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Mitral valve prolapse in five members of a family including the identical twins

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Summary

A family in which the five members including the identical twins had a mitral valve prolapse was described. None of these members had any known stigmata of Marfan syndrome and their auscultatory findings were different each other. M-mode echocardiograms disclosed a midsystolic buckling of the mitral valve in the identical twins, their parents and the mother's brother, but all were asymptomatic. Electrocardiograms revealed a wandering pacemaker in two members.

The index case was a 13-year-old girl whose apical late systolic murmur was detected incidentally by the mass screening examination for cardiac diseases. Both the inhalation of amyl nitrite and injection of methoxamine induced the augmentation of this murmur and made it holosystolic. The identical twin of the index case had multiple apical non-ejection clicks. However, a mitral regurgitant murmur was not induced by pharmacological provocations. Two-dimensional echocardiograms revealed prolapse of both the anterior and posterior mitral valve leaflets in both of them. Their mother had a late systolic click and the mother's brother had a cardiopulmonary murmur. The abnormal auscultatory findings were not observed in their father.

This familial study suggested the genetic background and the various clinical manifestations of mitral valve prolapse.

Key words

Mitral valve prolapse　Identical twins　Cardiopulmonary murmur　Echocardiography
Phonocardiography

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Since the last decade, mitral valve prolapse has been known as the most common valvular disorder. Recently, this entity was also reported to be the most common eitology of clinically isolated, severe and chronic mitral regurgitation[1]. Although the pathogenesis of this disorder is unknown, a number of studies suggested the genetic basis in some families[2~8]. We here report a family in which five members including the identical twins were found to have mitral valve prolapse.

Case reports

The identical twins, their parents and the mother's brother, who were all asymptomatic and had no history of cardiac diseases, were found to have mitral valve prolapse (**Fig. 1**). The identical twins and their father had slender figures but none of the family members had any known stigmata of Marfan syndrome. Although the electrocardiograms showed a wandering pacemaker in the first twin and her father, neither ST-T abnormalities nor extrasystoles were found in any members.

The first twin (the index case)

The index case was a 13-year-old girl and her abnormal heart murmur was detected incidentally by the mass screening examination for cardiac diseases in schoolchildren[9]. A high-pitched late systolic murmur (grade I/VI) was heard at the apex (**Fig. 2**). Both the inhalation of amyl nitrite and intravenous injection of methoxamine induced an augmentation of this murmur and made it a holosystolic murmur with an accentuation in late systole (**Fig. 2**). A midsystolic buckling of the mitral valve was demonstrated on the M-mode echocardiogram (**Fig. 3**). Two-dimensional echocardiography demonstrated prolapse of both the anterior and posterior mitral valve leaflets (**Fig. 4**).

The second twin

She was the identical twin of the index case. Examinations of blood specimens to confirm the monozygosity revealed the same results for 14 blood types as shown in **Table 1**. The index case was typed for HLA (human leukocyte antigen), and she was found to have HLA-A2, A26 and B15.

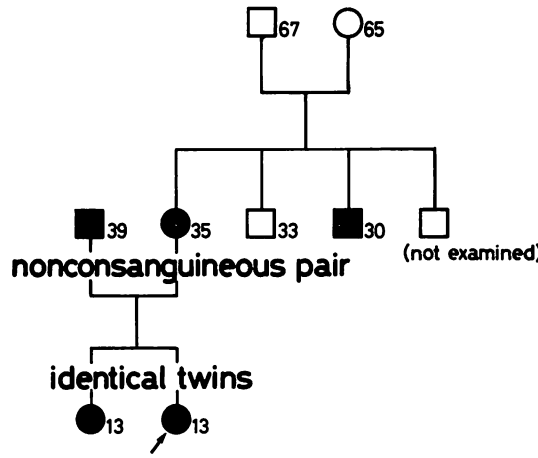

Fig. 1. Family pedigree.
□=male, ○=female, ■ ●=mitral valve prolapse, ↗=the index case. Numbers indicate the age of each case.

Three mid to late systolic clicks without a significant murmur was audible at the apex (**Fig. 5**). In contrast to the first twin, neither of

Table 1. Blood types of the identical twins

ABO	B
MNSs	Ns
Rh	ccDEE
P	P_2
Kell	K−k+
Duffy	Fy (a+b−)
Lewis	Le (a−b+)
Kidd	Jk (a−b+)
Secretor	Se
Haptoglobin	Hp 2−1
Gc	1F−1S
Gm	zagu/zab°st
Km	b/b
Protease inhibitor	M_1M_1
HLA*	A2, A26, B15

*HLA was typed only in the first twin.

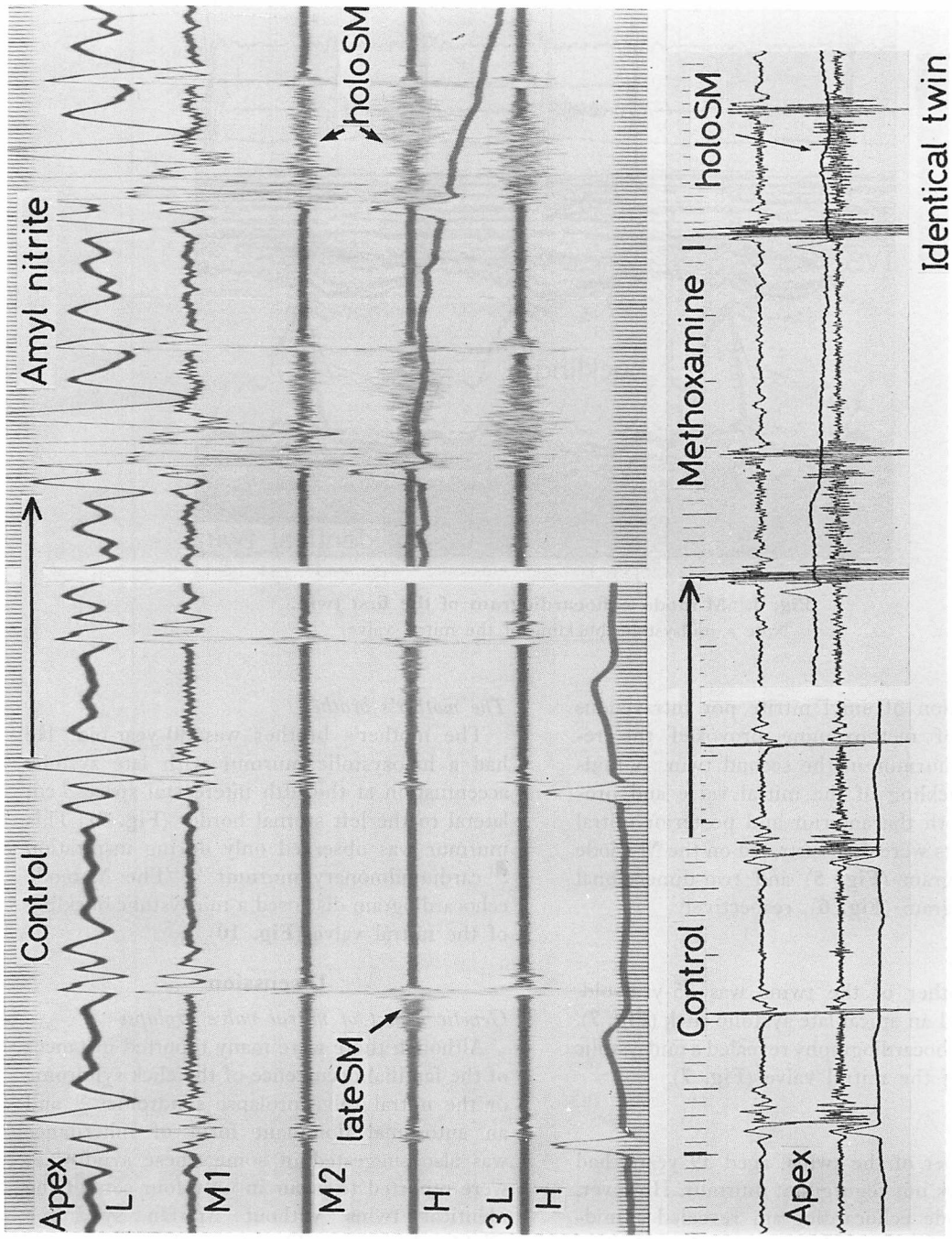

Fig. 2. Phonocardiograms of the first twin.
An apical late systolic murmur (grade I/VI) is increased in intensity and becomes holosystolic after both the inhalation of amyl nitrite (upper figure) and injection of methoxamine (lower figure). SM=systolic murmur.

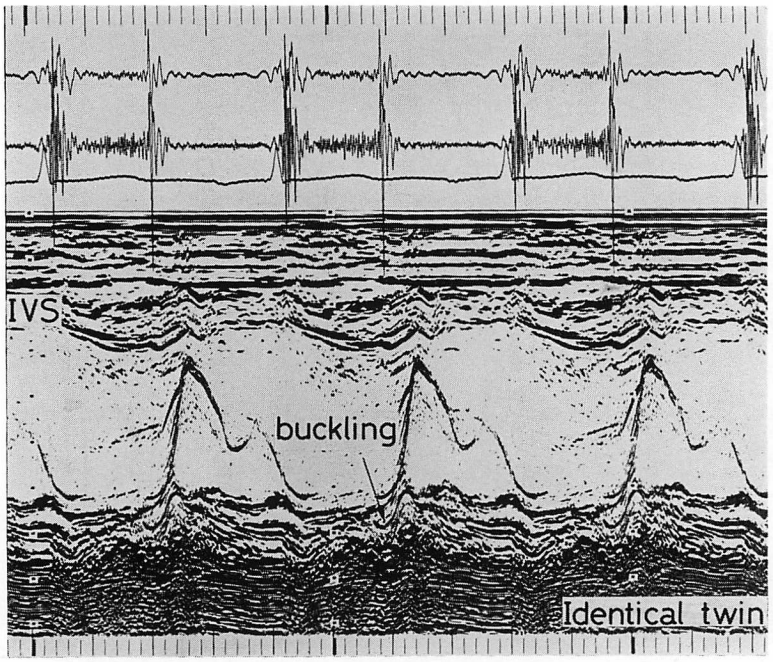

Fig. 3. M-mode echocardiogram of the first twin.
Note a midsystolic buckling of the mitral valve.

the inhalation of amyl nitrite nor intravenous injection of methoxamine provoked the regurgitant murmur in the second twin. A midsystolic buckling of the mitral valve and prolapse of both the anterior and posterior mitral valve leaflets were demonstrated on the M-mode echocardiogram (**Fig. 5**) and two-dimensional echocardiogram (**Fig. 6**), respectively.

The mother

The mother of the twins was 35-year-old, and she had an apical late systolic click (**Fig. 7**). M-mode echocardiography revealed a midsystolic buckling of the mitral valve (**Fig. 7**).

The father

The father of the twins, aged 39 years, had neither click nor regurgitant murmur. However, the M-mode echocardiogram revealed a midsystolic buckling of the mitral valve ("silent mitral valve prolapse") (**Fig. 8**). The mother and the father were nonconsanguineous pair.

The mother's brother

The mother's brother was 30-year-old. He had a holosystolic murmur with late systolic accentuation at the fifth intercostal space 5 cm lateral to the left sternal border (**Fig. 9**). This murmur was observed only during inspiration ("cardiopulmonary murmur"). The M-mode echocardiogram disclosed a midsystolic buckling of the mitral valve (**Fig. 10**).

Discussion

Genetic aspect of mitral valve prolapse

Although there were many reported instances of the familial occurrence of the click syndrome or the mitral valve prolapse syndrome[2~8] and an autosomal dominant form of inheritance was also suggested in some, these syndromes were reported to occur in only four sets of the identical twins without Marfan syndrome (**Table 2**)[4,5,10,11]. Therefore, the present report is the fifth set of the identical twins with mitral valve prolapse. To accept a significant

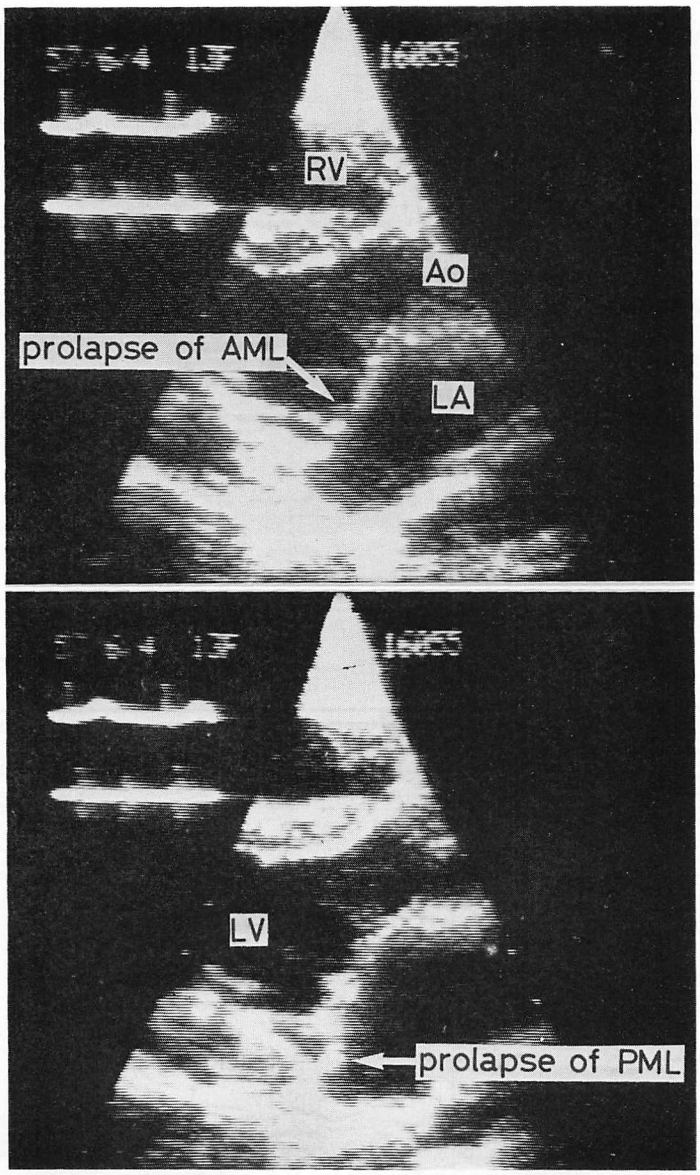

Fig. 4. Two-dimensional echocardiograms of the first twin.

Arrows indicate the prolapse of the anterior (upper figure) and posterior (lower figure) mitral valve leaflets. Both lesions cannot be demonstrated on the same plane because of the difference in the location of the lesions. RV=right ventricle, LV=left ventricle, Ao=aorta, LA=left atrium, AML=anterior mitral valve leaflet, PML=posterior mitral valve leaflet.

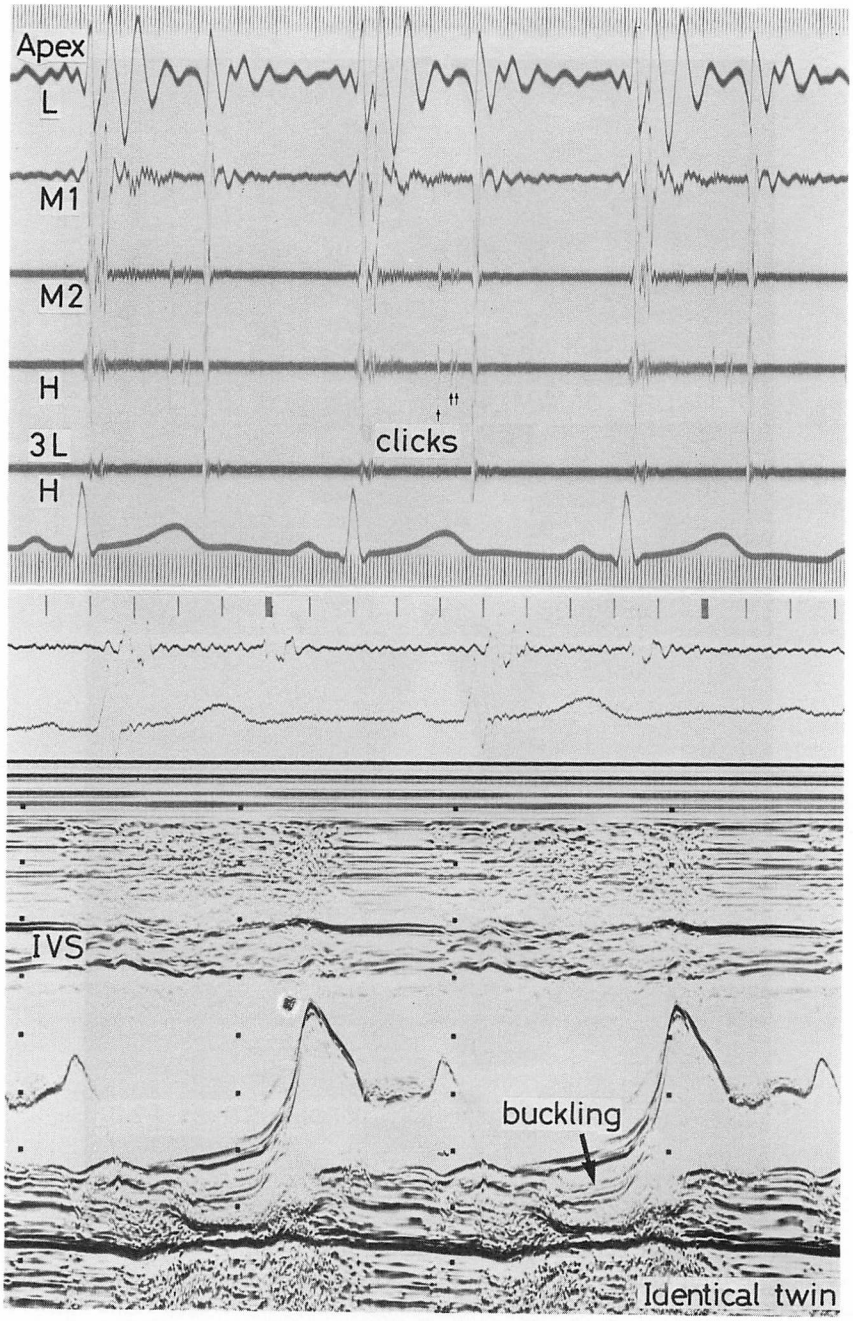

Fig. 5. Phonocardiogram and M-mode echocardiogram of the second twin.

Three mid to late systolic clicks are recorded at the apex on the phonocardiogram (upper figure). The M-mode echocardiogram (lower figure) demonstrates a midsystolic buckling of the mitral valve. IVS=interventricular septum.

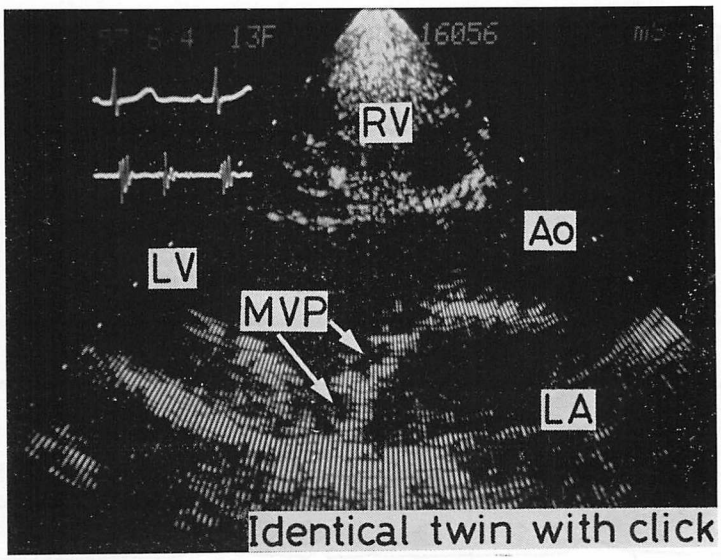

Fig. 6. Two-dimensional echocardiogram of the second twin.

Note the prolapse of both the anterior and posterior mitral valve leaflets, although the one of anterior cusp is not so marked.

RV=right ventricle, LV=left ventricle, Ao=aorta, LA=left atrium, MVP=mitral valve prolapse.

Table 2. Mitral valve prolapse in the identical twins

Author	Age	Sex	Findings
Rizzon et al[4]	17	F	click+late SM
			click
Jeresaty[5]	17	F	click+late SM
			click+AR murmur
Girard et al[10]	32	M	click, MVP*
			click, MVP*
Rotmensch et al[11]	13	M	click, MVP*
			(−) MVP*

*MVP (mitral valve prolapse) was demonstrated by M-mode echocardiogram.

F=female, M=male, SM=systolic murmur, AR=aortic regurgitation, (−)=absence of the auscultatory findings.

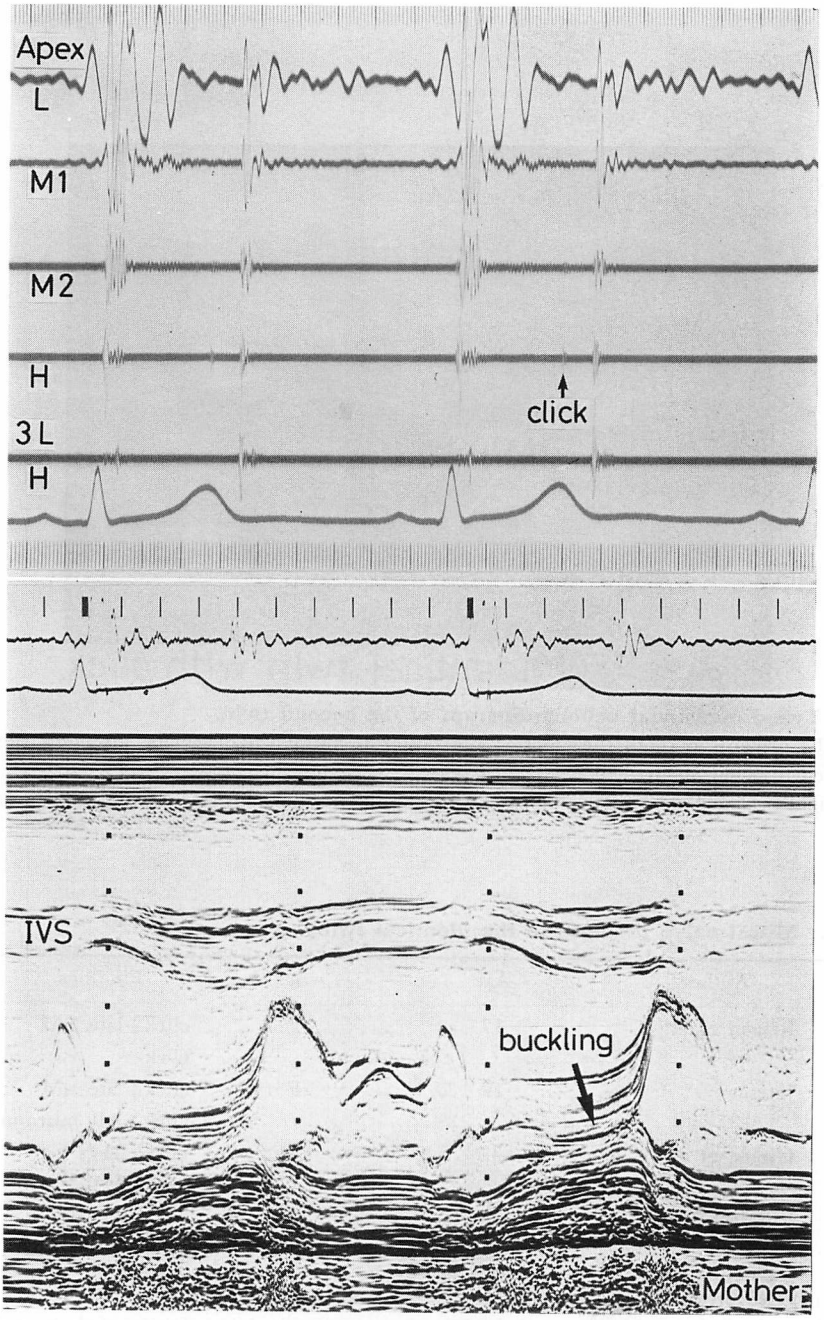

Fig. 7. Phonocardiogram and M-mode echocardiogram of the mother of the twins.
An apical late systolic click is recorded on the phonocardiogram (upper figure). The M-mode echocardiogram (lower figure) discloses a midsystolic buckling of the mitral valve which is only recordable in the vicinity of left atrial-left ventricular junction. IVS=interventricular septum.

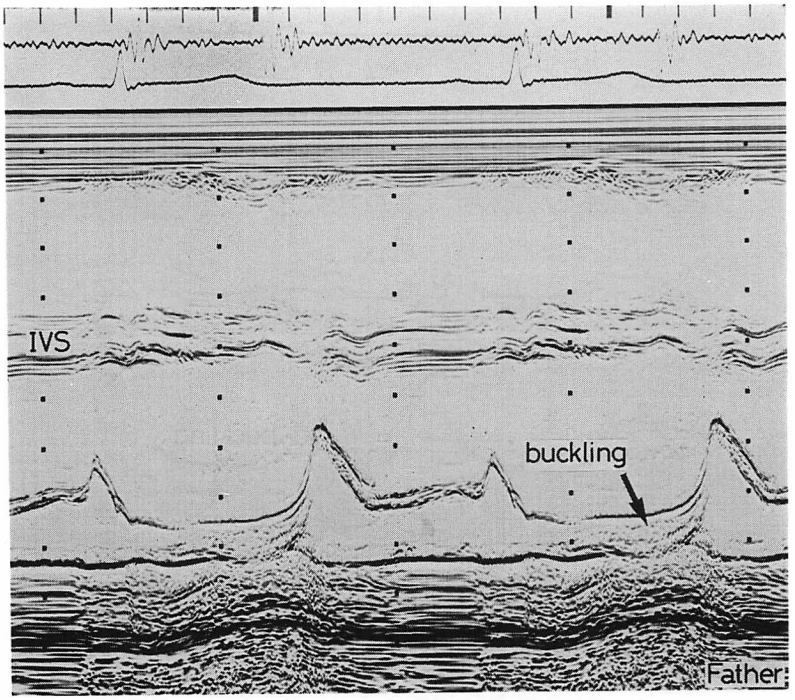

Fig. 8. M-mode echocardiogram of the father of the twins.
Note the midsystolic buckling of the mitral valve very close to the posterior wall of left ventricle. IVS=interventricular septum.

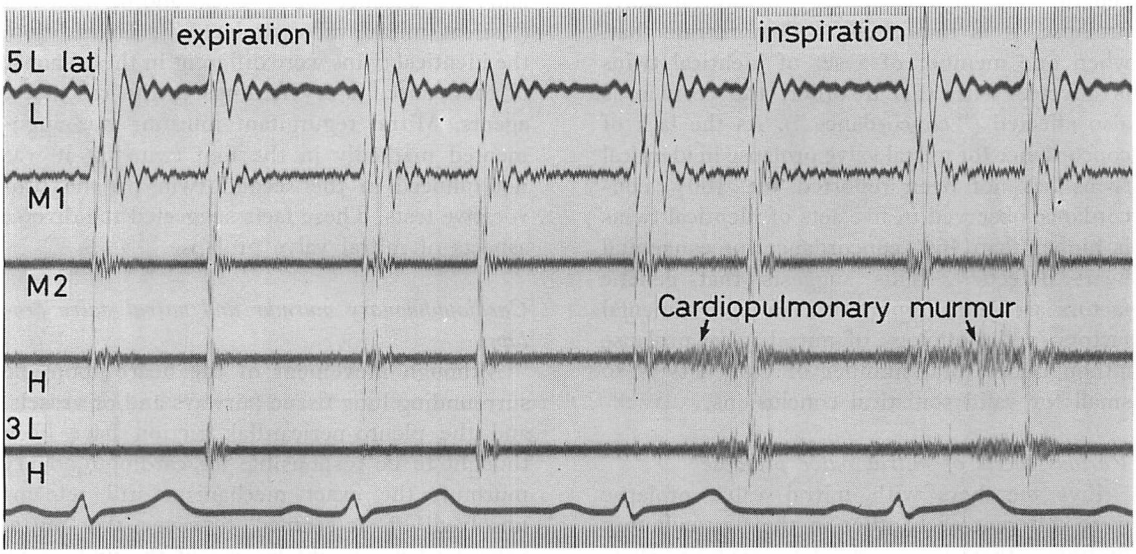

Fig. 9. Phonocardiogram of the mother's brother.
A cardiopulmonary murmur is recorded at the fifth intercostal space 5 cm lateral to the left sternal border.

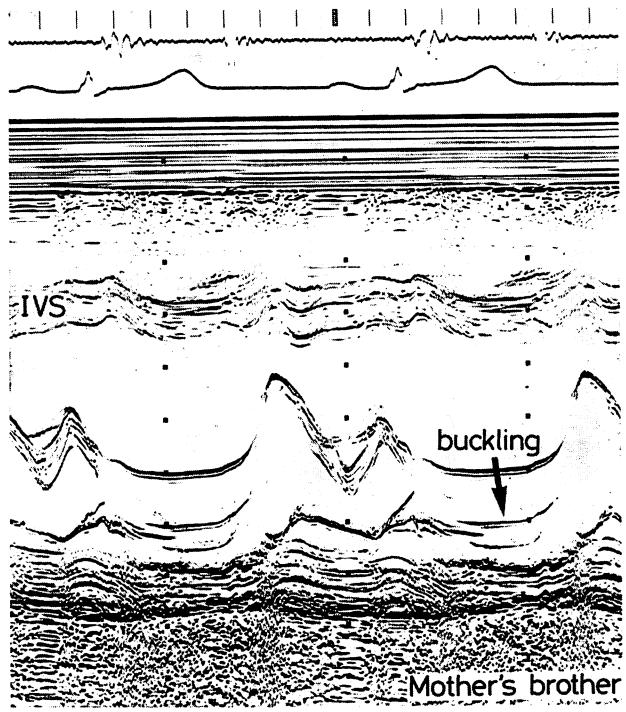

Fig. 10. M-mode echocardiogram of the mother's brother.
Note the midsystolic buckling of the mitral valve. IVS=interventricular septum.

genetic role in the etiology of mitral valve prolapse, it is important to demonstrate that, when one member of a set of identical twins is affected with this disorder, the co-twin is also affected (" concordance "). As the lack of concordance for mitral valve prolapse in identical twins has not been reported yet, 100% concordance observed in five sets of identical twins is higher than 46% concordance for congenital heart defects[12]. This suggests that genetic factors are more important than environmental factors in the etiology of mitral valve prolapse although the total number of twin sets is so small for valid statistical conclusions.

Various facets of mitral valve prolapse

Five members with mitral valve prolapse were different each other in their auscultatory findings, that is, single late systolic click, multiple mid to late systolic clicks, late systolic murmur without click, cardiopulmonary murmur and the absence of a click and/or murmur (" silent mitral valve prolapse "). In addition, the identical twins were different in the response of their auscultatory findings to the vasoactive agents. Mitral regurgitant murmur was augumented markedly in the first twin but it was not induced in the second twin by the provocative tests. These facts suggested the diverse aspects of mitral valve prolapse.

Cardiopulmonary murmur and mitral valve prolapse

Although movement of the heart upon the surrounding lung tissue (airways and/or vessels) and the pleuro-pericardial friction have been thought to be responsible for cardiopulmonary murmur, the exact mechanism still remains unsolved[13,14]. It seemed, however, that mitral valve prolapse might be one of the underlying mechanisms of this murmur because the prolapse was demonstrated echocardiographically

in the mother's brother. The fact that midsystolic click is sometimes associated with this murmur[13] further supports the present hypothesis.

HLA antigens and mitral valve prolapse

HLA antigens are known to have relation to many diseases which suggest the possibility of their genetic predisposition. Mitral valve prolapse was reported to be related to the specific HLA antigens by two groups in the United States[15,16]. In this point, it is interesting to note that thyrotoxicosis which is frequently associated with mitral valve prolapse[17,18] also has relation to the same HLA antigen[19]. Although both study groups revealed the association of HLA-Bw35 with mitral valve prolapse, we failed to demonstrate this association in the first twin and up to the present time, we were unable to explain this difference. Probably, this is due to the limited number of our patients and the difference in the human race, so that, further studies of the HLA antigens in patients with mitral valve prolapse may solve this problem.

一卵性双生児を含む僧帽弁逸脱の一家系

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一家系中の一卵性双生児，その両親および母親の弟の計5名に僧帽弁逸脱を認めた．家系中にマルファン症候群の特徴を有するものはなく，5名全員が無症状であるが，M モード心エコー図上，僧帽弁の midsystolic buckling を呈した．心電図上は2名に遊歩調律をみたのみであった．

発端者は，心臓検診にて収縮後期雑音を指摘された 13 歳女性で，この雑音は亜硝酸アミル，メトキサミンのいずれの負荷にても増大し全収縮期雑音となった．発端者と一卵性双生児の関係にある例では複数の非駆出性クリックをみたが，上記薬剤負荷にても僧帽弁逆流性雑音は出現しなかった．双生児の双方に断層心エコー図上僧帽弁前後尖の逸脱をみた．母親には収縮後期クリック，母親の弟には心肺性雑音を聴取したが，父親には聴診上の異常は認めなかった．

本家系の存在は僧帽弁逸脱の遺伝的背景とその表現型の多様性を示唆するものである．

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