Transmission of the abnormality by means of a dominantly expressed mutant gene or by a minute chromosome abnormality appears more likely (McArthur and Edwards, 1967). In less than 5% of the cases a structural abnormality of the chromosomes has been seen. However, the nature of the chromosome abnormality has varied greatly; hence, assignment of an aetiological role to the chromosome defect, even in these cases, would not seem warranted. The presence of structural defects, as well as the frequently variable manifestations, would be consistent with either a chromosome anomaly or with a dominant mutation. In the present case there is insufficient historical, clinical, or cytogenetic evidence to assign any particular mode of inheritance.

We wish to thank Doctors Marjorie Shaw and Charleen Moore for chromosome studies on patient Ta. C.

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REFERENCES


The de Lange syndrome in one of twins*

**Summary.** A pair of female monozygotic twins, one of them affected by the de Lange syndrome, is described for the first time. Monozygosity was established by most of the accepted standards in use at the present time. Speculation is offered as to whether the discordance in the manifestation of the syndrome provides any clues for understanding its

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controversial pathogenesis. In this regard two genetic mechanisms are discussed. One is the hypothesis of a chromosomal or mitotic instability. The other possibility would be a postzygotic new mutation of a gene of large effect.

In 1933 in Amsterdam, Cornelia de Lange described two infant girls with mental deficiency and a combination of characteristic clinical features. A comprehensive review by Berg et al (1970) illustrates many aspects of this worldwide recognized condition. There has been much speculation about its aetiology. Though there is some evidence suggesting a genetic origin, the available data do not provide evidence as to its nature. We present here the first observation of discordance for the de Lange syndrome in apparently monozygotic twins.

**Case reports**

When first examined the twins were 5 months old (Fig.), their mother was 34 and their father was 38 years old. There were two older sisters who appeared normal. The mother had had one abortion before the twins were born.

**Twin 1.** She was born after a normal full-term pregnancy. The delivery was uneventful and her birthweight was 1820 g, length 43 cm, head circumference 28.5 cm, chest circumference 29 cm, and Apgar score 4. There was no history of drug ingestion, x-ray exposure, or viral illness during pregnancy. At the age of 5 months her psychomotor development was obviously retarded and contrasted with the normal development presented by her twin sister. At that time her weight was 2960 g, length 52.8 cm, and head circumference 32 cm (all measurements were well below the 3rd centile).

Physical examination showed a small infant girl with peculiar facies. The following features were noticed: microcephaly, low-set ears, abundant dark hair, long eyelashes, synophrys, micrognathia, narrow palate, anteverted nostrils, and increased distance between the lip and the nose. The elbows were fixed in flexion and the fingers were short, with clinodactylysous fifth digits and proximally placed thumbs. The fifth fingers showed only a single flexion crease. One last feature of the hands was the second finger tending to override the thumb and the fifth finger overlapping the fourth. There was partial syndactyly between the second and third toes on both feet. A grade 2/6 systolic murmur was best heard at the lower sternal border. Radiological examination of the chest and electrocardiogram results were normal. X-ray films of both upper extremities showed subluxation of the radial head at the elbow joint. Rudimentary phalanges were seen bilaterally on the fifth fingers.

**Twin 2.** She was normal at birth with a weight of 3400 g, and length of 50 cm. At the age of 5 months her weight was 6480 g and her length 64.5 cm.

Chromosomal studies with a fluorescent staining procedure showed a normal karyotype in both twins. Dermatoglyphs were as follows. **Twin 1.** Left hand: ulnar loop (Lu), whorl (W), W, Lu, Lu; right hand: Lu, W, Lu, Lu. **Twin 2.** Left hand: Lu, Lu, W, W, Lu; right hand: Lu, W, Lu, Lu, Lu. Palmar features of twin 1 showed abortive simian creases on both hands and a"d angle in r position. The dermal ridges of the hypothenar and hallucal areas were hypoplastic.

Blood group antigen and serum protein studies under-

![General appearance of the twins at 5 months of age.](http://jmg.bmj.com/ on May 29, 2017 - Published by group.bmj.com)
taken in both twins and their mother strongly support monozygosity as depicted in the Table.

**TABLE**

<table>
<thead>
<tr>
<th>Blood groups</th>
<th>Twin 1</th>
<th>Twin 2</th>
<th>Mother</th>
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<tr>
<td>ABO</td>
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<td>Haptoglobin (Hp)</td>
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**Discussion**

The clinical diagnosis of the de Lange syndrome was not difficult to entertain in one co-twin described here, since a number of characteristic features involving the face and limbs were present.

The first authors to document the occurrence of the condition in twins were Choo and Bianchi (1965). They reported a pair of like-sex twins and monozygosity was established based on determination of 9 serological tests. Opitz et al (1965) reported female twins with striking similarity in facial features characteristic of the syndrome. Apparently the twins reported by Kroth (1965) do not have the de Lange syndrome.

The observation of a set of monozygous twins discordant for the de Lange syndrome is noteworthy because it contributes to the understanding of the pathogenetic processes which result in the condition. The aetiology and the genetic mechanisms of this syndrome are still controversial. The few descriptions of chromosomal anomalies showed inconsistent findings, and probably they represent a variable effect of the unknown causal agent which is responsible for the phenotypic features of the condition. Motl and Opitz (1971) suggested that chromosome breakage occurring shortly after fertilization or during early cleavage divisions could eventually be followed by subsequent reunion of the fragments. This might explain the cases in which no chromosomal changes are seen even by using more elaborate techniques (Sachdeva and Smith, 1973). We cannot be sure in either instance that the chromosome structural changes are in any way related to the phenotype of the syndrome. However, the hypothesis of a chromosomal or mitotic instability might establish a cellular relation to the congenital and postnatal dwarfism and organ hypoplasia frequently observed in the de Lange syndrome. This analogy may justify the lack of concordance for the syndrome which occurred in our pair of twins. It is possible that at almost any time after twin development has occurred minor chromosomal changes may develop in one twin and not in the other. Failure to find an abnormal karyotype in our affected co-twin does not disprove this assumption if we consider the possibilities of a successful realease of chromosome fragments or undetectable cell loss occurring at late embryonic stages.

A second genetic mechanism which might also explain the discordance in the twins would be a post-zygotic new mutation of a gene of large effect. A dominant mutation would be the best possibility, if we assume that the de Lange syndrome is a homogeneous entity caused by one factor. This same dominant mutation might also be responsible for the sibships with more than one affected sib, when instead of being a post-zygotic event it represents a gonadal mutation in a gametocyte precursor in one of the parents.

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