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Editorial Comment

The Carey–Fineman–Ziter Syndrome: Follow-up of the Original Siblings and Comments on Pathogenesis

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In 1981 at the Festschrift honoring the many contributions of David W. Smith, I presented a unique pair of siblings with a distinctive pattern of malformation. The paper from this presentation was published as part of a series in the *Journal of Pediatrics* [Carey et al., 1982], and this condition has come to be called the Carey–Fineman–Ziter syndrome (CFZ). The described disorder included the following components: facial diplegia with an opthalmoplegia comprising the Moebius sequence, the Pierre Robin sequence, short stature, postnatal-onset microcephaly, congenital and persistent hypotonia, brachydactyly with absent digital flexion creases, and a generalized muscular hypoplasia. The sibs, a male and female, showed normal intelligence, a characteristic face, and an apparent myopathy although no specific muscle disorder was recognized on biopsy. The family was described in the context of a review of the causes and pathogenesis of the Robin sequence [Carey et al., 1982]. In fact, the observation that these sibs had Pierre Robin sequence as a component of a generalized neuromuscular disorder lent support to the notion that the disruption of palatal closure could be due to altered jaw or tongue movement during early development (the so-called Robin complex as discussed by Cohen [1999]).

The purpose of my Commentary here is to provide an update on the original patients in the context of the ensuing articles in this issue of the *Journal* [Dufke et al., 2004; Maheshwari et al., 2004; Verloes et al., 2004]. In addition, I will discuss the nosology of the Moebius sequence and its associated syndromes and propose two candidate genes as the potential basis of the CFZ syndrome. The overall significance of this disorder and its place in our understanding of the Moebius and Robin sequences will be addressed briefly.

I have had the privilege of following the two original siblings with the CFZ syndrome since 1980. The original Patient 1 (Fig. 1) recently completed a 2 year mission for the Church of Jesus Christ of Latter Day Saints. Despite challenges in school related to hearing and verbal expression, the patient completed high school and is now enrolled in college. His medical problems since the original report have included longstanding GI disturbances related to biopsy-proven villous atrophy. Like his older sister, he has had significant scoliosis requiring surgery and placement of rods. At the time of this surgery at age 16 years, we performed a repeat muscle biopsy that again showed nonspecific findings and, in particular, there were no alterations of mitochondria. He continues to be in relatively good health and has not had the significant restrictive lung disease and pulmonary insufficiency that his older sister experienced.

The original Patient 2, the older sib of Patient 1, is shown in updated photographs in Figures 2 and 3. She also had normal intelligence and finished junior college. She, however, did have significant restrictive lung disease and died of pneumonia at age 37. She also had rods placed for her scoliosis as a teenager.

The physical examination of both patients was updated in 1996 when these most recent photographs were taken (Figs. 1 and 2). Note the consistent facial diplegia, but also the characteristic nasal configuration. Both had microcephaly and short stature (<2nd centile). Examination of hands showed absence of distal flexion creases on the 4th and 5th digits and brachydactyly. Both individuals had marked decrease in muscle mass and normal, but decreased, deep tendon reflexes.

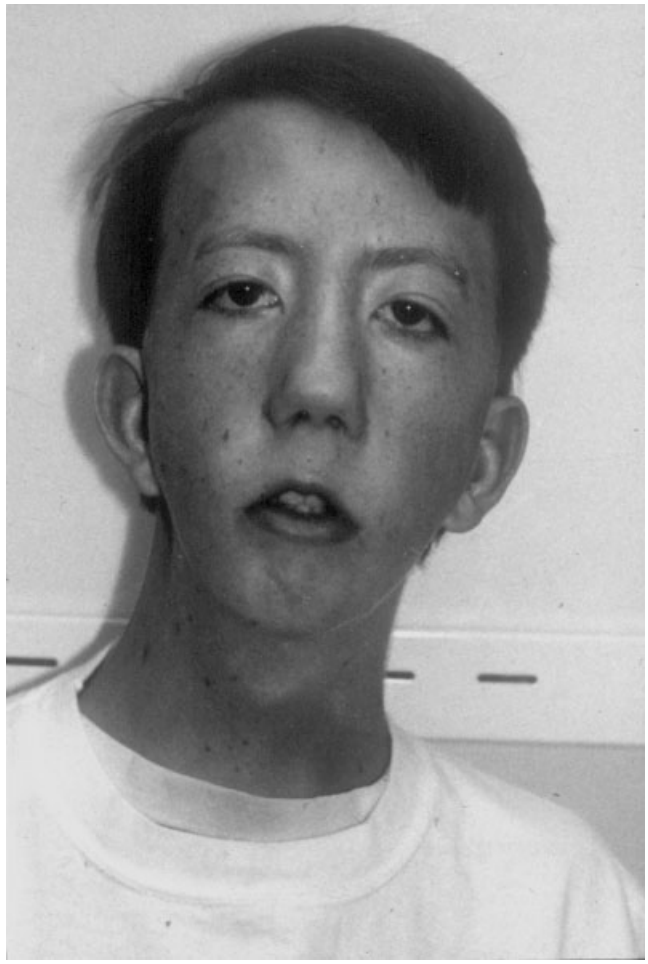

Fig. 1. The original Patient 1 at 18 years of age.

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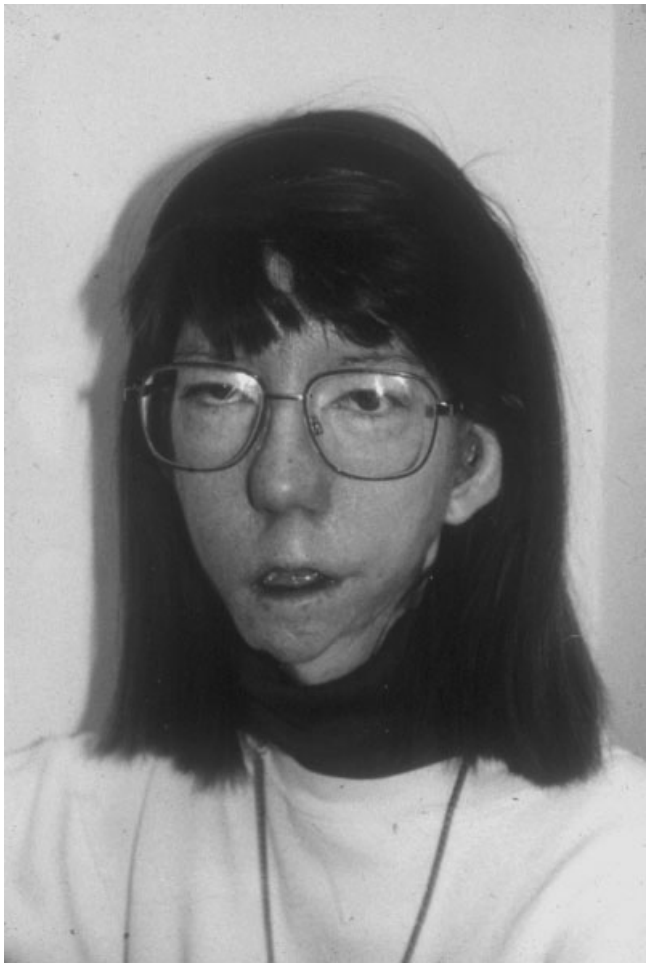

Fig. 2. The older sister, Patient 2, at 36 years of age.

Figure 3 is a selection of photos of both patients taken over the years. It shows the similarity of facial features and evolution over time. Patient 2 did have facial surgery to modify the facial diplegia which gave her a different gestalt and nasal contour when older.

As summarized nicely in the accompanying articles, there have been four additional cases reported with CFZ since the original article—two sporadic cases and one set of siblings [Schimke et al., 1993; Baraitser and Reardon, 1994; Ryan et al., 1999]. All have had some motor delay, and all have had normal intelligence except for the siblings of Ryan et al. [1999]. The Robin sequence was present in our patients and that of Schimke et al., but a Robin cleft was absent in the other three recently reported cases. Only our patients have had postnatal-onset microcephaly, but all patients have had significant feeding difficulties. Despite some difference in the presence of certain features, I have surmised that the patients of Schimke et al. and Baraitser likely had the same condition, while the siblings of Ryan et al. represent a different condition. Of note, the mother of our patients feels that none of the four patients have the same condition as her children.

Now let me discuss three themes that are raised by the delineation of the CFZ syndrome and related disorders. These are: the Robin cleft, the Moebius sequence, and potential candidate genes for CFZ syndrome.

The pathogenetic basis of CFZ syndrome, as pointed out by the authors of the ensuing articles, raises discussion of our

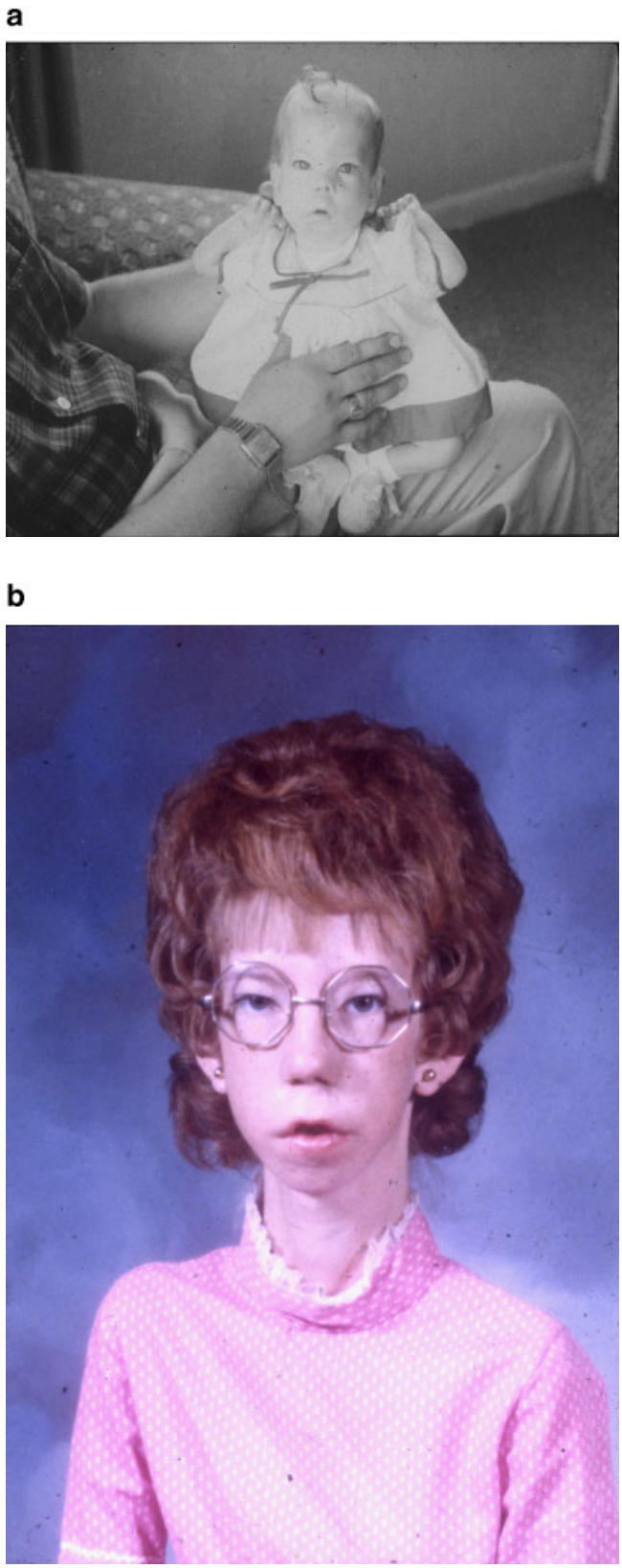

Fig. 3. **a**: Patient 2 as an infant. **b**: Patient 2 as an older child. **c**: Patient 1 at 11 years of age. **d**: Both patients as adults.

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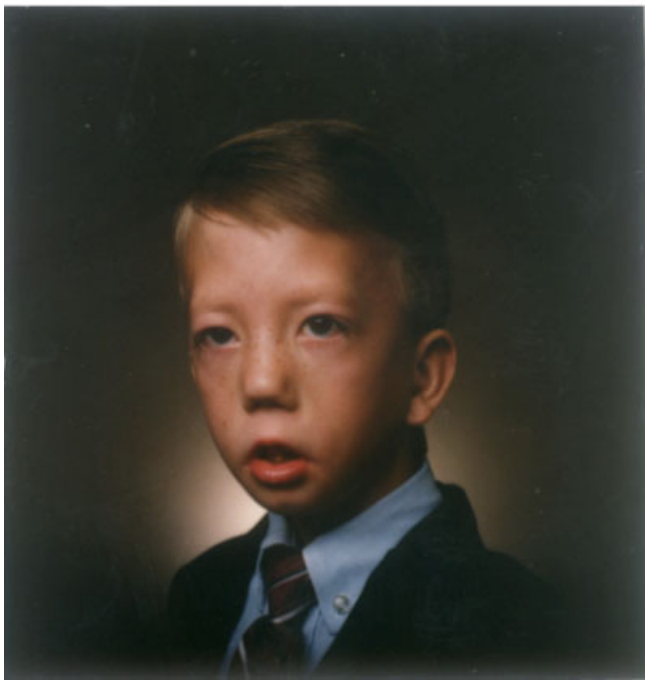

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Fig. 3. (*Continued*)

understanding of both the Robin and the Moebius sequences. As suggested in the original article [Carey et al., 1982], the presence of a cleft palate in individuals with a neuromuscular condition suggests that an alteration of jaw and/or tongue movement is related in some way to producing the palatal cleft. The occurrence of cleft palate in neuromuscular conditions in general is very uncommon. Indirectly, the association in the literature of cleft palate with conditions of arthrogyposis (where we postulate that movement is important in pathogenesis) also supports the idea that altered movement may be a pathogenic factor as is posited for CFZ syndrome (Table I) [Carey et al., 1982].

TABLE I. Neuromuscular Syndromes With Cleft Palate*

- CFZ syndrome
- Native American myopathy
- Myotonic dystrophy (rare)
- Escobar multiple pterygium syndrome
- Marden–Walker syndrome
- Association of arthrogryposis/cleft palate—many conditions

*Not necessarily Robin cleft.

The label Moebius syndrome, or preferably, sequence is used differently by various authors and clinicians. It is often applied loosely to any child with a cranial nerve dysfunction, or even facial diplegia by itself. I would agree with Baraitser [1982] who suggests a more strict use of the term. I would suggest restricting the term to cases with congenital cranial nerve VII paresis with paresis of either cranial nerve VI or XII. Patients with facial diplegia and the characteristic facial gestalt of Moebius patients and limb deficiency comprise the classic disorder. What has been labeled Moebius "syndrome" or sequence in the literature is clearly causally heterogeneous (Table II). The authors of the accompanying articles discuss this heterogeneity in more detail.

Investigations of particular animal models bring two potential candidate genes to mind for the genetic basis of the CFZ syndrome. Targeted disruption of *Hoxb1* in the mouse causes failure of formation of the motor nucleus of the VIIth cranial nerve in homozygous mice [Goddard et al., 1996]. The human homolog of this gene, *HOXB1*, is located on 17q and is the first of these proposed candidates. The second candidate gene of interest is the calcium channel gene *CACNL1A3* located in human chromosome 1q32.

The murine homolog of this gene, *Cacna1s*, was discovered to be the basis for a well-known mouse mutant called muscular dysgenesis (mdg) by Chaudhari [1992]. This is an autosomal recessive condition involving cleft palate, myopathy, and congenital contractures. I had proposed mdg as a murine model for CFZ syndrome in the original article [Carey et al., 1982]. Dominant missense mutations of *CACNL1A3* are known to cause hypokalemic periodic paralysis type I [Ptacek et al., 1994]. Analyzes of both of these genes are planned in order to test the hypothesis that one of the genes is, in fact, the cause of CFZ syndrome.

Having followed the original CFZ syndrome patients for 23 years, my own opinion is that the CFZ syndrome is a very discreet entity and different than most of the patients that are labeled Moebius sequence with or without a Robin cleft. As mentioned above, the mother of our patients does not feel that any of the reported patients (or any of the other cases that have been sent to me over the years as potential CFZ syndrome) have

TABLE II. Heterogeneity of the Moebius Sequence

- Moebius sequence ("syndrome")—classical
- MBS1—deletion and translocation at 13q12.2
- Autosomal dominant forms
  - MBS2—3q21
  - MBS3—10q21.3
- Teratogenic causes
  - CVS before 10 weeks
  - Misoprostol
- CFZ syndrome

the same disorder as her children. The mother of our patients characterized the condition and her family's experience in a recent book [Hanson, 2002]. There is a subtle difference in the facial features of our patients (Figs. 1–3) compared to other cases reported in the literature and depicted in the ensuing articles. While I certainly would agree with Verloes et al. [2004] that there is a spectrum here that includes patients with Moebius and Robin, I would propose that CFZ syndrome is a more discrete entity. Ideally, having a molecular basis for this and the related disorders will clarify the nosology of this interesting set of conditions.

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