Aposthia: a birth defect or normal quantitative recessive human genetic trait?

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انعدام القلفة: عيب خلقي أو خلة وراثية بشرية متنحية، عادية من الناحية الكمية؟

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الخلاصة: يقصد بانعدام القلفة (الختان الطبيعي) أن يولد الطفل بدون قلفة، والعادة أن تُذكر في المنشورات الطبية حالات فُرَادية. أما في هذه الورقة البحثية فإن الباحثين يعرضون لأول مرة الـمُرْتَـسَم الـوراثي لـثلاث أُسـر يحمـل أفرادُها خَلَّة انعدام القلفة، ويناقشون العوامل الوراثية المحتملة.

ABSTRACT Aposthia (natural circumcision) is the condition of being born without a prepuce. Usually sporadic cases are reported in the medical literature. In this paper for the first time we present the genetic profile of 3 families with aposthia trait and discuss the possible genetics.

L'aposthie : malformation congénitale ou caractère génétique récessif quantitatif normal de l'espèce humaine ?

RÉSUMÉ L'aposthie (circoncision naturelle) est l'absence de prépuce à la naissance. La littérature médicale ne décrit généralement que des cas sporadiques. Dans cet article, nous présentons pour la première fois le profil génétique de 3 familles porteuses du caractère de l'aposthie et discutons le mécanisme génétique possible.

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Introduction

Aposthia (natural circumcision) is the condition of being born without a prepuce. The prepuce is a common anatomical structure of the external genitalia that forms the covering of the glans penis and clitoris of all human and non-human primates [*1,2*].

Religious literature from various sources reflects the history of aposthia. Trait aposthia was first referenced in Jewish law of 1567 CE, in relation to a child born circumcised [*3*]. Later, the Prophet Muhammad ﷺ was said to have been born with "natural circumcision" (in Ibn Sad *Tabaqat-ul-Kubara*). However certain studies have reported that the trait aposthia with normal development of the urethra and glans is very rare because it is generally accepted that normal preputial development is required for the successful canalization of the glans urethra [*4*].

It is interesting that the literature discussing the advantages and disadvantages of circumcision does not refer to aposthia trait. Usually an organism with recessive trait or disorder is used as model for understanding the problem as a natural condition. We think that the person with aposthia trait is a suitable model to study the importance and genetics of the prepuce. But this trait has been ignored for reasons that are unknown and no work is available about its genetics.

Here we report the genetic profile of aposthia trait in certain families of Dera Ghazi Khan city, Pakistan, in order to provide the baseline for future molecular and medical studies.

Methods

A door-to-door survey to study various human physical and genetic traits was conducted in the municipal committee area of Dera Ghazi Khan city, a district headquarters in southern Punjab. The population of the city (190 542 persons) is divided into 2 main ethnic groups: about 70% Seraiki-speaking natives and 30% Urdu-speaking Indian migrants. Among them 98% are Muslims, for whom male circumcision at an early age is a religious recommendation (*sunnah*) [*5*]. So the identification of males with aposthia is easy in this community at the time of circumcision.

A sample of 1200 families (830 native and 370 migrant) was studied in which 6 families having aposthia individuals were identified when artificial circumcision was not possible. All the aposthia trait-bearing individuals underwent clinical examination by a qualified physician. The extensive pedigrees of the families were constructed by interviewing the elders of the families.

Results

During the survey, 6 families with aposthia individuals were identified among the 1200 families (830 native and 370 migrant). There were 3 families with sporadic cases and 3 with more than 1 aposthia male: family DG-01 had 4 living cases, family DG-02 had 2 living and 1 dead case and family DG-03 had 2 living aposthia cases.

Description of sporadic cases

The clinical study of 3 sporadic cases showed that 2 had aposthia and mild hypospadias for whom no surgery was required, while 1 needed surgery because of severe hypospadias. The parents of these cases were first cousins. In addition, strict endogamous history was evident in their families.

Descriptions of families

Family DG-01

The family comes from Dera Ghazi Khan city and has 5 generations (PPD–V). The elders of this family were Indian migrants

belonging to Karnal district and settled in this area after partition of the Indian subcontinent in 1948. They are Muslims who converted from Hindu Rajput. Most of the family members were agrarian by occupation. Marriages were strictly endogamous within the Rajput sub-caste Toor. First cousin marriages (brother's daughter and sister's son) were found frequently as a custom. The pedigree, consisting of 37 individuals including 4 trait-bearing males, is shown in Figure 1. All the trait-bearing males had a normal structural and functional penis without prepuce. Aposthia trait appeared in the offspring of only the aposthia father. Among offspring of all other male or female family members, no aposthia cases were born. No reliable information was available about the first generation.

Family DG-02

The family comes from Dera Ghazi Khan city and has 6 generations (PPD–VI). The elders of this family were also Indian migrants belonging to Rohtak district and settled in this area after partition of the Indian subcontinent in 1948. They are Muslims converted from Hindu Rajput. Most of the family members were sub-agrarian by occupation. Marriages were strictly endogamous within the *biradri* (caste). Non-cousin marriages used to be common but after migration, restricted cousin marriages started (sister's children marry brother's children but not among brother's children). The pedigree consists of 111 individuals including 3 trait-bearing males, as shown in Figure 2. All the trait-bearing males had a normal structural and functional penis without prepuce except for slightly abnormal canalization of the glans urethra, i.e. hypospadias. But hypospadias condition varied in expression, i.e. was not evident in III-4, slightly visible in V-16 and in VI-14 a very small change. The aposthia male offspring VI-14 was born as a result of aposthia father V-16 marriage with cousin V-21. Among the offspring of all other male or female family members no case was reported. Aposthia male III-4 died just after marriage because of an infectious disease without any progeny. The propositus (V-16) was 45 years old.

Family DG-03

This family is from Dera Ghazi Khan city and has 5 generations (PPD–V). The elders of this family were native and belonged to the Nutkani tribe and settled near the west bank of the Indus river. They are Muslim and mostly agrarian by occupation. Marriages were strictly endogamous within the tribe (equivalent to caste). Cousin marriages were common but marriages among brother's children were found most frequently. The pedigree consists of 38 individuals including 2 trait-bearing males (Figure 3). All the trait-bearing males had a normal structural and functional penis without prepuce, except for a slight abnormal canalization of the glans urethra, i.e hypospadias. Aposthia male V-6 was born in a family of aposthia father IV-11 who married a cousin IV-4. No case was reported among the offspring of all other male and female family members. The propositus (IV-11) was 63 years old.

Discussion

The prepuce is a common anatomical covering of the glans penis and clitoris of all human and non-human primates [*6*], but aposthia trait rarely found in the human population [*2*]. The aposthia persons were considered as sporadic cases or birth defects without ill-effects.

In South Korea in 1999, Kim et al. found 69% "naturally circumcised" among uncircumcised males during a survey. Their

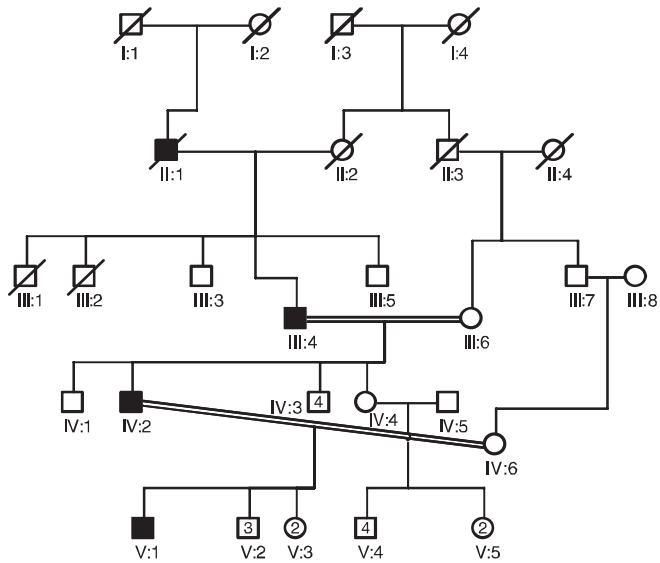

Figure 1 **Pedigree of family DG-01 with aposthia. Circles denote female family members, squares denote male family members, and symbols with a diagonal line indicate deceased family members. Black symbols indicate individuals with aposthia**

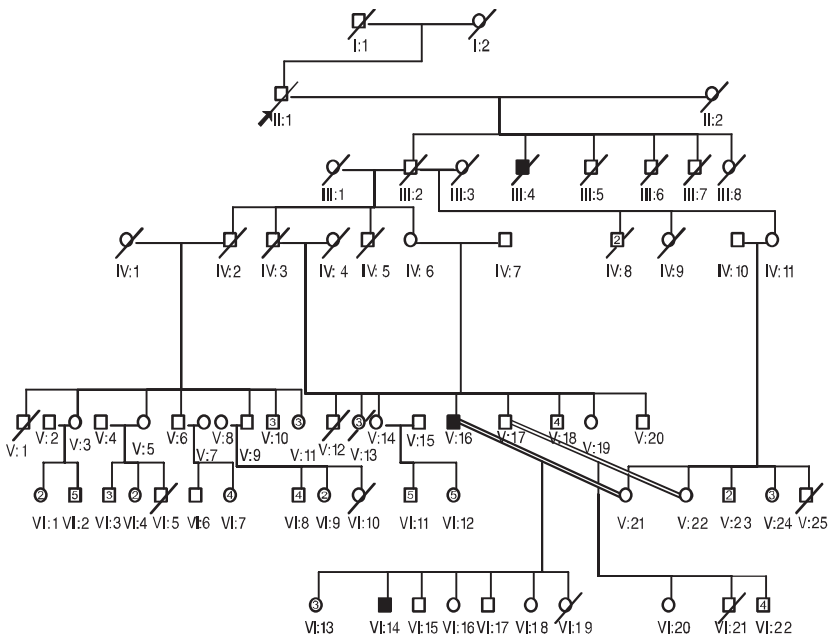

Figure 2 **Pedigree of family DG-02**

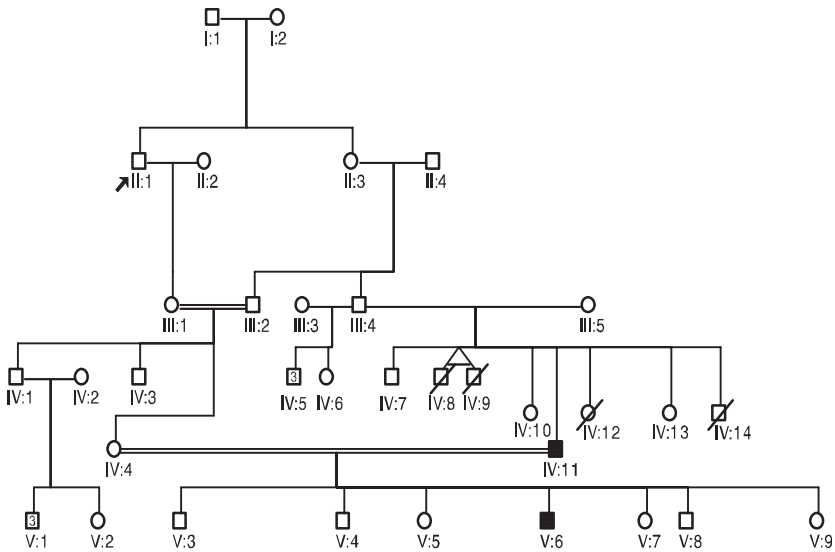

Figure 3 **Pedigree of family DG-03**

explanation of the word "naturally circumcised" included the following conditions: (1) having no phimosis; (2) having relatively short prepuce but not "phimosis"; (3) having prepuce fully retractable during erection; (4) having a penis that looks more or less like a circumcised penis even when not erect. The last condition was actually aposthia condition [*7*].

Recently Radojicic and Perovic found 6 various morphological forms of prepuce indicating its quantitative nature—"monk's hood", "cobra eyes", "normal" (intact), "flat", "v-shaped" and "collar-scarf" [*8*]. So the length of prepuce in the human population varies from large to problematic to very small (unable to circumcise) or absent i.e. aposthia condition. This variation in shape and size of the prepuce in the population suggests that it may be a dominant quantitative trait.

During the present study we found 3 sporadic cases and 8 living and 1 dead person with aposthia trait having a positive family history. All affected cases belonged to strictly endogamous groups that are a cultural characteristic of the Indian subcontinent [*9*]. In the study population, consanguineous marriages were 71.1%, with 0.0325 inbreeding coefficient [unpublished data]. It is commonly reasoned that populations with simpler histories (i.e. fewer founders, less admixture) should exhibit less variability in the genes underlying complex traits [*10*]. This is why aposthia, being a quantitative trait, appeared in certain families of the population being studied.

The genetic analysis of our families showed that the trait is inherited from aposthia father to aposthia son. No aposthia female was recorded in this study because no parent was prepared to report them.

Similarly, to our knowledge, no cases in females have been reported in the literature to date.

The modes of inheritance of aposthia trait from male to male indicate that the expression of aposthia condition requires certain Y-linked modifier loci in addition to a number of autosomal recessive genes. The first appearance of the trait in sporadic cases and in families may be due to aggregation of recessive loci and special Y-chromosome with modifier locus because of strict endogamy and frequent consanguineous marriages that increases inbreeding. The same situation is observed in the families we studied. These are patrimonial, in which the Y-chromosome is inherited from forefathers.

Along with aposthia, hypospadias trait was also found inherited in family DG-02 and family DG-03. The variation in expressivity of hypospadias also gives an indication of its quantitative nature. Appearance of both traits in these families is not surprising because it is generally accepted that normal preputial development is required for the successful canalization of the glans urethra [*4*]. But hypospadias [*11*] and epispadias [*12*] have also been reported with normal preputial development. Yucel et al. reported the presence of prepuce in 15 children with hypospadias [*13*]. Actually the embryology of the penile prepuce has been controversial since the original account given by Schweigger-Seidel in 1866 [*14*].

From the study of our families, it seems that aposthia and hypospadias are 2 independent quantitative recessive traits. But the co-inheritance of these traits stresses that the loci of both traits are closely linked.

It is concluded that aposthia trait is under genetic control in the 3 studied families. However, confirmation of our finding would require more extensive molecular studies that depend on cooperation of families, availability of facilities and accumulation of reasonable data.

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Guidelines for the early detection and screening of breast cancer (WHO EMRO Technical Publication Series, No. 30)

Studies have shown that most patients with breast cancer in the WHO Eastern Mediterranean Region present for the first time at stages 2 and 3, indicating the need for increased community awareness and early detection of the disease. Well conceived and well managed national cancer control programmes are able to lower cancer incidence and improve the lives of people living with cancer. These evidence-based guidelines have been designed to support ministries of health in their policy-setting for early detection and screening of breast cancer, as will as to assist health care providers and patients in decision-making in the most commonly encountered situations.

The document is available online at: http://www.emro.who.int/dsaf/dsa696.pdf

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