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Familial Sex-Linked Mental Retardation

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DURING the study of a Roman Catholic family of Austro-German extraction which settled in Saskatchewan at the turn of the century, in which mental retardation appeared to be transmitted by a sex-linked recessive factor,[1] a second unrelated but similarly afflicted family was encountered by one of us (H.R.). The purpose of this report is to present details of the latter family, members of which now live in two of the prairie provinces and in which mental retardation has been found to occur exclusively in males, and to be transmitted by normal females. Genetic factors play an important role in the causation of mental retardation, but unless the latter is associated with certain specific features, which may be biochemical, as in phenylketonuria, or which may be recognized by the eye, as in mongolism, it cannot always be clearly characterized and defined. In the family to be reported we have not detected any associated biochemical disorder or characteristic physiognomy, but the clinical picture in the affected subjects is sufficiently uniform and its predilection for males so constant that it seems certain that we are dealing with a single disorder.

In a search for reports of analogous families we have encountered only three which bear any resemblance to the family we are now recording; they are those reported by Martin and Bell,[2] by Allen, Herndon and Dudley[3] and by Losowsky.[4] In the family reported by Martin and Bell there were 11 severely retarded males; between them they had eight normal brothers, the retardation being passed on by normal females. A close analysis of this family, however, reveals that the factor for mental retardation appears to have been passed on to the normal females in two instances by normal males. In the family reported by Allen *et al.*, details of six generations are given, and in every instance severe mental retardation occurred only in the sons of normal females; this mental stunting was also associated with widespread muscular weakness. The mode of transmission of the disorder reported by these workers was similar to that in the family to be described in this communication, but the clinical manifestations differed, for muscular weakness has not been characteristic of our patients. In the family described by Losowsky there were nine severely retarded males whose mothers were all mentally normal, but in two of the families there was a sister who was mentally retarded though to a less extent than her corresponding retarded brother.

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METHODS AND RESULTS

The family described in this report (Fig. 1) is of Dutch Mennonite extraction, and had probably moved to the Ukraine from Holland after 1820. Mrs. Mary A (1),* the mother from whom the families stem, and whose maiden name is not known, was married three times. Her first husband (2) was, like her, born in the Ukraine and came to southern Manitoba, to Plum Coulee, in the

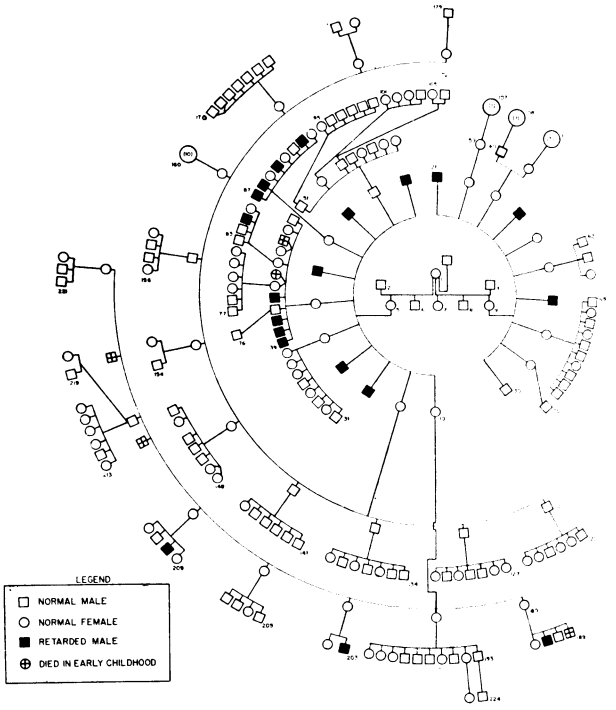

Fig. 1

1870's; by him she had two children, Mary (5) and David (6). By her second husband (3), also a Mr. A., she had three children, Susie (7), Peter (8) and Margaret (9). By her third husband (4), called Mr. B., she had no children. Her eldest daughter, Mary (5), married Joseph C.; her youngest daughter, Margaret (9), married Martin D. These two families then migrated, between 1900 and 1908, to western Saskatchewan and settled near Swift Current. From there two branches of the family moved to Alberta, one to Coaldale in the south, and the other to the Peace River region in the north. Several other branches of the family later moved farther afield to Mexico and are not directly accessible.

*Figures in parentheses refer to the numbers on the genealogical table (Fig. 1).

THE C FAMILY

Jacob C. who married Mary A. (5) was a Dutch Mennonite farmer who had had little formal education, but who was of normal intelligence. As far as can be ascertained there were no known cases of mental retardation in his forbears. He died at the age of 69 of diabetes and an unspecified heart disorder. His wife, Mary, was also normal mentally and, as far as can be ascertained, came from a family free from mental retardation. She died at the age of 66 of a cerebral hemorrhage.

Mary and Jacob C. had 11 children (10-20), five of whom were girls who were all normal mentally; six were boys, and one was normal but five were mentally retarded. Four of these retarded boys are presently in the Moose Jaw Training School (12, 13, 16, 18); the fifth (20) and youngest died in childhood. Mary's normal children all married. We shall not concern ourselves with her son, for all of his offspring have been mentally normal; the daughters, however, like their own mother, have produced an excess of mentally retarded males. The eldest daughter (10) had six daughters, all normal mentally, and three sons, one who died at the age of six months of febrile convulsions and who was probably mentally normal, and a second who died at the age of five days of unknown causes. Although she had no surviving retarded sons, she carried the defective trait, for three of her daughters (180, 182, 184) in their turn bore retarded sons.

The three daughters with retarded sons had between them four normal daughters and six sons. One son died in infancy and three of the five survivors are mentally retarded. The three daughters who did not carry the trait for mental retardation had 12 normal sons and 12 normal daughters between them. The third daughter (14), who had three normal sons and five normal daughters, has moved to Mexico. Her children, who are all married, and their grandchildren, have not been seen, but are reported to be mentally normal, except for one son of the eldest son who is retarded.

The fourth daughter (15) had seven sons and five daughters; one son and one daughter died in infancy. Of the six surviving sons, four (39, 40, 41, 43) are retarded mentally, and all of the four surviving daughters are mentally normal. The four retarded sons were admitted to the Moose Jaw Training School in 1948, following which their parents and the remainder of the family moved to Mexico. The retarded children have been examined, but the rest of the family have been contacted only by mail. Only two daughters (44, 46) have as yet married. One (44) has two normal sons and four normal daughters; the second (46) has three sons, one (85) of whom is retarded, and one normal daughter.

The fifth daughter (17), now living in the Peace River region, has five sons, four (87, 88, 90, 93) of whom are retarded; her three daughters are normal.

THE D FAMILY

The second branch of this family stemmed from Mary's marriage to a second Mr. A. (3). Whether he was or was not related to the first, history does not record, but their names were identical. By this second husband Mary A. had two daughters and one son. We have been unable to trace the offspring of the first two children (7, 8), a daughter and a son, but the offspring of her younger daughter, Margaret (9), who married a Martin D., have been traced. Martin D., a Mennonite of Dutch extraction, was a successful farmer who died at an advanced age of heart disease; he was also a diabetic and became blind in his later years. None of his relatives were known to be retarded mentally. His wife, Margaret, lived to a ripe old age. She had 10 children (21-30). Six of these were girls who were all normal mentally and four were boys, of whom three (21, 24, 27) were retarded and are now inmates of the Moose Jaw Training School.

The six normal daughters, as far as we can ascertain, have produced only normal sons and daughters, but this is the younger branch of the family and their full story still remains to be revealed.

TABLE I.—DETAILS OF PATIENTS WITH THEIR LEVELS OF INTELLIGENCE AND SKULL CIRCUMFERENCES

Number on genealogical table	*Age*	*Location*	*I.Q.*	*Wassermann reaction*	*Seizures*	*Skull circumference (inches)*	*Comment*
12	70	Institution	15	—	—	19.5	Blind
13	64	"	28	?+	—	20.25	
16	57	"	13	+	+	20.75	
18	53	"	39-27	+	—	20.5	
39	37	"	20	—	—	20.0	
40	35	"	30	—	—	19.5	
41	33	"	45	—	—	19.25	
43	30	"	18	—	+	19.7	Bilateral colobomata and left cataract
203	19	Home	25	—	—	18.75	
210	14	"	70	—	—	19.25	
191	11	"	30	—	—	19.75	
21	67	Institution	35	—	—	20.5	
24	60	"	37	—	—	19.0	
27	54	"	24	—	—	19.0	Diabetes

The Characteristics of the Retarded Children

There are in this family, as far as we can ascertain, 21 retarded males; 20 of these are depicted in Fig. 1. One subject is omitted because we have been unable to examine him. He lives in Mexico and we think that his retardation is due to a factor or factors not present in his retarded relatives, for he is the son of a normal male and not of a normal female member of this family.

There are more than 90 males without the genetically determined form of mental retardation, and it is not surprising that one of these should be

retarded, since approximately 3% of the general population has some degree of mental retardation. Nineteen of the 20 retarded males are alive; 11 of these are in institutions and have been examined by us; eight are still at home. Of the eight at home, three have been examined by us, four have been seen and questioned by a public health nurse, and one, who lives in Mexico, has escaped our scrutiny.

The men are well built, physically strong, and have no definitive features apart from somewhat prominent ears. Their colouring tends to be fair, but the eyes of some are brown and of others are blue. Their heads are not obviously microcephalic, though their skull circumferences tend to be at the lower limits of normal. The measurements of the latter together with intelligence quotients are given in Table I. Two of the patients had positive Wassermann reactions, and the reaction of a third was doubtfully positive. Two have had seizures, a third is blind, a fourth developed diabetes, and a fifth had bilateral colobomata with a left cataract. As children these subjects were all slow to develop, learning to walk at two and three years of age, and learning to say simple words at the ages of three or four. They have, on the whole, been docile and easy to manage, and have been able to carry out simple tasks on farms under supervision. Only one child has been able to attend public school; this child is 11 years old and is in grade three. He has an intelligence quotient of 70. Specimens of urine have been examined from all except one of these patients; none contain phenylpyruvic acid. Aminoacid chromatography of urine from 14 patients revealed no evidence of any pathological aminoaciduria. Chromosomal studies on three have revealed normal karyotypes.

The Mode of Transmission of Mental Retardation

Mental retardation in this family is manifested only in the males and is transmitted by normal females. This mode of transmission is characteristic of a sex-linked recessive or of a sex-influenced autosomal dominant gene. The defect must have been carried, in the first instance, by Mary A. (1), from whom both these families stem. By her first husband she had five normal daughters and six sons, five of whom were retarded. By her second husband she had six normal daughters and four sons, three of whom were retarded. In keeping with the supposition that the defect is transmitted by a sex-linked recessive factor is the finding that half the daughters at risk have defective sons and half have not. The second branch of the family is not, as yet, sufficiently numerous for satisfactory analysis, but an analysis of Mary's (5) family reveals that there are 13 daughters who are potential carriers of the factor, who have married and have families; six of these daughters have retarded sons and seven have not, which is as would be anticipated. An analysis of all of the families in which there are retarded sons reveals that they contain 23 girls, one dying in infancy, and 29 boys, two dying in infancy. All of the females are normal mentally, 20 of the surviving males are mentally retarded, and only nine are normal. The increase in the incidence of retarded males over normals is probably fortuitous, and does not necessarily indicate that the ovum carrying the defective factor is more likely to be fertilized or survive than that not carrying the defective factor. The incidence of those carrying and those not carrying the trait amongst the females is equal.

DISCUSSION

This large family in which mental retardation has afflicted many of the sons of otherwise normal daughters might well have remained undisclosed had it not been for a chance remark by one of us (H.R.) during the course of a survey of another similarly afflicted family. Unfortunately, our studies have not revealed any biochemical or clinical features which distinguish the retarded subjects of this family from others with "non-specific" forms of mental retardation. For this reason the mothers of the retarded boys have not been submitted to a battery of biochemical tests. On clinical grounds these mothers do not differ from their more fortunate sisters, and only when a daughter produces a retarded son can it be inferred that she carries the trait. In four of the families, two being the original ones, the birth of a retarded son did not appear to lead to any limitation in the size of the family. This, however, is not true of three of the youngest families visited, where the arrival of a retarded son immediately led to steps being taken to try to limit the size of the family. In such families voluntary sterilization of the mother should not only be allowable but should also be encouraged.

SUMMARY

A family is described, the members of which are living in two of the prairie provinces, in which mental retardation is confined to males and is transmitted by normal females. The defect has made its appearance in three successive generations. The defect is probably transmitted as a sex-linked recessive.

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