



## Testicular Feminization or Androgen Insensitivity Syndrome (AIS) in Iran: a Retrospective Analysis of 30-Year Data

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### Abstract

**Background:** Androgen insensitivity syndrome (AIS) or testicular feminization is a partial or complete inability of cell response to androgen. The cause is enzymatic defect in synthesis of testosterone, resulting sexually immature phenotypically female, with primary amenorrhea. There are three categories of AIS, complete, partial and mild, depending on the degree of external genital masculinization. The aim of this study was to find out chromosomal abnormalities, and correlation between AIS and maternal/paternal age, parents' consanguineous marriage, family history and clinical observation, in Iranian AIS patients.

**Method:** This study includes a retrospective data analysis of 72,000 families' medical records in the Genetic Clinic in Tehran, during a 30-yr period (1984-2014). The essential basis for the patients' referral to the clinic by gynecologists was primary amenorrhea. Cytogenetic abnormalities has been confirmed by chromosome G-banding and conventional staining methods.

**Results:** Seventy AIS female patients with 46XY pattern were cytogenetically diagnosed and the frequency of AIS syndrome was estimated about 0.05% (~70/140000). The results showed no association between AIS and maternal or paternal age nor were the marital pattern of the parents. The clinical findings illustrated that primary amenorrhea had the highest indication for referral of AIS patients for genetic counseling and cytogenetic study.

**Conclusion:** No correlation was observed between AIS and maternal or paternal age or consanguineous marriages. Amenorrhea is the most clinically observed sign of AIS patients.

**Keywords:** Androgen insensitivity syndrome (AIS), Testicular feminization, Human androgen receptor (HAR), Amenorrhea, Iran

### Introduction

The first report on androgen insensitivity syndrome (AIS) was published in 1953, by John Morris, an American gynecologist, who called it testicular feminization, as the phenomenon causing feminization effect and testis observed in their body (1).

The prevalence of AIS has been estimated to be one case in every 20,000 to 64,000 male newborns complete androgen insensitivity syndrome (CAIS), the prevalence is unknown for the partial androgen insensitivity syndrome (PAIS). However, the incidence of this syndrome in population would

be unstable as it depends on AIS observed. The rates would be varying in complete, mild (MAIS) and partial AIS (2-4).

Studies indicate a prevalence of 2:100,000 to 5:100,000 for CAIS (5). A survey in the Netherlands over a ten-year period based on reported cases of AIS concluded that the minimal incidence was 1:99,000 (6).

PAIS is at least as common as CAIS. The incidence of PAIS has been estimated to be 1 in 130,000 (7). The prevalence of MAIS has not yet been determined. However, it is much less frequently reported than CAIS and PAIS (8).

The AIS, an X-linked recessive disorder, is the result of dysfunctional androgen, that is, inability of the cell to respond to androgen, caused by disorder in the human androgen receptor (HAR) for attachment of androgen to cytosol. This protein is essential for attachment of testosterone and dihydrotestosterone to the plasma membrane and transfer of androgen to the nucleus, the essential and specific location of androgen activity (2, 8-10). AIS affected individuals have female external genitalia, female breast development, blind vagina, absent uterus and female adnexa, and abdominal or inguinal testes, despite a male 46, XY karyotype (2, 8-11). AIS is divided in three categories the complete (CAIS), mild (MAIS) and partial (PAIS) androgen insensitivity, that they indicate the different degree of external genital masculinization (4, 12, 13).

The HAR is a protein encoded by a gene located on the Xq11-Xq12 (14). As there is lack of response to androgen, masculinization of male genitalia is impaired in the fetal stage. The male secondary characterization is also affected afterward and together with spermatogenic deficiency, secondary terminal hair reduction and feminine habits. Breasts have normal growth process, since the testes produce estrogen, but testosterone produced in the body and converted to di-hydro-testosterone, has no effect on the target organs, even with additional therapy. As the external genitalia have female appearance, the disorder is not recognized in the infants. The short vagina, absence or infantile uterus and fallopian tubes are only distinguished after careful examination, usually realized due to primary amenorrhea.

The testes are intra-abdominal and sometimes appear as hernia and hence it has to be carefully followed up. Sertoli cells are present, but not spermatogonia and spermatozoa. There is hyperplasia of Leydig cells. Pubic hair is reduced and the affected person has female type of behavior (2, 8, 15-17). The diagnosis is confirmed by determining the exact mutation in the androgen receptor gene (15, 18-20).

In AIS patients, abnormal testis development and risk of gonad malignancy increase after puberty (21). Testis tumor risk is thought to be 3.6% by 25 years and 33% by 50 years (22, 23). Other malignancies such as sertoli adenoma or tumor, hamartomas, sertoli cell adenomas, seminomas, intratubular germ cell neoplasm have also been reported (22, 24).

This study considers finding out chromosomal status, correlation between AIS and maternal/paternal age, consanguineous marriages of parents, family history, and clinical observation in Iranian AIS patients.

## Materials and Methods

This retrospective study was carried out reviewing 72,000 medical records of families referred for genetic counseling to the Genetic Clinic in Tehran. The survey was extracted from the cytogenetic study in 70 individuals with AIS. These females had been karyotyped by banding method (G-banding and conventional chromosome staining), and XY pattern had been diagnosed and confirmed. The most frequent reason for their referral was primary amenorrhea. The individuals with AIS were in the range of 15 to 24 yr of age.

## Results

The frequency of AIS syndrome was estimated about 0.05% (~70/140000). The results in Tables 1, 2 and 3, indicate no association in maternal and paternal age, parents' consanguinity marriage aspects among AIS patients. The Table 1 and 2 analyses showed that the percentages of affected individuals with AIS in advanced paternal and maternal age groups (35-39, 40 and 40≤) were higher than the other age groups.

**Table 1:** The AIS frequency in maternal age groups

Age groups (yr)	Frequency	
	(n)	(%)
20-24	4	10.25
25-29	4	10.25
30-34	6	15.40
35-39	10	25.64
40≤	15	38.46
Total	39	100.00

**Table 2:** The AIS frequency in paternal age groups

Age groups (yr)	Frequency	
	(n)	(%)
20-24	4	11.10
25-29	5	13.90
30-34	8	23.00
35-39	19	52.00
40≤	4	11.10
Total	36	100

The result of Table 4 illustrated the family history of infertility and amenorrhea has a corresponding high percentage.

**Table 3:** The AIS frequency in consanguineous or foreign marriages of the parents

Relationship	Frequency	
	(n)	(%)
First degree relative marriage	26	39.40
Second degree relative marriage	20	30.30
Foreign marriage	20	30.30
Total	66	100

**Table 4:** Major family history in AIS affected patients

History	Frequency	
	(n)	(%)
Infertility	8	40.00
Amenorrhea	6	30.00
Abortion	4	20.00
MR	1	5.00
Bigender	1	5.00
Total	20	100.00

**Table 5:** Clinical observations in 70 AIS patients

Clinical Observe	Frequency	
	(n)	(%)
Amenorrhea	54	77.10
Sexual confusion	5	7.15
Leanness and lack of growth	3	4.30
Infertility	3	4.30
Trans-sexuality	2	2.85
Lack of Uterus	2	2.85
Skin diseases	1	1.45
Total	70	100.00

The result of Table 5 shows that amenorrhea has a high percentage as possibility of the first referral symptom of AIS patients.

## Discussion

According to this investigation, no correlation was found between AIS and maternal or paternal age. Amenorrhea was the most clinically observed sign of AIS. In addition, consanguineous marriage, which is common in Iran, did not have a meaningful increase in the AIS patients.

In this study, the percentage of AIS patients in higher paternal and maternal age groups was more than other age groups. However, the fertility age in paternal and maternal age group is increased due to modern, urban, life style. Therefore, the values seem not to be statistically significant. No report was found in literature to prove relationship of this disorder with high paternal and maternal ages.

The number and percentages of parents' consanguineous marriages in this study (first and second-degree relatives) was high. This is due to the cultural reasons in the region (25). However, no statistically significant association was found between consanguineous marriage and increased risk of AIS.

Family history of our AIS patients showed that incidence of infertility (40%), amenorrhea (30%) and abortion (20%), are high. However, the cytogenetic analyses of the family members could not be followed up.

Table 5 shows that amenorrhea is the first symptom of AIS in clinical observation with 77% frequency. The frequency in clinical observation and reason of consult showed expected distribution, coordinated with the literature in case and group studies (26-29). A recent study in Spain has showed various phenotypes observed, but with primary amenorrhea as the first key (3). A 10 years study in India was carried out on AIS disorder in phenotypic normal females with primary amenorrhea (30).

## Conclusion

The most significant index in AIS patients, according to the present study in the Genetic Clinic in Tehran, was primary amenorrhea, as confirmed by the literature. It is suggested that molecular study be considered to clarify any genotype-phenotype correlation, and finding AR mutation pattern in Iranians' AIS.

## 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.

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