A Pedigree of Aniridia with a Discussion of Germinal Mosaicism in Man[1]

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INTRODUCTION

CONGENITAL aniridia is an abnormality of interest to both the ophthalmologist and the human geneticist. This defect, occurring in about one person in 100,000 (Møllenbach, 1947), concerns the former because of the severe visual handicap it produces and because of the questions about embryology of the iris it raises. The latter is interested because it is inherited as if due to a dominant gene of high penetrance and so may be studied with regard to its formal genetics, mutation rate, selective value, and linkage with other genes.

In a strict sense "aniridia" is not a precise term since some iris is always present microscopically, and because the iris may be affected in several different ways. The anterior layer of the iris, the stroma, is of mesodermal origin and appears first; the posterior layer, which is an extension of the optic cup and hence of neuro-ectodermal origin, appears after the mesodermal layer is in place. Aniridia may involve the absence of the stroma only, the absence of the posterior layer only, or both. In addition to the absence of some of the elements of the iris, congenital aniridia is usually characterized by aplasia of the macula, nystagmus, and photophobia. In early childhood, and perhaps until middle age, an aniridic person may have fair visual acuity, but in later life blindness often sets in as a result of secondary changes in the eye. Although unilateral aniridia is known, the amount of iris present tends to be equal in the two eyes of an individual, and is fairly constant in affected members of a given family. Not infrequently, however, considerable variation is found, ranging from nearly complete absence of the iris to a very mild coloboma.

Aniridia is characteristically inherited as if due to a simple autosomal dominant gene (Bell, 1932; Waardenburg, 1932; Møllenbach, 1947; Sorsby, 1951). Other modes of inheritance have been reported (Sorsby, 1951) but appear to be uncommon. The penetrance of the gene is high but perhaps not unity. Cases are known in which a person having an aniridic parent and an aniridic child has only a slight coloboma, and less authenticated cases are reported in which such persons are reported to be normal. An estimate of the penetrance will be given later in this paper. Two linkage studies have been made (Beattie, 1947; Mohr, 1953); no linkage was found between the locus of the gene for aniridia and the loci for the ABO, MN, Rh, P, Lewis, Lutheran, and Duffy blood groups or with the locus for taste sensitivity to phenylthiocarbamide. The first occurrence of aniridia in a family is believed by Møllenbach

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(1947) to be caused by mutation of the normal allele to the aniridia-producing allele and has been estimated by him to occur with a frequency of 0.5×10^{-5} mutations/gene/generation. From Møllenbach's data, showing 22 of 44 cases to be mutants, it is estimated (Haldane, 1949) that the relative fertility of persons with aniridia is about 0.5. However, Beattie (1947) found no reduction of fertility in his single large kindred. It may be noted that these estimates of frequency, mutation rate, and fertility derived from Møllenbach's data are not mutually consistent for a population in equilibrium.

MATERIAL AND METHODS

This paper reports on studies made on a kindred living in the Lower Peninsula of Michigan and consisting of 99 apparently normal and 23 aniridic individuals. Thirty-eight of the normal persons and 20 of the aniridic persons were examined ophthalmologically and blood typing was done on samples from 27 persons whose blood types could give information as to the existence of linkage between the locus of the

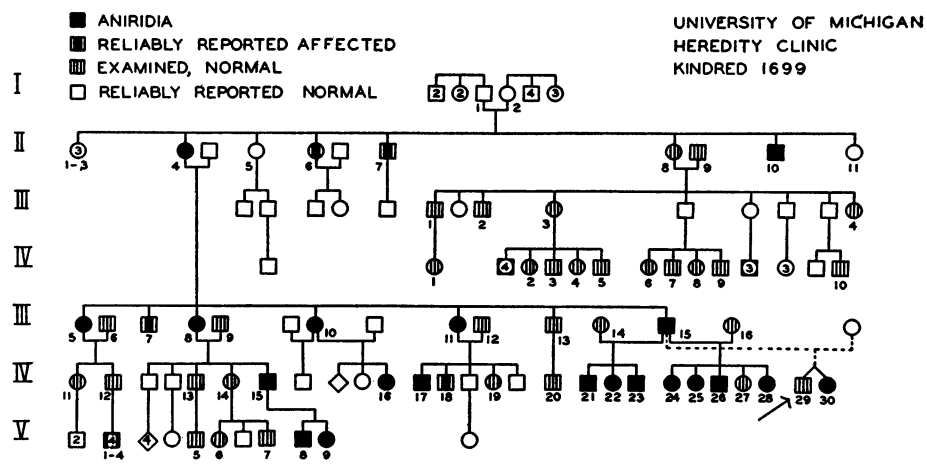

FIG. 1. Pedigree of the kindred studied

gene for aniridia and the loci of the genes for the ABO, Rh, and MN blood groups. The members of the kindred are of Caucasian ancestry and, among the living, range in age from two months to 73 years, distributed in four generations. A pedigree of the kindred is shown in Figure 1. The propositus through whom the kindred came to be studied is IV-29, a normal, five-year-old illegitimate boy who is a twin of an aniridic girl. He was referred to the Heredity Clinic for an appraisal of the possible effect on his adoption of having aniridic relatives. The information obtained on the condition of the eyes of persons who could not be examined is believed to be quite reliable, at least as regards the presence or absence of aniridia, since whenever descriptions were later checked they were found to be correct.

RESULTS

The results of the ophthalmological examinations and blood grouping are given in Table 1.

TABLE 1. DESCRIPTIONS AND EXAMINATION RESULTS

Individual	Sex	Age if Living	Age at Death	Ophthalmologically Examined	Aniridic	Blood Groups
I- 1	M		65	−	−*	
2	F		84	−	−*	
II- 1, 2, 3	F		<6	−	−	
4	F	73		+	+	O; N; R_1R_1
5	F		24	−	−	
6	F		32	−	+	
7	M		64	−	+	
8	F	64		+	−	O; N; R_1R_1
9	M	77		+	−	
10	M	62		+	+	O; MN; R_1R_1
11	F		1	−	−	
III- 1	M	44		+	−	
2	M	39		+	−	
3	F	36		+	−	
4	F	18		+	−	
5	F	55		+	+	O; N; R_1R_2
6	M	65		+	−	O; MN; R_1r
7	M		23	−	+	
8	F	50		+	+	O; MN; R_1R_1
9	M	63		+	−	A; M; R_1r
10	F	45		+	+	
11	F	44		+	+	O; MN; R_1R_2
12	M	53		+	−	AB; MN; R_1R_1
13	M	42		+	−	O; MN; R_1R_2
14	F	32		+	−	A; N; R_1r
15	M	38		+	+	O; MN; R_1R_2
16	F	28		+	−	O; N; R_1R_1
IV- 1	F	10		+	−	
2	F	9		+	−	
3	M	7		+	−	
4	F	6		+	−	
5	M	4		+	−	
6	F	12		+	−	
7	M	11		+	−	
8	F	10		+	−	
9	M	9		+	−	
10	M	3		+	−	
11	F	36		+	−	O; MN; R_2r
12	M	34		+	−	O; MN; R_1R_1
13	M	28		+	−	O; MN; R_1R_1
14	F	27		+	−	O; MN; R_1r
15	M	23		+	+	
16	F	8		+	+	
17	M	26		+	+	B; M; R_1R_2
18	M	25		−	+	
19	F	13		+	−	A; MN; R_1R_2
20	M	16		+	−	
21	M	16		+	+	O; MN; R_2r
22	F	14		+	+	O; N; R_1r
23	M	12		+	+	A; N; R_2r
24	F	8		+	+	O; MN; R_1R_1

TABLE 1—*Continued*

Individual	Sex	Age if Living	Age at Death	Ophthalmologically Examined	Aniridic	Blood Groups
25	F	7		+	+	O; N; R_1R_2
26	M	5		+	?†	O; MN; R_1R_2
27	F	3		+	−	O; MN; R_1R_2
28	F	2		+	+	O; MN; R_1R_1
29	M	4		+	−	
30	F	4		+	+	
V- 1	F	11		+	−	
2	F	10		+	−	
3	F	8		+	−	
4	M	6		+	−	
5	M	4		+	−	
6	F	4		+	−	
7	M	1/12		+	−	
8	M	3		+	+	
9	F	4		+	+	

* Considered non-aniridic on basis of report by a reliable, normal daughter and inspection of photographs taken at age 28 and 22. I-1, however, appeared to have a slightly elliptical, centrally positioned, right pupil. Since the photograph is a somewhat fuzzy enlargement it is not known whether this defect is real or not. No ocular abnormality or visual dysfunction was known to the normal daughter.

† Brown iris was present but in both eyes there was hypoplasia of the iris stroma, ectopia pupillae (displaced up and in), dyscoria, nystagmus, alternating convergent strabismus, photophobia, and narrowed palpebral fissures. Vision in each eye was 6/30 −1.

The pedigree data have been examined for possible aberrant segregation ratios of aniridic to normal among the children of aniridic parents. Using data from the eight matings in which most or all of the children were examined, and making all possible comparisons with respect to sex and presence or absence of aniridia, no significant departures from equality of the numbers of affected and non-affected and numbers of males and females were found. Individual IV-30 was omitted from the count when determining segregation ratios, and her affected father, III-15, who served to call attention to his sibship, was likewise omitted from the segregation count. Three aniridic persons, II-6, II-7, and III-10, had children of whom most or all were not examined. When their children are added to those of the previous eight matings there are still no significant departures from equality. The data are consistent with the interpretation of simple dominant inheritance of aniridia, although, as is evident from Table 1, especially in the description of IV-26, the expression of the condition in various persons may vary widely.

The possibility of genetic linkage between the locus of the gene for aniridia and the loci of the ABO, MN, and Rh blood groups was investigated. The data provide no information with regard to the ABO system since all aniridic parents have O blood. Four useful matings were available for the MN and Rh systems and, using the method of Finney (1940, 1942), λ and κ_c scores were calculated, being −2 and 14 respectively for MN and −5 and 15 for Rh. Thus there is no suggestion of linkage. One study of

linkage with aniridia, that of Beattie (1947), made use of the ABO, MN, Rh, and P blood groups as well as taste response to phenylthiocarbamide. Slight evidence for linkage with the locus for the ABO system was found and the matter was thought worth further investigation. Another linkage study, that of Mohr (1953) made use of these markers and also the Lewis, Lutheran, and Duffy blood groups. No evidence for linkage was found.

There are too few individuals for a reliable calculation of the relative fertility, but it is clear that, in this kindred, persons with aniridia suffered little loss of fertility.

DISCUSSION

The gene producing aniridia in this kindred has been found to segregate in the normal manner, showing simple autosomal dominance and high penetrance, and cannot be shown to be linked with the genes for the ABO, MN, and Rh blood group systems. These facts require no comment but the question of the origin of the gene, which apparently first became evident in four aniridic sibs in Generation II, raises some fundamental questions. (The probability of four separate mutations would appear to be so small that this possibility will be disregarded.) The explanation for this multiple appearance of affected sibs therefore seems to lie in one of two possibilities: either a parent, I-1 or I-2, had the gene for aniridia and did not show it, or a mutation at the aniridia locus from normal to aniridic occurred early in the development of a parental gonad, so that an appreciable portion of the gonad became heterozygous for the aniridia-producing allele, making a so-called germinal or gonadic mosaic. Since the gene for aniridia is believed to have high penetrance, and since there are at least six demonstrated cases of germinal mosaicism (GM) in experimental mammals, the choice of explanation is not immediately obvious.

Failure of a usually dominant gene to express itself in a heterozygous individual, as well as varying expression of the gene in different individuals is, of course, well known in human genetics. The ophthalmological data of the present paper provide evidence of the variable expression of the gene for aniridia. Among 16 aniridic persons who were examined by the authors, five were found to have small peripheral tags of iris, no tags being visible in the remaining 11 persons. Particular consideration is due the description of IV-26, a five-year-old son of an aniridic man. Although appearing grossly normal, more thorough examination showed that IV-26 has hypoplasia of the iris stroma, ectopia and dyscoria of the pupils, nystagmus, photophobia, and poor vision (6/30 − 1). There is, therefore, a strong presumption that this boy has the gene for aniridia but does not manifest the most characteristic feature of the pathological complex. If this is the case, the argument for non-penetrance as an explanation for the presence of the four aniridic individuals in Generation II is strengthened. However, as indicated in Table 1, the parents of Generation II are not known to have had any of the above-mentioned defects of IV-26.

In order to ascertain the frequency with which carriers of the gene for aniridia are described as being normal or nearly normal, a survey of the available literature was made, looking for descriptions of persons who are reported to have had an aniridic parent and an aniridic child. The results of this survey are summarized in Table 2. It is seen that only 13 persons were located who, with their parent and child, were

TABLE 2. TABULATION OF AVAILABLE DATA GIVING DESCRIPTIONS OF THE IRIDES OF PERSONS HAVING BOTH AN ANIRIDIC PARENT AND AN ANIRIDIC CHILD

Source	Number Aniridic	Number Not Aniridic	Remarks on Non-aniridic Individuals
All three generations medically examined			
Bell, 1932	5	1	Ped. 1104. Bilateral colobomata to margin of cornea.
Komai, 1934	1	0	
Neher, 1938	2	0	
Vogt, 1941	1	0	
Beattie, 1947	1	1	Slight bilateral irregularity in the pupillary margin, slight hypoplasia of iris stroma of left eye.
Møllenbach, 1947	1	0	
Total	11	2	
All three generations *not* medically examined			
Bell, 1932	23	2?	Pedigrees 1105 and 1130: descriptions seem uncertain.
Brooks, 1935	0	1?	Parent stated only to be "blind at early age."
Detroy and Bisiaux-Aufort, 1938	1	0	
Neher, 1938	2	0	
Vogt, 1941	1	0	
Beattie, 1947	9	0	
Pincus, 1948	5	0	
Schachter and Ourgaud, 1948	2	0	
Callahan, 1949	2	0	
Kříž, 1951	2	0	
Total	47	3?	

medically examined. Of these 13, two did not lack irides; one of these two persons had bilateral colobomata to the margin of the cornea and the other had slight bilateral irregularities in the pupillary margin and a slight hypoplasia of the stroma of the left iris. An additional 50 persons were located where all three generations were not medically examined and, of these, three were reported not to have aniridia. The reliability of the descriptions of two of these three persons is a matter of conjecture, being obtained indirectly from lay persons, while in the third case the person was ophthalmologically examined but the only information on the parent is that she was "blind at an early age."

It therefore seems established that a person may have the gene for aniridia and have almost normal irides or have only colobomata of the irides. The question of a person's having the aniridia gene and completely normal eyes remains unanswered. Several estimates of the penetrance of the gene may be calculated from the above data: Using only the 13 cases in which all three generations were examined, the pene-

trance with respect to clinically demonstrated aniridia (excluding colobomata and slight pupillary irregularities) is 11/13 or 0.846 ± 0.100, while if all cases are combined and treated as if reliable, the penetrance is 58/63 or 0.921 ± 0.034. The estimate of penetrance, defined as producing *any* congenital irregularity in the pupillary margin, is unity for the 13 completely examined cases but cannot be estimated from the 50 partially examined cases since slight abnormalities would probably not be recorded.

The alternative possibility, that of GM, is less obvious and in man, as well as in the extensively investigated domestic fowl (Hollander, 1944; Hutt, 1949), has not been demonstrated to occur. MacKenzie and Penrose (1951) suggested that GM occurred in one of their pedigrees of ectrodactyly, 3 of the 8 children of a normal person (with 2 normal spouses) being affected. Since the expression of ectrodactyly is known to be quite variable in some families and this family contains only 5 affected members, it is not possible to rule out non-penetrance as an alternative explanation. However, because of the similarity of expression of the trait in this pedigree to that in their other, much larger pedigree, which exhibited complete penetrance, they preferred the hypothesis of GM. Possible somatic mosaics, in contrast to gonadic mosaics, have been described in man (Zlotnikoff, 1945) and the fowl (Hollander, 1944; Hutt, 1949), as well as in many other organisms. Convincing evidence for the natural existence of mosaic gonads, shown by the production of two or more mutant offspring (having the same mutant character) from a single non-mutant parent (having one or more non-mutant mates), has been presented for *Drosophila melanogaster* (Bridges, 1919; Muller, 1920; Mohr, 1923; Morgan, Bridges, and Sturtevant, 1925), the guinea pig (Wright and Eaton, 1926), and the house mouse (Grüneberg, 1952; Dunn and Gluecksohn-Waelsch, 1953). Artificial production of gonadic mosaics has been reported in Drosophila, both by means of X-rays (Harris, 1929; Auerbach, 1950) and chemical mutagens (Auerbach, 1946, 1950). The proportion of mutated gametes, which, within statistical limits, is equal to half the proportion of gonad which is mutant, varies greatly; in the five cases in the mouse described by Grüneberg, the range is from 2 out of 63 tested gametes to 4 out of 9. The one case in the guinea pig produced 79 mutant gametes out of 228 tested, a proportion of 0.35.

A reliable estimate of the frequency of GM in mammals is not possible at present since the number of inspected animals is not known, but some data are available concerning the proportion of observed new mutations in the mouse known to have resulted from a mosaic gonad. Out of 9 genes listed by Grüneberg (1952) which first appeared in a laboratory as mutations and had easily visible effects in heterozygotes, 3 appeared in two or more progeny of a normal parent. As Grüneberg (1952) and Dunn and Gluecksohn-Waelsch (1953) point out, this form of mutation, in the mouse at least, may be more common than has been previously thought. Muller (1920) pointed out that the fact that a dominant mutation usually first manifests itself in one mutant individual, and not in a cluster of two or more, does not necessarily mean that, on a "per cell" basis, mutation is more likely in mature gametes than in cells of the early undifferentiated gonad. There are many more cells produced in late stages of gonadal development than in early, and the cells remain longer in the later stages. The usual observation—most mutants occurring singly—can result if mutations are as likely to occur at one stage as another.

It is pertinent at this point to survey the studies made on dominantly inherited traits in man to see whether evidence is available for demonstrating GM. The ideal proof will be the presence of more than one affected individual in the first (chronologically speaking) affected sibship, where the trait is inherited as a simple, rare, easily recognizable dominant with complete penetrance and uniform expression. A rare trait is preferable in order to minimize the effect of possible illegitimacy. This ideal situation does not yet exist and, in particular, there is a weakness in most studies in that there is no independent determination of penetrance and presence of more than one affected sib in the first affected sibship, the same data being used for both. Table 3 lists studies made on aniridia and other rare, dominant, highly penetrant traits, presenting data concerning the penetrance of the trait and existence of several affected individuals in the first affected sibship. It should be noted that two of the studies, Bell (1932) and Reese (1949), are based on surveys of the literature and, because of lack of uniformity of diagnosis and inclusion of very early reports, are therefore much less satisfactory than the other studies. These two studies contain the largest number of kindreds with several affected persons in the first affected sibship. The traits appearing to be most reliable for our purpose are chondrodystrophy and osteogenesis imperfecta, being recognizable at an early age and completely penetrant (in the osteogenesis imperfecta syndrome, blue sclerae, at least, being present), according to the studies quoted. Out of a total of 145 kindreds from these two studies in which the first affected sibship is known (i.e., the parents reported normal by the author), none was observed to have more than one affected member in the first affected sibship. This negative result makes GM as an explanation for Bell's data seem quite unlikely, assuming, as seems justified, that the proportion of germ cell mutations which occur early in the development of the zygote and give rise to two or more mutant offspring is approximately constant for different dominant genes. If perfect dominance and accurate diagnoses obtained in her data, the probability is less than 0.001 of obtaining the observed results of 3 kindreds out of 13 showing several affected in the first affected sibship and the corresponding figures of none out of 145 for chondrodystrophy and osteogenesis imperfecta. Therefore it appears that non-penetrance and/or misdiagnoses occurred in her data. The result of Reese (1949) seems less significant in view of the finding of Falls and Neel (1951) of a definite instance of non-penetrance of the gene for retinoblastoma. They had 71 kindreds in which the first affected sibship was known; two kindreds had two or more affected individuals in the first affected sibship, but here again non-penetrance is a definite probability.

Borberg's (1951) one kindred (No. 71), however, seems to offer more convincing evidence for GM in man, since, according to his study and that of Crowe, Schull, and Neel (unpublished) neurofibromatosis behaves as a regular dominant. Both parents of the first affected sibship were alive and reported normal at ages 79 and 71. The author examined each parent over the entire body without finding any café-au-lait spots (Borberg, 1953). There were only 16 persons in his study who had both a parent and a child affected with neurofibromatosis, but all 16 were themselves affected.

If chondrodystrophy and osteogenesis imperfecta are as regularly dominant as the studies of Mørch (1941) and Seedorff (1949) seem to indicate, the absence of evidence for GM in a total of 145 kindreds can be used to provide an estimate of the upper limit

TABLE 3. TABULATION OF STUDIES MADE ON ANIRIDIA AND OTHER TRAITS INHERITED AS RARE DOMINANTS OF HIGH PENETRANCE, WITH REGARD TO PENETRANCE AND PRESENCE OF FIRST-AFFECTED SIBSHIPS CONTAINING MORE THAN ONE AFFECTED INDIVIDUAL

Trait	Author	Penetrance*	No. of Kindreds in Which First Affected Sibship is Known	No. of Kindreds Having 2 or More Affected in First Affected Sibship	Remarks
Data from own research					
Aniridia	Møllenbach, 1947	See table 2	22	0	
Chondrodystrophy	Mørch, 1941	Unity?	98	0	No kindreds with more than 2 generations affected were observed. No skipping of generations observed.
Neurofibromatosis	Borberg, 1951	16/16	1	1	First affected sibship considered known only when both parents alive and reported normal. No. 71 is the aberrant kindred.
Neurofibromatosis	Crowe, Schull & Neel (unpub.)	11/11	29	0	Both parents examined and found normal. The affected individual was examined and often some or all of his sibs.
Osteogenesis imperfecta	Seedorff, 1949	37/37	47	0	Blue sclerae, with or without fractures, were considered to indicate the presence of the gene for the osteogenesis imperfecta syndrome.
Retinoblastoma	Falls & Neel, 1951	?	71	2	Only one 3-generation kindred. A case of definite non-penetrance was found in this study. Kindred #71 not counted. Nos. 4 and 35 are the aberrant kindreds.
Data from survey of literature					
Aniridia	Bell, 1932	See table 2	13	3	Nos. 1099, 1124, & 1134 are the three aberrant kindreds. In 1099 both parents of the first affected sibship were examined; one had corneal opacities, strabismus and nystagmus. Not known whether the parents of other two kindreds were examined; they were reported normal.
Retinoblastoma	Reese, 1949	Not given	605	7	No details given.

* When 3-generation data are available the penetrance is estimated by the following fraction:

$$\frac{\text{No. persons with both an affected child and an affected parent who are themselves affected}}{\text{No. persons with both an affected child and an affected parent}}$$

of the proportion of all mutations which give rise to two or more affected sibs in first affected sibships. It is found that when this proportion is 0.031 the results observed in the 145 kindreds—one mutant per first affected sibship—will occur once in a hundred times. Therefore the proportion of mutations which give rise to detectable clusters of mutants is probably less than 3 per cent. If this order of magnitude is correct, it is not surprising that there is little convincing evidence for GM in man.

The fact that among the human dominant traits known to have mutated several times, there are none which can be proved with considerable statistical confidence to have a non-penetrance rate of less than 3 per cent, makes it unlikely that convincing proof for GM will appear in the immediate future. We must conclude that the original question prompting this discussion must remain unanswered; non-penetrance and GM are both possible explanations for the presence of four aniridic individuals in the first affected sibship of the kindred described in this paper. The known existence of GM in the mouse and guinea pig, however, makes it worthwhile to keep this possibility in mind when situations similar to the one described occur.

SUMMARY

A kindred containing 23 cases of congenital aniridia distributed in four generations was studied. Complete ophthalmological examinations were performed on 20 affected individuals and 38 of their normal relatives. Except for one probable case of incomplete expression the gene determining aniridia in this kindred appears to behave as a dominant of high penetrance. No linkage between the locus for aniridia and the loci for the MN and Rh blood groups could be demonstrated. Data concerning linkage with the ABO blood group locus were not informative.

The first occurrence of aniridia was in a sibship containing four affected and six normal individuals. This appearance of aniridia in several children of an apparently normal couple is interpreted to be due to the occurrence, in one of the parents, of either non-penetrance of the gene for aniridia or to germinal mosaicism (GM) (gonad composed of normal and mutant tissue). It was not possible to decide between these two alternatives.

Documented cases of GM are known in the mouse but none is definitely known in man. However, a survey of certain well-studied rare dominant traits revealed some evidence for the occurrence of GM in man. This survey further indicated that the proportion of human dominant mutations which produce a cluster of mutant individuals (two or more mutant children from normal parents) is probably less than 3 per cent. Conclusive evidence for GM in man, therefore, may not become available for some time to come.

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