THE INHERITANCE OF ALLERGY WITH SPECIAL REFERENCE TO MIGRAINE¹

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For some years during the course of treatment of different forms of allergy at the BALLYEAT HAY FEVER AND ASTHMA CLINIC in Oklahoma City, various facts concerning the inheritance of allergy have been noted. It is the object of the present study to determine as far as possible from the material thus collected the type of inheritance displayed by that form of allergy called migraine. The study was made entirely from a genetic point of view and the material used began with the available records of patients of the BALLYEAT HAY FEVER AND ASTHMA CLINIC.

Studies on the heredity of allergy are not numerous. Work seems to have begun about 1909 with DRINKWATER's results which indicate that asthma acts as a dominant character. Since that time a number of investigators have written on some phase of allergy. Some, though reporting on one form of allergy, have realized that various others have occurred in one family. A connection of migraine with the sex endocrines has been observed, several investigators noting that affected females suffer with migraine more frequently during the menstrual period.

ADKINSON has made an extensive study of bronchial asthma (1920) and she concluded that it is a recessive character, since normal people transmit the asthmatic tendency. These normals she regarded as heterozygous. Her findings do not all bear out this conclusion, for she states that children of two heterozygous normals are three times as likely to be asthmatic as normal, whereas one fourth should be asthmatic if the character is a true recessive. She seems to have overlooked the possibility of incomplete dominance. ADKINSON found that bronchial asthma, hay fever, some urticaria, and eczema must be accepted as equivalent in their inheritance. She states that "asthma is inherited with equal frequency from the family of either parent."

BUCHANAN in 1920 considered migraine as a recessive trait. SMITH (1922) concluded that migraine is a dominant trait, in some way sex determined. The work of STUDY, referred to by BAUR, FISCHER, LENZ, indicated that hay fever is a dominant character, manifesting itself in the older members of a family as gout, but in the younger as hay fever. GÄNSSLEN (1921)

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showed that one individual, and sometimes a number in the same family, often are subject to hay fever, asthma, urticaria, and eczema, gout and gall stones.

LENZ (in BAUR, FISCHER, LENZ), using the charts of UNGER and WIETZ, concluded that migraine is probably a sex-linked dominant and that "the sexual life seems to have an influence upon the occurrence of migraine. There are women who suffer from migraine only when they are menstruating, and never have an attack during pregnancy."

FETSCHER (1927) suggested that hay fever is sex-linked. He found that sons only were affected if both parents were negative and daughters were affected if one parent was allergic. Since he did not prove that hay fever is transmitted to sons from their mother only, and since he showed only three charts, his results are not conclusive.

ALLEN (1927-28) analyzed 400 cases of migraine and concluded that it is inherited as a dominant character. He found that menstruation influenced the onset of migraine. JORDAN (1928) published a family record to show that eczema is inherited.

In 1928, BALYEAT showed that inheritance appears to be the chief factor in determining hay fever and asthma and that the earlier in life an individual becomes sensitive, the greater the tendency to develop a sensitivity to more than one group of proteins. He found that the environment to which an individual is exposed has much to do with the sensitivity which develops. Also he stated that eczema and migraine are interchangeable with hay fever and asthma, and that the thing inherited is the ability to become sensitive, but not the specific state, and that this is inherited as a dominant character.

In 1929, the writers of this paper made a preliminary genetic study of twelve family pedigrees. They concluded that there is probably only one gene involved in the different allergies and that the gene acts as a dominant Mendelian unit, although its dominance is often incomplete, that it sometimes skips a generation, and that the environment is at least to some extent responsible for the expression of this gene.

In 1930, APPERLY published a family tree showing five generations, in each of which allergy occurred. In the same year ELY showed that migraine is an hereditary disease.

In the study of the inheritance of migraine from a genetic point of view it might be of interest to point out some clinical observations. BALYEAT (1931) in a study of a series of 202 cases of migraine concluded that migraine appears to be common in children since nearly one-third of all cases developed symptoms during the first decade, that the syndrome is more common in business men, professional men and teachers than in laborers, that about 7 percent of all people in the United States some-

time in life suffer from the symptom complex, that not unlike asthma symptoms of migraine in childhood may vary greatly from those of the adult, and that migraine is interchangeable in the linkage with other allergic diseases. In an unpublished paper (RINKEL and BALYEAT 1932) in a series of 65 cases of headache (migraine) proved to be due to food hypersensitiveness, a family history of headache was obtained in 84.4 percent. It appears from our clinical study that a patient transmits from one generation to another only the ability to become sensitive and not the specific state. Apparently the type of sensitivity from which the antecedent suffered has no relation to the type the descendant may have.

In using the term "migraine," we refer to those patients who have paroxysmal headaches characterized by hemicrania (also bilateral headaches), and who have symptomatic evidence of cortical involvement. There are headaches due to hypersensitiveness that cannot be classified as migraine since they do not have cortical features. These cases have not been used in our study. It may be remarked that this restricted definition of migraine makes even more striking some of the genetic situations later described, in which persons who have only migraine transmit several other allergies to their descendants.

The methods used in the present work are similar to those by which material was collected for our preliminary paper. Detailed questionnaires to patients were employed to obtain the family histories used for our pedigrees. The questionnaires asked for specific facts concerning each member of the family. When there was any doubt as to an answer, letters were written about specific points, and in many cases a series of letters was sent to a single individual. Since the patients treated by the clinic are of a high type of intelligence (see below), the information obtained is looked upon as very trustworthy.

We realized at the outset the necessity of getting full pedigrees of both maternal and paternal sides of the families. The work was done as far as possible with methods commonly employed in genetics. This is in contrast with methods sometimes used in studies of this nature in which records are kept only of the affected parents of the individuals being studied, omitting the contribution to the inheritance made by the parent who may not happen to show the character. Of this latter nature are many of the charts referred to by BAUR, FISCHER, LENZ including the pedigrees relating to allergy from GÄNSSLEN, UNGER, CROWDER, ULLMAN, and STUDY.

Data as complete as could possibly be obtained were collected from fifty-five families, both maternal and paternal sides of each pedigree being included. Forty-one of these pedigrees gave a sufficiently complete history for genetic use. We have retained only the pedigrees which gave fairly complete information about two and usually three generations. Most of

the people to whom questionnaires were sent have suffered from migraine. The preliminary report concerning hay fever was based upon a study of twelve families. Including the pedigrees of the earlier paper, therefore, fifty-three out of sixty-seven different family histories complete enough for genetic study form the basis of this report.

In the preliminary report we found that hay fever and other forms of allergy may act as a dominant character but that their dominance is irregular, for it is often incomplete and sometimes an unaffected individual may transmit the ability to become sensitive to several or to all of his or her children. In the earlier paper the various forms of allergy were considered as different expressions of a single gene, although the possibility of multiple factors as a cause was not overlooked. The genetic evidence then available led to this conclusion, but it is to be noted that it was quite in harmony with the clinical behavior of the diseases.

After studying allergic families for several years we have found that if allergy is present in a strain, it is extremely rare (families 2 and 23) for a generation to occur without some member of the family being affected. We have only five cases of this kind. Unaffected individuals may pass on the allergy to their children, but usually these individuals have allergic brothers or sisters even though they themselves have no allergic diseases. In no case which we have studied does allergy skip two generations; that is, allergic individuals have never been found to appear after the family has been negative for two generations. Occasionally one generation may be entirely skipped, but we have no record of two negative generations followed by a third allergic one, and we have sought carefully for cases bearing upon this point. For these reasons we have come to regard a family as incapable of transmitting the gene for sensitivity if in our pedigrees it has been entirely negative for two generations, or if the parental generation and the two grandparents also are negative.

The changing or incomplete dominance of allergy may best be explained by quoting a couple of paragraphs from our earlier paper:

"The time of appearance of the sensitivity in the ontogeny of the individual differs greatly in different people. In some cases a child develops a sensitivity very shortly after birth and in other cases individuals who have never before had trouble develop a sensitivity at the age of seventy. Between these two extremes are a whole series of ages, at any of which a sensitivity may develop. Consequently, if an individual belongs to an affected family and has had no trouble, there is still a great probability that he may later develop it. Thus no chart of an affected family can ever be considered as complete, for those once classed as normal may later develop some form of allergy.

"Another point must also be considered. In order for any form of sensi-

tivity to become manifest there must be, in addition to the sensitivity, the external factor that causes the trouble. A child sensitive to certain forms of protein will not develop urticaria or eczema unless he eats that protein. Similarly an individual sensitive to a certain kind of pollen develops hay fever only when exposed to that pollen. In recent years much has been added to our knowledge of the interaction of heredity and environment. Apparently the study of inheritance of hay fever, etc., reveals another case in which a definite environment as well as a definite inheritance is necessary to produce a definite character."

These statements of our earlier paper apply equally well to migraine. This form of allergy sometimes occurs in young children and on the other hand many people from allergic families develop this difficulty much later in life. The environment necessary to produce allergy in members of an allergic family differs with respect to the different allergies. Hay fever does not develop unless the patient comes in contact with a particular kind of pollen which furnishes the necessary irritation. For example, a patient born with the ability to become sensitive, who comes in contact with Russian thistle pollen develops a sensitivity to Russian thistle and may have hay fever symptoms on adequate contact. Likewise, those who live in the timothy section of the United States and who come in adequate contact with timothy pollen have developed a sensitivity to timothy and have hay fever symptoms from contact with timothy pollen. Similarly migraine, eczema, etc., develop only when the foods to which the individual is sensitive are eaten. Both the pollen in the one case and the particular food in the other may be regarded as the environment necessary to bring out the allergy.

The data upon which these conclusions in regard to migraine are based are less open to criticism than in the case of hay fever on the score of the environmental condition necessary to bring out the sensibility. That is, there is less possibility that the negative cases are not truly negative but have merely not happened to meet the proper environment to cause the allergy to manifest itself. The reason for this is that with the normal varied diet which most adults enjoy there is little chance that a person can escape the sensitizing protein long after reaching adulthood.

That both a definite heredity and a definite environment are necessary to produce a given character is well known and many cases of both animals and plants can be cited to support this principle. The early work of BAUR on the effect of temperature on the color of the primrose was perhaps the first case of this kind noted. Since that time modern work has shown that many adult characteristics are dependent on a special environment as well as on a special gene for their fulfillment. MORGAN's work on abnormal abdomen in *Drosophila* showed that this character is largely dependent upon moisture. IRA WILSON's hereditary tumor in *Drosophila* is dependent to a

large extent upon the amount of food. The work of the senior author on extra legs in *Drosophila* (HOGÉ 1914) has shown that this character appears only when the conditions of temperature are suitable. Similarly KRAFKA has demonstrated that the number of facets of "bar eye" in *Drosophila* varies in relation to temperature. Also there are many examples to show that age may operate to make manifest the determining factor in various characters. Pink-eyed flies have light eyes when young, but when old their eyes are almost as dark as those of the wild red fly. Black-bodied flies when young are as light colored as the normal fly and they develop black pigment only with age. These examples are sufficient to show that

Key to Charts

○	female	A Asthma
□	male	B bronchitis
● ■	allergic individuals	C colitis
⊙ ⊠	on known facts concerning individual	E eczema
○ □	individuals known to be negative	H hay fever
⊕ ⊞	individuals who died young	M migraine
⊙ ⊠	individual considered negative, but data incomplete	U urticaria
⊗ ⊞	family history incomplete as to members; except in cases so marked, every individual in every family is listed	
● ■	allergic, but type unknown	
⊙ ⊠	individuals from families with no allergy	
○ □	negative individuals from families known to be allergic	

both environment and heredity are determining factors in the development of a particular individual. Studies on the inheritance of allergy show that with it, just as with these cases of the lower animals and plants, an individual does not become allergic unless the environment to which he or she is subjected is such as to bring out the latent sensitivity.

An interesting fact early observed in this study was that allergic persons commonly marry into allergic families. This is still true even in the cases where one or both of the individuals concerned are themselves negative. Our records include only a few cases in which marriage occurs between a person from an allergic family and one from a negative line. The explanation for this fact can only be conjectured. Allergic families have

been found to be usually of a high grade of intelligence, and, as BALYEAT (1929) has shown, a hay fever sufferer customarily has a higher intelligence quotient than does the average person. It may be surmised that this fact has something to do with the frequent marriages between allergic families and that in some cases their higher intelligence serves as a mutual attraction. Since allergic persons make up only a small percentage of the entire

population, their frequent marriage is worthy of note, although no means is at present known which favors the mating of these persons.

In our paper on hay fever we have stated that some families show only one form of allergy. It is seldom, however, that any family is specific for one allergy alone. Only one of the twelve families of our earlier paper showed no allergy but hay fever. One had only asthma and hay fever, and the other ten had in addition either eczema, bronchitis, urticaria, migraine, or a combination of several of these allergies.

Our present study of forty-one families shows similar conditions. Only five (for example families 22, 23, 27, 37) exhibit branches which before crossing with other allergic families show nothing but migraine, and in most of the families there are various combinations of the different allergies, a single individual sometimes suffering from four to five types (example, family 8). In eleven families there are two kinds of allergy and in twenty-six there are three or more.

Since in the families from whom we have collected data so many forms of allergy are present, and since allergics commonly marry individuals from similar families, it is extremely difficult to determine positively the number of genetic factors that cause the different forms of sensitivity.

In our present study we have endeavored to ascertain whether our pedigrees could be explained as due to the operation of several genes acting

together, perhaps one gene being necessary for an individual to become allergic and a special modifying gene being necessary to produce each type of allergy. This possibility, mentioned in our previous paper, has been suggested by several critics, but the number of pedigrees previously considered was insufficient to settle the point.

In order to gain some light on this matter we have examined carefully the pedigrees of those families in which an allergic individual marries into a negative line. As already stated, a line is considered negative when for two generations no member has exhibited an allergy or when the parental generation and the two grandparents also are negative. The study of this type of mating has proved the most productive phase of our research.

Obviously a cross of this kind will show at once what types of allergy are dominant, for if any allergy appears again in the F_1 from such a cross its dominance is certain.

Unfortunately, as we have stated before, marriages of this type are not numerous. We have among our fifty-three pedigrees twelve matings of this

type (Nos. 1, 5, 12, 18, 29, 32, 34, 37, 38, 41, 42, 43). In pedigree 1, hay fever and migraine act as dominants, in No. 12, hay fever; in No. 29, urticaria and migraine, in No. 34, eczema, and in No. 43, asthma acts in a similar manner. Thus each of these five types of allergy may show dominance.

However, in spite of this dominance, not even half of the F_1 , as we should expect if the allergic parent were heterozygous, develop the sensitivity. In family 29 a man affected by migraine and urticaria married into a negative family and had four children; one of the four had hay fever, urticaria and migraine, but the other three were negative. In family 32, a woman with migraine and hay fever married into a negative line and

had two children, one of whom had eczema, the other hay fever. In family 18, a woman with asthma married into a negative line and had a daughter with migraine. In family 38 a man with hay fever and asthma married into a negative line and had nine children, of whom only one daughter had any trouble—hay fever and eczema. In family 34 a woman with eczema married into a negative line and had four children only one of whom showed any allergic trait, and this child had migraine, urticaria, and ec-

zema. In family 41 a man with migraine married into a negative line and had six children, four of whom were allergic, a son and a daughter each having hay fever, a son migraine, and a daughter urticaria and eczema.

If we consider sensitivity as due to one gene and each allergy as due to a modifying gene, then we must assume that in each of these cases the negative line brought in the special modifiers necessary to produce the different types of allergy. If these modifiers exist, then, as has just been

shown, they must act as dominants when present in connection with the gene for sensitivity. Since these possible modifiers are dominant, the negative lines referred to above would have to bring in one or more dominant modifying genes for the different forms of allergy, these modifying genes being unable to express themselves without the gene for sensitivity which is lacking in the negative line. Following out this line of reasoning and assum-

ing that there is a specific modifying gene for each allergy, we would expect these dominant modifiers to cause new allergies in a fair percentage of the children. If the negative parent were heterozygous for the modifying gene, only half the children would have the new allergy. In any event we should never expect complete dominance, since we have shown that the dominance is variable. However, the new combinations in the F_1 are of various

kinds, one individual having one new allergy, another a second, and still others having different combinations of them. Sometimes only a small percentage of the progeny show the dominance of a particular type of allergy, and in other cases the same allergy that has been shown in similar crosses to act as a dominant does not appear in the F_1 although it may be present in the parent.

Another fact revealed by this type of mating is that a person with one form of allergy may transmit other forms to his or her children. Examples to illustrate this condition are to be found in many pedigrees and are of two kinds: Either the allergy not present in the parent may have been

FAMILY NUMBER	NEGATIVE LINE CROSSED WITH	ALLERGY IN PARENT FAMILY BUT NOT IN PARENT	ALLERGIES IN PARENT AND ALSO IN F_1	ALLERGIES OF PARENT FAMILY ALSO IN F_1	NEW ALLERGY IN F_1
1	MH	A	MH	A	E
5	EM		M		
12	H		H		M
18	A	M		M	
29	UM		UM		H
32	MH		H		E
34	E		E		MU
38	HA		H		E
41	M	H	M	H	UE
42	HA		HA		BE
43	A		A		H

observed in other members of his family, or in other cases some form entirely new to the strain may appear.

A summary of the results of some of the matings between allergic and negative families will make these facts more evident. (Note: A-asthma; B-bronchitis; E-eczema; H-hay fever; M-migraine; U-urticaria.)

41

42

43

As this chart shows, the allergy of the parent may not appear at all in the F_1 , although in other cases this same allergy acts as a dominant. Since the person from the negative line, after crossing with the allergic line, produces various combinations of allergies, some present in the allergic parent, some present in members of the family of the allergic parent, and others entirely new in the family, and since these allergies, old and new to the family, do not appear in any regular proportion, it seems illogical

to consider that the negative line has brought in modifying factors for a new set of allergies. If such were the case these new allergies, being dominant as we have shown, should appear in a fairly large proportion of the F_1 , a result not found to be true.

Matings between allergic families also establish this point. In family 8, migraine had appeared for two generations on both sides and no other allergy had been manifest. The father and mother, both free from allergy, had seven children, two of whom suffered from migraine, and another from five allergies, namely, migraine, eczema, asthma, urticaria, and hay fever. How was it possible for four allergies, apparently new to both sides of the family (three of which have been shown in our other crosses with negative lines to be dominants) to be present for two generations without manifesting themselves?

Other matings of two individuals, both from allergic families, also produce children with allergies which have not appeared in either family. Thus in families 2, 20, and 13 urticaria appears as a new allergy; in family 17 eczema; in family 31 hay fever. In this last case, as in the cases with negative lines, two allergies present in the family did not appear in any of the progeny. One parent had asthma and a grandparent had bronchitis, neither of which reappeared in the children.

These facts all lend support to the theory that there is only one gene for sensitivity and that this gene expresses itself in various ways in different individuals. This point, we believe, is definitely established by our crosses with negative lines. We must admit, however, that we have no explanation to offer for the five pedigrees in which there is only one allergy. It is of course possible that some of the individuals in these pedigrees may develop other allergies later in life.

We have one case of identical twins in family 14. Both of the twins have the same three forms of allergy. It is probable that the environment of the twins is very similar which may account for the occurrence of the

same allergies. Obviously, however, no conclusion can be drawn from one case and we shall hope to find other allergic identical twins.

In reviewing our charts, it is at once evident that migraine is more prevalent in females than in males. Among our pedigrees we find 64 males with migraine and 126 females so affected. At first sight, it might seem that migraine has something to do with the sex chromosome, for if it were dominant, as we have shown, but also sex linked, we should expect more migraine females than males. Our records show, however, that a son may inherit migraine from either his father or his mother. He may have migraine if his mother is from a negative family (family 41) and his father has migraine; or if his father is from a negative family and his mother has migraine (family 5). Apparently a son may be allergic if his parents are from allergic lines, regardless of which parent has migraine, or even if neither has that special form of allergy. The following chart makes this matter clear. In these cases both father and mother are most probably from allergic families. (Note: See p. 134, for meaning of letters. [. .] no allergy.)

SON	FATHER	MOTHER	FAMILY
M	..	M	15, 17, 21, 51
M	..	MEA	31
M	M	..	51, 21
M	H	MU	33
M	E	M	26
M	..	HB	3
M	..	..	8, 17
M	..	A	15
M	M	M	21, 22

It has been suggested that allergy might be due to a factor which would bring it about in females when in the heterozygous condition, but that the homozygous presence of the gene would be necessary to cause the allergy to appear in the male. A condition just opposite to this exists in cattle where if the gene for "hornless" is present in the duplex condition in a female she is hornless, whereas only the simplex condition is necessary to make a hornless male. The inheritance of migraine obviously is not comparable to this case, for a male may develop migraine when he inherits the gene for sensitivity from only one side, that is, when he is heterozygous. Since our records show that with the same inheritance females are more likely to have this allergy than males, the reason for this difference must probably be sought in the physiological differences between the sexes. One might conjecture that the hormones related to sex may be the cause of the different proportions.

The conclusions of this paper are in harmony with the work of most other students of the inheritance of allergic diseases. Except for the works

of ADKINSON and BUCHANAN the types of allergy have been considered as due to dominant factors. ADKINSON's results can be explained as due to a dominant gene, dependent for its expression to some extent upon the environment. Migraine has been regarded as a sex-linked character by several writers because of the large number of females who have it. However, we have shown that migraine may be inherited by the son from the father when the mother's line is negative and therefore cannot be sex-linked. Also migraine is interchangeable with the other allergies and acts as the expression of the same gene for sensitivity which obviously has no connection with sex. Since allergic women are apt to suffer from these headaches during the menstrual period (a fact which has been referred to a number of times in the literature and which we also have observed), the preponderance of migraine females can best be explained as correlated in some way with the sex hormones and with physiological processes. Finally, we have found no connection (as did STUDY and GÄNSSLEN) between gout and the allergic diseases mentioned.

We have shown that any allergy may act as a simple dominant, and an allergic individual may transmit either the same or another type of allergy. There is thus no regularity in the transmission of the different types of allergy and the individual known to carry the gene for sensitivity may be normal. Our evidence thus shows that most probably allergy is not due to multiple factors but rather to the expression of a single gene for sensitivity which manifests itself in different ways, depending to some extent upon the environment of the individual. The gene for allergy is not sex linked. The greater number of migraine females cannot be explained as due to a sex-linked gene.

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