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FIVE GENERATIONS OF CEREBELLAR ATAXIA IN THE HUMAN AND POSSIBILITIES OF ITS GENETIC CONTROL

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Hereditary traits in human beings are often congenital, and can be recognized from the birth or soon after the birth of an affected person. However, not all hereditary traits are congenital. If the trait does not appear until very late in life, a person may succumb to some other disease before he has reached the proper age for the development of the hereditary defect. As a consequence, the genetics of the trait is often difficult to determine.

Cerebellar ataxia occurs as a hereditary trait in the human race. The ataxia does not appear in a person until adult life. Often the weakness, the staggering gait, and the other expressions of the disease are not recognized until after several children have been produced by the affected person. The disease is always fatal.

The family history of cerebellar ataxia which is shown here[1] has been followed through five generations. Starting with one ataxic member representing generation I, the family history shows that in generation II four of the six sibs who lived to adult age had the disease. In the one sibship studied in generation III, seven of the nine members were ataxic. Generation IV contains some members who are not yet old enough for the disease to develop; but among the children of ataxic parents, ten (possibly eleven) of the twenty-five children over twenty-seven years of age have developed ataxia; and among thirteen others past twenty-one, three can be considered as probably ataxic. In generation V, one of the seven children twenty-one years of age or older has developed the disease. Others in generations IV and V will likely develop the trait as they reach the age of onset.

Unfortunately, the appearance of the disease has not acted as a check on the production of children. The affected members of generation III have had families (generation IV sibships) as large as the families of non-affected members. Although the disease was recognized as one associated with the family, the members (of the older generations at least) did not clearly understand the association.

In genetic behavior, the disease seems to be a simple, Mendelian, dominant, hereditary defect. As shown in the pedigree, each ataxic person has one ataxic parent who is a blood relative of the family. The proportion of adult ataxic children produced by the ataxic parents closely approaches fifty percent, the frequency expected on the

[1] For the family chart, see Gray, R. and C. P. Oliver, Heredofamilial Ataxia which appeared in Minnesota Medicine for May, 1941.

basis of a Mendelian dominant. The observed frequency of ataxic children, counting the one questionable member, is fifty-three percent of those twenty-seven years of age or older; and it is forty-six percent, counting the four questionable members, of all children twenty-one years of age or older.

Supporting evidence of the dominance of the trait is found with the two normal members of the sibship in generation III. All of their children are normal for the trait, with twelve of the sixteen children over twenty-seven years of age. The grandchildren (generation V) are less than twenty-seven.

Sex-linkage is not involved. Two males in generation III passed the trait to sons of generation IV (families three and eight).

The age of onset for the disease cannot be determined definitely. Older generations did not recognize the disease as quickly as the younger sets, due to the increased interest of the younger generations in the familial relationship. The members now watch for the first sign of the ataxia, possibly seeing the signs on occasions when they are not there. The earliest recognized onset occurred in a member at age twenty; the latest, at thirty-three.

Death has occurred in the more accurately known cases in this family within seven to ten years after the disease was recognized. The average age at death of the ataxic members in this family has been approximately thirty-seven, with an age range of twenty-eight to forty-eight. A lower average age at death in generation IV is due apparently to the living ataxic individuals whose average age in 1939 was two years more than the average age of those individuals who had died.

Once the disease has developed in a person, it becomes fatal. No cure is known.

Any attempt to use genetic methods as a means to control the passage of the trait is complicated by the late age of onset for the disease. Many members will have produced children before the disease becomes expressed; and he can expect that one half of his children, on the average, will also become ataxic. In an intelligent family, as this family is, such prospects must disturb a parent.

Fortunately there are possibilities for relief of the situation; but the relief can be brought about only through the help of the individual members of the family.

A person whose parent was ataxic cannot know whether he will become ataxic until he has reached the age of onset. If he wants to be relatively certain that he will not pass the ataxia to some of his children, he must postpone having children until he has passed the age of onset. Accurate data are known for seven ataxic members in generation IV; and their average age of onset is twenty-four, ranging from twenty-one to thirty. In one person in generation III, the disease was not recognized until he was thirty-three. A child of an ataxic parent, then, should not feel himself free of the potentiality until he approaches the age of thirty. He will be wiser if he has no

children until he has reached the latest known age of onset in the family, thirty-three. If at that age he has not developed ataxia, he can be reasonably certain (but not absolutely sure) that he will be free of the disease and that his children will not be ataxic. If he does develop the disease, however, he can know that some of his children are likely to become ataxic.

A person whose parents lived past the age of onset without becoming ataxic can assume that he will not be ataxic and that his children will not be ataxic.

The possibility of control of this disease by genetic means, then, rests upon the willingness of the children of ataxic members to cooperate.

This family can eliminate the ataxia from its descendants, provided the child of an ataxic parent is willing to wait until he has reached the age of thirty before he produces children. If he shows symptoms of the ataxia before or by that age, he should not, under the conditions, have children. However if he remains free of the defect at age thirty, his children probably will not be ataxic. The few exceptions to the rule, those with the onset of the disease occurring after thirty, will be only of slight importance in the general benefit to the family.

The late production of children may decrease the number of descendants for a few generations; but it does have the advantage that those who remain free of the disease will be relatively sure that their descendants will not be bothered with the disease.

THE INTERACTION OF CERTAIN GENES IN BRISTLE DEVELOPMENT OF *DROSOPHILA MELANOGASTER*

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One of the foremost problems of modern genetics is the study of gene action, the manner in which genes affect developmental processes. We are all familiar with the adult phenotype of various mutants, both in *Drosophila* and in other experimental animals, but regarding their developmental behaviour we know comparatively little. Although physiological or developmental genetics, as this field is called, has a history of some twenty or thirty years, it has been only in the last ten years that workers have focussed much attention upon it. At the present time many geneticists and embryologists consider it one of the most promising fields for biological research, and in the words of Curt Stern[1] "the use of different genetic constitutions which pure genetics makes available as tools in the

[1] Stern, C., 1940. Recent work on the relation between genes and developmental processes. Growth Supplement 19–36.