY, X22, HPRT, DX981, DSX742, DXS1189, DXS8377, TAF, and SRY for the sex chromosomes (Figure 3).

Because of the heterogeneity of STR markers in different populations, all markers were used for analysis. Fragment analysis PCR product was evaluated using the capillary electrophoresis method of the ABI sequencer. The GeneMarker v 2.2.0 software was used for analysis; distinct peaks with area ratios between 0.8-1.4 were considered normal, and the presence of two distinct peaks was interpreted as heterozygous normal. While ratios below and above this range were interpreted as trisomy, the presence of 3 distinct peaks was also considered trisomy. Furthermore, one-and-a-half peaks were considered trisomy because it shows two homozygous with the same peak plus a half due to heterozygosity. One distinct peak was deciphered uninformative.

Results

In this study, STR markers were evaluated for detection of aneuploidy among 741 prenatal samples.

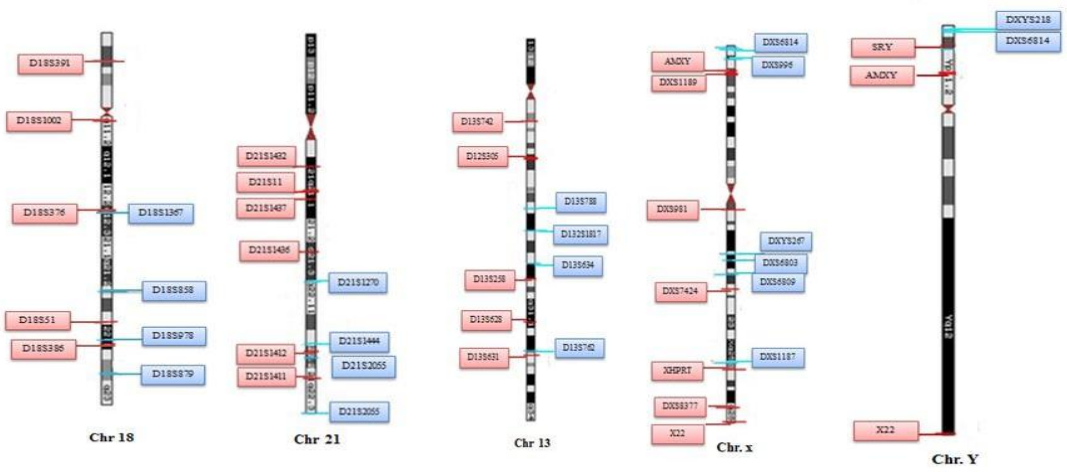

Figure 3. Ideogram of STR marker

Women with one or more of the risks of biochemical markers in initial screening tests, fetal ultrasound abnormality, NT ≥2.5, and advanced maternal age (≥ 38 years) were evaluated. According to the Table.1 mother's gestational rate was about 16 weeks, and the mean age of the mothers was approximately 33.18 (± 5.96). The most common reason couples were referred to the cytogenetic laboratory was the risk of trisomy 21 (76%) and after that, was high NT (11.4%). The most common aneuploidies are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and numerical abnormalities of the sex chromosomes that are evaluated in this study.

Table 1. Demographic Characteristics of Referral Mothers

Features		Rate (n = 741)	Percentage
The mean age		33.18 ± 5.96	
Gestational week		16w5d ± 1w2d	
Sonography		21	2.8%
History	T21 Risk	563	76%
	T13 Risk	12	1.6%
	T18 Risk	13	1.7%
	Others	17	2.3
NT		85	11.4%
Others		30	4.04%

Table 2 shows the results of the QF-PCR test and its comparison with karyotype. In cytogenetic tests on amniotic samples, 363 fetuses were female (50.8%) and 351 were male (49.2%). Based on the karyotype, there were 28 abnormal cases. A total of 20 (2%) patients with Down syndrome and 4 cases of trisomy 18 were reported. Regarding sex chromosomes, one case of XYY and one case of xxx was detected in both karyotype and QF-PCR. In karyotype, 2 cases of sex chromosome trisomy (XXY) were detected, but only one case of XXY was detected in QF-PCR. In total, out of 741 pregnant mothers, 28 cases of trisomy were detected in karyotype but 27 cases were detected by QF-PCR. Notably, QF-PCR and the conventional cytogenetic method had 99.8% concordance in test results, and just one case could not be detected with QF-PCR due to mosaicism. Despite 12 cases of referral because of the risk of trisomy chromosome 13, no case of Patau syndrome was reported. Accordingly, no statistical analysis was performed for this syndrome.

As listed in the Table 3, there were some contradictions between QF-PCR and karyotyping results that included sex chromosomal rearrangements and one case of mosaicism, which were reported as normal.

As illustrated in the Table. 4, 85 samples with NT ≥ 2.5 were divided into four groups. Our findings support that as the fetal NT increases, the rate of trisomy 21 pregnancy rises, especially in the last two groups. Additionally, one Klinefelter and one trisomy 18 fetuses were detected among pregnancies with higher levels of NT.

Table 2. Karyotype and QF-PCR Test Results

Test	Statuses	N	Result	N	Percentage
QF-PCR	Normal	714	XX	363	50.8%
			XY	351	49.2%
	Abnormal	27	Trisomy21	20	2%
			Trisomy18	4	0.5%
			Trisomy13	0	0%
			XO	0	0%
			XXY	1	0.125%
			XYY	1	0.125%
			XXX	1	0.125%
Karyotype	Normal	713	XX	363	50.9%
			XY	350	49.1%
	Abnormal	28	47,XX, +21	10	1%
			47,XY,+21	10	1%
			47,XX,+18	3	0.4%
			47,XY,+18	1	0.125%
			47,XX,+13	0	0%
			47,XX,+13	0	
			45,X	0	0%
			47,XXY	2	0.25%
			47,XYY	1	0.125%
			47,XXX	1	0.125%

Table 3. Chromosomal Rearrangements and Mosaicism

Karyotype	QF-PCR
46,XY,inv(Y)(P11.2;11.2)	XY
46,XY.inv(Y) (p11.2-q11.23)	XY
46,XX,der(4)t(4;11)(q31.3;q23) inv(4)p(15.1q31.3)	XX
46,XY,inv(Y)(p11.2q11.23)	XY
46,XY, del (q11.2 ;qter)	XY
46,XY,t(1,15)(q23,q25)	XX
46,XY[48]/47, XXY[25]	XY

Therefore, there is a direct relationship between increased NT and trisomy, especially trisomy 21, because 66% of people in the fourth group (NT 5.5-6.4) had Down syndrome.

Table 4. T21 Pregnancy Results of Abnormal NT

NT level	Number of samples in each group	Down syndrome detection (percentage)
2.5-3.4	59	6 (10%)
3.5-4.4	19	1 (5%)
4.5-5.4	4	1 (25%)
5.5-6.4	3	2 (66%)
Total	85	10 (100%)

Heterozygosity analysis of STR markers: Hence, markers for sex chromosomes typically show the presence of one peak in males due to their Homozygosity for genes on X and Y chromosomes, although we considered one peak as uninformative for autosomal markers. Therefore, autosomal and sex markers were analyzed separately to prevent any misunderstanding. The results of heterozygosity of autosomal and sex chromosome markers evaluated by QF-PCR among 741 Iranian pregnant women are given in Tables 5 and 6, respectively. Markers with more heterozygosity percentages are the most reliable for detecting aneuploidy in any population.

According to Table 5, the results obtained for chromosome 21, D21S1411 and D21S11 markers show the highest heterozygosity and D21S1432 and D21S1435 markers show the lowest heterozygosity. On chromosome 18, markers D18S51 and D18S386 show the highest heterozygosity and marker D18S391 shows the lowest heterozygosity. On chromosome 13, marker D13S258 shows the highest percentage of heterozygosity, and marker D13S631 shows the lowest heterozygosity.

About sex chromosome According to Table 6, in males, SRY and TAF markers

Table 5. Heterozygosity Markers for Autosomal Chromosomes

Name	Location	Heterozygosity	Homozygosity
D21S1432	21p11.2	370 (67.9%)	172 (31.6%)
D21S1411	21q22.3	485 (82.1%)	95 (16.1%)
D21S1435	21q21	379 (69.5%)	141 (25.9%)
D21S1437	21q21.1	401 (73.6%)	118 (21.7%)
D21S1412	21q22.2	377 (69.2%)	110 (21.7%)
D21S11	21q21.1	438 (80.4%)	99 (21.7%)
D18S51	18q21.33	441 (80.9%)	100 (18.3%)
D18S391	18p11.2	391 (66.2%)	197 (33.3%)
D18S1002	18q11.2	442 (74.8%)	136 (23.0%)
D18S535	18q12.2	447 (75.6%)	136 (23.0%)
D18S386	18q22.1	431 (79.4%)	55 (10.1%)
D13S742	13q12.12	400 (73.5%)	64 (11.8%)
D13S628	13q31-q32	322 (59.2%)	123 (22.6%)
D13S258	13q21	457 (77.3%)	93 (15.7%)
D13S631	13q31-32	386 (71%)	119 (21.9%)
D13S305	13q21	404 (74.3%)	108 (19.9%)

showed 100% Heterozygosity, and then AMXY showed 86.3% Heterozygosity. Also, DX981 showed 90.9% Homozygosity. Also in females, AMXY (amelogenin XY) markers showed 89.4% Homozygosity.

Discussion

Currently, many countries include QF-PCR in their national prenatal screening programs. There is no limitation in terms of the quantity and quality of fetal cells (amniocytes) in the sample of amniotic fluid because it does not require cell culture. DNA analysis of amniotic samples using the QF-PCR technique amplifies STR located on chromosomes.[15] STR markers are important, and they can provide lots of information about chromosomal aneuploidy and anomaly. The degree of heterozygosity is relatively variable between STRs.[1] Appropriate selection of STR markers for analysis needs to take into consideration the ethnicity of the population based on genetic variation parameters, so evaluation of the genetic variation of STRs in the population is required before applying QF-PCR in the national program.[15]

Here 741 amniotic fluid (AF) samples were analyzed to detect common chromosomal abnormalities by QF-PCR and compare it with the conventional cytogenetic method. The highest frequency of recourse for AF analysis was due to the risk of initial screening, NT > 2.5, fetal ultrasound abnormality, and family history of having a child with one of the aneuploidy disorders, respectively. According to the results, all samples were matched by QF-PCR and karyotyping except for 27 cases with chromosomal rearrangement and mosaicism.

Table 6. Heterozygosity Markers for Sex Chromosomes

Name	Location	Male		Female	
		Heterozygosity	Homozygosity	Heterozygosity	Homozygosity
AMXY	Xp22.1-Yp11.2	246 (86.3%)	34 (11.9%)	29 (9.6%)	270 (89.4%)
X22	Xq28 Yq (PAR2)	134 (50.8%)	72 (27.3%)	140 (50.7)	77 (27.9%)
HPRT	Xq26.1	18 (6.8%)	239 (90.5%)	174 (63.0%)	99 (35.9%)
DX981	Xq13.1	20 (7.0%)	259 (90.9%)	168 (55.6%)	124 (41.1%)
DXS7424	Xq22.1	24 (9.1%)	228 (86.4%)	187 (67.8%)	77 (27.9%)
DXS1189	Xp22.2	19 (7.2%)	239 (90.5%)	202 (73.2%)	67 (24.3%)
DXS8377	Xq28	19 (7.2%)	228 (86.4%)	202 (73.2%)	39 (14.1%)
SRY	Yp11.2	285 (100%)	0 (0%)	0 (0%)	0 (0%)
TAF	Xq13 3p24	285 (100%)	0 (0%)	285 (100%)	0 (0%)

However, mosaicism can be suspected during QF-PCR analysis. Although, based on our results with the concordance of 99.8% between QF-PCR and karyotyping, using both could lead us to the most reliable results. To perform QF-PCR, 25 markers (STR) were used to diagnose Down syndrome, Patau syndrome, Edward's syndrome, and numerical abnormalities of sex chromosomes.

Among the studies where QF PCR results were the same as karyotype results, including Manasatienkij, Miri et al., and Nasiri et al. Manasatienkij compared the accuracy of prenatal diagnosis of common aneuploidies using QF-PCR with standard karyotyping in Thai pregnant women. They observed the QF-PCR and karyotyping results were identical, and no false positive or negative results were observed in either test.[15,16] Miri et al. observed, that all normal, Down syndrome, and indeterminate samples were accurately identified by the STR-SD-based multiplex QF-PCR, showing 100% sensitivity and 100% specificity. Also, karyotype analysis confirmed all the cases with normal or trisomic results.[16] Nasiri et al found most of the STRs analyzed had acceptable heterozygosity for use in prenatal diagnosis based on QF-PCR. Also, results obtained from karyotype and QF-PCR were consistent with each other for all samples.[17]

Similar to our studies, the accuracy of QF-PCR was slightly lower than the karyotype, including the investigations of Badenas et al., De Moraes et al., Jing et al., Kaya et al., and Zhang et al. In Badnas et al.'s study, the results of QF-PCR and karyotype coordination were obtained in 98.75% of the samples. Also, an abnormal karyotype associated with adverse clinical outcomes that was not detected by QF-PCR was found in 0.05% of their samples.[18] In the study of Moraes et al., QF-PCR results were consistent with the results of cytogenetic analysis in 95.4% of all samples.[19] Jing et al., observed the positive rate of chromosomal abnormalities confirmed by QF-PCR was 75.18%, which was not significantly different from that by karyotyping (79.36%) and copy number variation (CNV) detection methods (71.43%).[5] Kaya et al., reported normal results in 2711 cases by fetal karyotyping and in 2706 cases by QF-PCR. Anomaly detection rates were similar for the two methods (5.09% for karyotyping and 4.02% for QF-PCR).[20] Results of the Zhang et al.'s study. unveiled that the detection rates of numerical chromosomal abnormalities were nearly the same in these two groups.[9]

Analysis of STR markers that indicate heterozygosity is a necessary step before using QF-PCR to improve results.[1] In our study, among the evaluated markers, D13S258, D18S51 and D21S1411 had the highest frequency of heterozygosity, therefore, we considered these markers to be the most informative for QF-PCR testing. We compared the most heterozygosity marker results of this study with previously published reports designed for the Iranian population in Table 7. Since QF-PCR is an STR-based technique, one of its main disadvantages is the possibility that some STR markers can be uninformative in a portion of patients, especially in countries with high rates of consanguineous marriage.[16]

Table 7. The Most Reported Heterozygote Markers in the Iranian Population

Reference	for ch.13	for ch.18	for ch.21	for sex chromosomes
Rostami et al.[8]	D13S634	D18S976	D21S1414	DXYS267
Nasiri et al.[17]	D13S634	D18S386	D21S1444/1435	DXS6803
Masoudzadeh et al.[1]	D13S742	D18S386	D21S1411	-
Saberzadeh et al.[21]	D13S742	D18S386	D21S1411	DXS2390
Our study	D13S258	D18S51	D21S1411	DXS1189/8377

Using this information could lead to designing a special kit for that population or could be helpful for paternity tests. As our study and other studies showed, heterozygosity varies in different populations; therefore, future studies should focus on identifying specific STR markers in each population. Also, we concluded that QF-PCR is a rapid and reliable prenatal diagnostic method and is preferred as prenatal screening in pregnant women. However, there is a need for further studies with larger populations and more markers.

Conclusion

In conclusion, we identified the high concordance between karyotyping and QF-PCR, the latter could be used as a stand-alone method for reporting the first result to the parents about common aneuploidies. Although, to lead to the most reliable results using both is the best solution. In addition, we found D13S258, D18S51, and D21S1411 markers as the highest frequency of heterozygosity in the Iranian population; therefore, they could be used to design special kits for Iranians. Besides, this analysis could be implemented in other populations to find the most informative markers based on theirs.

Conflict of Interest

Authors have no conflict of interest.

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Ethical Considerations

The present study was approved by Shahid Sadoughi University Ethics Committee (IR.SSU.SPH.REC.1399.253).

Author's Contribution

M.M. and M.Y. conceived and designed the analysis; M.M., M.Y. and H.N. collected the data; H.N., S.B. and S.E. wrote the manuscript; S.B. and S.E. edited the manuscript. The authors read and approved the final manuscript.

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