

## Consanguineous Marital Union Resulting in a Progeny of Whistling-face Syndrome and Hemophilia: A Case Report

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### Abstract:

Many different types of genetic disorders are noted to be prevalent among consanguineous progeny. Although the most common type of consanguineous union in all major societies is between first cousins, the importance of customary influences is apparent from variations in the specific types of first-cousin marriages contracted. Epidemiological data for the prevalence of whistling-face syndrome (WFS) are not available, but less than a hundred cases reported in the literature are noted. We are presenting a case where a consanguineous marriage resulted in two of their children presenting with WFS and one with hemophilia.

**Key Words:** Consanguinity, hemophilia, whistling-face syndrome

### Introduction

A consanguineous marriage is usually defined as a union between two individuals who are second cousins if not closer. It is thought that universally at least about one-fifth of the human population living in close communities prefer consanguineous marriages and at least 8.5% of offsprings have consanguineous parents.<sup>1</sup> Economic and socio-cultural benefits are the main factors governing occurrence of consanguineous marriages.

The offspring of consanguineous relationships is at greater risk of genetic disorders. Most cases of WFS are sporadic, though evidence of autosomal dominant transmission is noted. Previous reports of WFS in affected siblings of unaffected parents, suggest that WFS can be inherited as an autosomal recessive or an X-linked recessive pattern.<sup>2</sup> There are two alternative explanations for such observations. First, some of these reported cases mostly did not have WFS though there are few well documented examples of other distal arthrogryposis (DA) disorders transmitted in any pattern other than autosomal-dominant. Second, an autosomal- or

X-linked-recessive pattern can be also noticed in cases in which a parent has nonpenetrant somatic mosaicism. We, therefore, presume that both alternatives will eventually be found to explain most cases in which transmission deviates from an autosomal dominant pattern.

### Case Report

A 7-year-old girl was referred to our department with a complaint of microstomia (Figure 1). She was the second child born to young, healthy but consanguineous parents. The mother was 34 years of age and the father 37 years. The parents were first cousins. The mother had not taken any drugs, nor was exposed to X-rays during pregnancy.

On repeated questioning, her parents informed us that they had a total of 4 children. The eldest one was a daughter 13 years of age who was apparently a normal child. The second child was the patient referred to our clinic. The third was a 5-year-old male child who was both deaf and dumb. He was also diagnosed with hemophilia-A on an earlier occasion. The fourth girl child aged 3 years was similar to the second sibling (Figure 2).

The patient referred to us had a history of recurrent chest infection on change of weather conditions. She managed her routine activities pretty well but was not involved in any extracurricular physical activities as she could not run at a fast pace. Her cognitive development was appropriate for chronological age. She calmly interacted with her examiner. Vision and hearing were apparently normal.

Physical examination indicated weight as 16 kg, height of 2 feet 7 inches, pulse at 83. Cardiac auscultations were phonetically normal. The lung functions were also normal. The patient did not have any visceromegaly. Spinal column had no pathological deviations. Ophthalmic evaluation revealed mild telcanthus and ptosis of both eyes. Puckered lips resembling the act of whistling was noted with micrognathia. "H"-shaped cutaneous dimpling on the chin was an obvious feature noted. A short neck along with muscle contractures leading to an inability to extend completely the neck was noted. The patient could not raise arms above her shoulder level.

Intra-oral examination revealed a small tongue, high-arched palate, mild crowding in both the arches and delayed eruption

of permanent teeth, all features common to whistling-face syndrome (WFS). All teeth were caries free and had no obvious periodontal pathology.

The fourth girl sibling was examined, and similar findings were noted. The male child was not cooperative during examination but seemed to be apparently normal except that he was deaf and dumb, and his medical records and laboratory investigations confirmed his hemophiliac state. He was not cooperative even to be photographed. The pedigree analysis showed that no other family members had similar features. The patients other relatives from paternal or maternal sides were not examined but were reported to us as free from the disorder. Genetic studies of the patients with WFS revealed no genetic mutations. The father (Figure 3) of the children, hoping of having a normal male child, and unaware of the consequences of a consanguineous marital union, was counseled regarding the further risks involved.

### Discussion

Consanguineous marriages and its effects continue to draw attention among social scientists, clinicians, and geneticists. As a matter of fact, a marriage is considered consanguineous if it has been conceived between individuals who are related as second cousins or closer, since the levels of homozygosity beyond that level differ only to a minor degree from those observed in the general population. Therefore this underestimates the actual level of homozygosity perceived in an individual, but the decision is taken largely on practical situations as in many communities the family pedigree show complex multiple pathways of consanguinity that are difficult to interpret. Both social and economic reasons are given for the popularity of consanguineous unions.

Frequency of the disease allele in the genetic pool inversely correlates to the risk that an autosomal recessive disorder to be expressed in the offspring of a consanguineous marriage.<sup>3</sup> Once a specific mutation has been identified within a consanguineous pedigree diagnosis can be greatly simplified. The consanguinity rate among families with autosomal recessive disorders significantly differs from that among the general population where its prevalence is between one in 500,000 to 1 in two million among the homozygous forms. The effect is significant for rarer disorders as a carrier is not likely to find a partner that carries a similar disorder unless individuals are related. Thus, autosomal recessive genes are not obvious within the family for quite a few generations and only express pheno-typically in children after new consanguineous unions in the family. Reports also show a high prevalence of incidence of rarer bleeding disorders.<sup>4</sup> Consanguineous unions have shown an increased risk of occurrence of many bleeding disorders.<sup>5</sup> Studies estimate that in nations where such unions are frequent, inherited coagulation defects are so frequent that they cross the prevalence of less common disorders as hemophilia B.<sup>6</sup>



**Figure 1:** Patient showing features of whistling-face syndrome.



**Figure 2:** Sibling of the patient showing similar features.



**Figure 3:** Both siblings with one parent.

Approximately, 1 in 3000 children are born with multiple congenital contractures (MCCs), and whereas these cases are usually sporadic, children with MCCs are frequently found to have an underlying syndrome diagnosis. Accordingly, autosomal- dominant, autosomal-recessive, and X-linked transmission of MCCs is well-documented in multiple studies.<sup>7</sup>

Children with MCCs are frequently labeled with the diagnosis of DA, defined as nonprogressive congenital contractures of more than two different body areas. Syndromes involving arthrogryposis were classified into 10 hierarchically related disorders, i.e., DA1-DA10 as to the proportion of characters they shared among themselves. This classification has been useful for increasing the accuracy of diagnoses, improving patient management and as a prerequisite to identifying the genetic basis of DA syndromes.<sup>8</sup>

Among the DA types, the phenotype of DA2 is called WFS.<sup>9</sup> WFS is a rare MCC syndrome that is relatively well-known because affected children often have, in addition to contractures of the limbs, striking contractures of the facial muscles. These contractures result in a significantly reduced mouth opening, just only a few millimeters wide, so the name WFS.<sup>10</sup> Additional facial characteristics include down-slanting palpebral fissures, prominent nasolabial folds, hypoplastic alae nasi, a long philtrum, “pinched” lips, a small mouth, and “H-shaped” dimpling of the chin. The known genetic etiologies of DA syndromes involve abnormalities of the contractile apparatus of fast-twitch myofibers.

### Conclusion

In populations where consanguineous marriage is widely practiced, genetic disorders will continue to contribute significantly to population ill health issues. However, this increase will partly be negated by people moving to larger cities and increased nuclear family trends, with the resultant decline in the incidence of consanguineous marriages.

Though culturally desirable, social and economic benefits associated with non-consanguineous marriages can be

predicted. Therefore, new diagnostic, counseling and treatment skills need to be rapidly developed in conjunction with appropriate community education programs.

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