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Two pairs of proven monozygotic twins discordant for familial amyloid neuropathy (FAP) TTR Met 30

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Abstract

Twin studies are an important tool in medical genetics for the evaluation of the relative roles of genetic and non-genetic factors in several diseases. Familial amyloidotic polyneuropathy type I (FAP-I), TTR Met 30, was present in two sets of proven monozygotic (MZ) twins, one from Majorca and the other from Portugal. Monozygosity was established by analysis of DNA polymorphisms. Both pairs were discordant for age at onset and some clinical manifestations of FAP-I. We reviewed the differences in age at onset and clinical features in both sets and in two other pairs of presumed MZ twins with FAP-I and compared them with those in MZ twin pairs with other Mendelian disorders, such as neurofibromatosis type 1, Huntington's disease, facioscapulo-humeral muscular dystrophy, and myotonic dystrophy. We conclude that, in addition to the postulated modifying genes, there must be a significant contribution from non-genetic factors to the phenotypic variability of FAP-I (age at onset and clinical expression), either because of environmental differences or stochastic events during (or after) the twinning process.

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Keywords: hereditary amyloidosis; discordant MZ twins; non-genetic factors; stochastic process

FAP type I (FAP-I) is an autosomal dominant systemic amyloidosis mainly involving the peripheral nerves. It was first described in Portugal¹ and later on in many other countries. The areas with the highest prevalence are Portugal, Japan, Sweden, Brazil, and the island of Majorca (Spain).² The genetic defect of FAP-I³ is a single point mutation in the gene encoding the plasma protein transthyretin (TTR), located on chromosome 18; for this reason, the modern nomenclature of FAP-I is FAP followed by the mutant TTR.

So far more than 60 amyloidogenic TTR mutations have been reported. TTR Met 30 is by far the most common and the only one identified in all Majorcan patients and in virtually all patients from Portugal, Japan, Sweden, and Brazil. In the majority of TTR mutations there is a substitution of one amino acid for another in the 127 chain; in a few families, two amino acids have been substituted in that

chain, and in one family only there is a deletion of one amino acid.

No clinical differences have been found in these areas, though there is considerable variability in the age at onset; on average this was higher in the Majorcan patients (46.7 years) than in Portugal (33.5 years),⁴ Japan (35.6 years),⁵ or Brazil (32.4 years),⁶ but lower than in Sweden (56.7 years).⁴ As a consequence, the number of old asymptomatic carriers is much greater in Sweden, intermediate in Majorca, and very small in Portugal.

We present here two sets of MZ twins with FAP-I, one from Majorca and the other from Portugal. To our knowledge, these are the first two pairs of proven MZ twins with FAP TTR Met 30.

Case reports

TWIN SET 1

This set consisted of white male twins (J and G) born in Majorca in 1931, who were thought, from birth, to be identical, though no zygosity studies had been performed. They were reared together until the age of 26, when twin G got married; thereafter, they always lived in the same neighbourhood. They had similar social and economic levels and their jobs were both related to car maintenance and repair (twin J was a panel beater and twin G worked in a service station). Neither of them smoked or drank alcohol regularly. There was a striking physical resemblance, despite twin G having hypotrophy of his right arm, as a result of a brachial paralysis after delivery. One of us (MMQ) knew both men before they developed FAP-I and could verify their resemblance.

Twin G was followed by us from the age of 57 years, by which time his twin J had already died. Clinical information on twin J was kindly provided by several physicians. The clinical diagnosis on twin J was confirmed by demonstration of amyloid deposits in an intestinal biopsy and on twin G through detection of TTR Met 30 in serum. There was no history of FAP-I in their ancestors. One son of twin J became affected at the age of 27 and two years later underwent orthotopic liver transplantation (OLT) with good results.

The clinical picture was discordant in the twins. Twin J had onset of FAP-I at the age of 38, whereas twin G had onset at 50 years of age, two years after twin J had died. In both, the initial symptom was a sensorimotor syndrome, but this was more aggressive in twin G as he was confined to a wheelchair seven years later,

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whereas twin J was still walking with two sticks when he died 12 years after onset. Twin J had diarrhoea with encopresis, but twin G suffered from severe constipation. Both had urinary problems owing to a neurogenic bladder and impotence; twin J had renal involvement with proteinuria and progressive renal failure seven years after onset, whereas twin G developed similar symptoms nine years after his first symptoms. Only twin G showed amyloid deposits in both eyes nine years after onset and for this reason he underwent bilateral vitrectomy. Death occurred at the age of 48 in twin J (after 10 years disease duration), while twin G died at the age of 63 (a disease duration of 13 years).

Study of monozygosity in this set of twins was a challenge, because we had only old paraffin blocks of intestinal biopsies from both patients, performed on twin J in 1976 and on twin G in 1991. DNA was extracted from the blocks for analysis of DNA polymorphisms. The posterior probability of monozygosity was 99.03% (table 1).

TWIN SET 2

This set consists of white male twins (twins J and A) born in Portugal in 1959, who were also thought to be identical. They were reared together until the age of 21, when twin J got married; thereafter, they had no significant environmental differences that could be detected and their professions, after university graduation, were the same. There was a strong family history of FAP-I. At the age of 25 they were diagnosed as carriers by detection of TTR Met 30 in serum. Both had a sacrococcygeal cyst, for which they were operated on in the same year.

Twin A had onset of FAP-I at the age of 30, whereas twin J had onset at 34 years of age. The clinical picture was also discordant. The initial symptom in twin A was a very aggressive sensorimotor syndrome with early involvement of the upper limbs, while in twin J it was a severe loss of weight. Later on, twin A had cardiac rhythm disturbances, orthostatic hypotension, occasional episodes of diarrhoea, and neurotrophic ulcers on both feet, but twin J had only a minor sensorimotor syndrome and gastrectasia. Twin A underwent OLT at

the age of 34 but he died seven months later, after successive peritoneal complications; twin J underwent a successful OLT at the age of 35.

Analysis of DNA polymorphisms was performed after extraction of DNA, from paraffin blocks of necropsy material in twin A and from a fresh blood sample in twin J. The posterior probability of monozygosity was 99.99% (table 1).

Discussion

CLINICAL DISCORDANCE IN MZ TWINS WITH SPORADIC OR CHROMOSOMAL DISORDERS

Twin studies are an important tool in medical genetics in the evaluation of the relative roles of genetic and non-genetic factors in several diseases. In particular, the occurrence of MZ twins clinically discordant for a presumably hereditary disorder may be crucial to resolve diagnosis⁷ or to determine its true aetiology⁸ or pattern of inheritance.⁹ Some chromosomal abnormalities that have occurred postzygotically, such as undetected mosaicism or small deletions below the cytogenetic resolution level, could explain discordant MZ twins with usually sporadic disorders, such as Brachmann-de Lange,¹⁰ Rubinstein-Taybi,¹¹ McCune-Albright,¹² Beckwith-Wiedemann,^{13 14} Williams,¹⁵ and other syndromes.

CLINICAL DISCORDANCE IN MZ TWINS WITH MENDELIAN DISORDERS

The high correlation in clinical variation of neurofibromatosis type 1 (NF1) in MZ twins, as compared to other relatives, suggests an important role of modifying genes.¹⁶ Also, in Huntington's disease (HD), age at onset seems to have a major genetic component; 12 twin sets, proven or presumed to be MZ, either had onset in the same year or less than three years apart. However, clinical presentation was rather different in two pairs of MZ twins with HD¹⁷; in one additional pair of proven MZ twins, reared apart from birth, age at onset and clinical evolution were remarkably similar.¹⁸ In myotonic dystrophy (DM), MZ twins were discordant for lens opacities and other phenotypic findings.¹⁹ Different clinical expression in MZ twins with DM may be explained by a variable number of CTG repeats,²⁰ owing to different patterns of somatic mosaicism. In a pair of MZ twins, one was severely affected with facioscapulohumeral muscular dystrophy, while the other was almost asymptomatic.²¹ No evidence for somatic mosaicism of a postzygotic, pre-twinning mutation was found; it was thus hypothesised that an anti-rabies vaccine, received by the more severely affected twin, might have triggered an inflammatory immune response, which enhanced muscle fibre damage.

CLINICAL DISCORDANCE IN MZ TWINS WITH FAP-I
Besides our two pairs of proven MZ twins, two other sets of presumed MZ twins are known to us: one pair of female twins, born in Indonesia in 1937,²² and one pair born in Sweden in

Table 1 Estimation of posterior probability of monozygosity

Locus	Genotype	Twinning index (TI)	Twinning probability (TP) (%)
<i>Twin set 1 (Majorcan)</i>			
CD4	6-10	2.760	73.40
FES	12-13	3.770	79.04
TP53	6-8	2.545	71.79
TPO	11-11	1.250	55.56
Total	51.081		98.08
Considering sex: TI=51.081×2; TP=102.162			
Posterior probability of MZ=99.03%			
<i>Twin set 2 (Portuguese)</i>			
D3S1358	15-17	3.158	75.95
D5S818	11-13	3.090	75.55
D8S1179	15	1.330	57.08
D13S317	11-12	2.741	73.27
D21S11	30-32.2	3.602	78.27
F13A	5-6	2.882	74.24
MBPB	11	1.216	54.87
TH01	7-9.3	2.958	74.74
TP53	6-8	2.545	71.79
VWA	14-17	3.041	75.25
Total	10 280.279		99.99
Considering sex: TI=10280.279×2; TP=99.99			
Posterior probability of MZ=99.99%			

Table 2 Four pairs of monozygotic twins with FAP-I

Origin	Indonesia ²²	Sweden ²³	Majorca	Portugal
Sex	Female	Male	Male	Male
Symptoms of FAP-I	Both	Only one	Both	Both
Difference in onset age (y)	4	? (>7)	12	4
Different clinical expression:	Yes	NA	Yes	Yes
in sensorimotor syndrome	Yes	NA	Yes	Yes
in digestive disturbances	Yes	NA	Yes	Yes
in renal involvement	Yes	NA	Yes	NP
in vitreous deposits	NP	NA	Yes	NP
in cardiac involvement	Yes	NA	NP	Yes
Probability of monozygosity	Presumed	Presumed	99.03%	99.99%

NA=not applicable (only one affected); NP=not present in any.

1940.²³ The main data from these four sets of MZ twins with FAP-I are summarised in table 2.

In the latter two sets, there is also clear discordance in clinical expression. The Indonesian twins had a very strong family history of FAP-I and were diagnosed by detection of amyloid deposits on rectal biopsies. Onset was four years apart; twin 1 (onset at the age of 33) had a more severe peripheral neuropathy, but also a multiple cranial neuropathy, as well as cardiac and renal failure, not present in twin 2 (who had onset at the age of 29). Environmental differences or similarities were not reported. The Swedish pair was diagnosed by DNA analysis; FAP-I was present in their paternal uncle. Onset in twin 1 was at the age of 48 with a progressive sensorimotor neuropathy, gastrointestinal symptoms, and orthostatic hypotension. Recently, at the age of 54, he received a successful OLT, while twin 2 was still asymptomatic.

The simultaneous occurrence of a sacrococcygeal cyst in both Portuguese MZ twins is noteworthy, contrasting with their relative discordance for age at onset and clinical symptoms of FAP-I.

GENETIC MODIFIERS, AGE AT ONSET, AND CLINICAL SEVERITY

The importance of genetic modifiers in age at onset and clinical expression has been postulated in NF1,¹⁶ HD,¹⁸ and DM,¹⁹ as well as in FAP-I.²⁴⁻²⁵ However, the margin for clinical variation existing in HD indicates that this is only partly influenced by the genome.¹⁷ Overall, there were significant differences within each of the four (three male) pairs of MZ twins, both in clinical severity and age at onset (which may be as much apart as 12 years), clearly showing that the TTR mutation and its genetic modifiers are not the only determinants of age dependent penetrance and variable expressivity of FAP-I. Other, non-genetic, factors (that is, either undetected environmental factors or stochastic events at the molecular/cellular level occurring before or during the twinning process) must be operating.

THE POSSIBLE EFFECT OF STOCHASTIC, POSTZYGOTIC EVENTS

In diseases with known Mendelian inheritance, differences between MZ twins in terms of age at onset, clinical picture, and severity are usually taken as an indicator of the interaction of the mutant gene with environmental factors; this is, however, influenced by strong observa-

tional biases. While most environmental differences between MZ twins will remain undetected, the occasional finding of a single difference is too often followed by a hasty conclusion of a causal effect.

Not all non-genetic factors, however, need to be environmental. Non-random or skewed lyonisation, for instance, will explain discordance for chromosomal disorders and also some instances of discordant female MZ twins for X linked Mendelian disorders²⁶⁻²⁷; the same may apply for autosomal diseases with modifying loci on the X chromosome. Also, somatic mosaicism for aneuploidies, including small deletions, or for expanded trinucleotide repeats, may explain differences between (female or male) MZ twins with chromosomal disorders or those resulting from unstable dynamic mutations (such as HD or DM). In classical mutations, such as FAP TTR Met 30, different patterns of somatic mosaicism for (nuclear) modifying genes or different distributions of mitochondrial modifiers could, in theory, explain different expressions of the mutant gene in either twin.

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