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# HYPERTRICHOSIS OF THE EAR RIMS

## *Two Remarks on the Two-Gene Hypothesis*

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SUMMARY

Two remarks on Rao's Two-Gene Hypothesis for the inheritance of hypertrichosis of ear rims are offered here. First remark provides justification for the particular location of NH- and H-loci on the sex chromosomes in man. A single-case longitudinal study is also reported, which gives rise to the possibility of testing the two-gene hypothesis on family data.

## INTRODUCTION

It is widely suspected that Y-linkage is the most probable genetic theory for the inheritance of hypertrichosis of the ear rims, with rather frequent failures of penetrance and variable ages of onset. Dronamraju (1964) suggested that there might be different alleles responsible for the differences in the ages of onset. If that be so, one would expect all sons of an affected father to manifest the trait around the same age. Available evidence, however, does not support this view, though the range of variation of ages of onset within a male line is rather narrow.

It is known that there is too much of variation involved, quantitatively and otherwise, in the expression of the trait to be explained by a single dominant gene. Dronamraju (1964) suggested that several genes may be involved in controlling the expression of the phenotype. Also Stern et al. (1964) reported a striking positive correlation between the grade of expression in the propositus and mean grade among the relatives, from where they inferred that the positive correlation was most likely due to genetic determination of the degree of the phenotype. Therefore it appears quite meaningful to introduce, as the first approximation at least, another gene to account for the quantitative variation in the trait. However, the dominant gene responsible for the very incidence of the trait being most probably Y-linked, there is no reason to believe that the second gene meant to control the degree of hairiness could be on any autosome. It is expected that if more genes are involved, they should all be confined to sex chromosomes only. An attempt was made by the author (Rao 1970*a*) to introduce one additional gene which is expected to explain the quantitative variation

* Part of this works was carried out when the author was a research scholar at the Indian Statistical Institute, Calcutta.

in the trait. In order to get a clue as to where the corresponding additional locus could be located on the sex chromosomes, a brief discussion on partial sex-linkage is offered here.

## DISCUSSION ON SEX CHROMOSOMES IN MAN

Partial sex-linkage was first described by Aida (1921) in cyprinodont fishes, and such cases in the genera *Lebistes*, *Aplocheilus*, and *Platypoecilus*, have been described by Winge (1923) and Fraser and Gordon (1928). It was also discovered by Philip (1935) in *Drosophila melanogaster*. De Zulueta (1925) has reported an identical series of genes in both sex chromosomes, but did not observe any cases of crossingover.

Through " a search for incomplete sex-linkage in man ", Haldane (1936) was the first to report any result on partial sex-linkage in man. He suggested partial sex-linkage for retinitis pigmentosa, both recessive and dominant types, xeroderma pigmentosum, achromatopsia, Oguchi's disease and epidermolysis bullosa dystrophica. He was not very sure about partial sex-linkage of the remaining four traits, but concluded this mode of inheritance to be extremely probable in case of xeroderma and achromatopsia. Also, he proposed a provisional map for the loci of these genes in the homologous segment of the male sex chromosomes, which created a great controversy (for example, see the discussion by Woolf in Smith 1953).

It is generally assumed that chromosome association during meiosis is conditioned by homology, and consequently the pairing segments of any two chromosomes are assumed to be identical in their internal organization. The members of an unequal chromosome pair are necessarily composed of two regions, a pairing and a nonpairing or differential segment. With these comments, Koller (1937) presented a huge cytological study in order to expose the genetical and mechanical properties of sex chromosomes in man. He observed the occurrence of both asymmetrical and symmetrical XY bivalents during meiosis, which he considered as a definite cytological proof that crossingover takes place freely in the region which is identical in the X and Y chromosomes that represents the pairing segment. Thus he supported fully Haldane's findings on partial sex-linkage. It may be noted that he observed nonpairing of the sex chromosomes occasionally.

Woolf (in the discussion on Smith's paper, 1953) has criticised the way Haldane (1936) had demonstrated partial sex-linkage in man. In his opinion, Haldane's tests could very well give rise to misleading results if there is some kind of heterogeneity in the data. However, Woolf has finally indicated that partial sex-linkage is a possible phenomenon in human genetics.

In a very penetrating paper on sex-linkage and sex chromosomes in man, Sachs (1954) had offered a brief review on all the cytological investigations on sex chromosomes in man, and also interpreted all these observations, including his own, as showing no evidence in favour of the formation of chiasmata between the two sex chromosomes of man. To describe the various aspects of his study in his own terms, "A characteristic feature of the X and Y in man is the development of a special sex vesicle during the early stages of meiosis. As meiosis proceeds the X and Y move together

until both are included in one vesicle. This inclusion in one vesicle is, however, not always complete, and the separate sex chromosomes, each with its own vesicle, can sometimes be seen lying next to one another in the pachytene nucleus." The existence of the sex vesicle at meiosis was also observed by him in the rhesus monkey, the marmoset, and the house mouse. The associated movement of the two sex chromosomes of man, in the sense of being confined together, most often in the same sex vesicle, is suggestive of some sort of homology between the two sex chromosomes.

An examination of the different stages of meiosis after pachytene shows (Sachs 1954) that the sex vesicle has usually disappeared by the time the spindle is formed. At this stage of first metaphase the autosomes are connected as bivalents by chiasmata. The X and Y, on the other hand, are either unconnected, connected end-to-end, or connected by a thin thread. Remnants of the sex vesicle may still persist after the spindle is formed, and these can be found as the thin thread-like connections between the X and Y at first metaphase. The sex chromosomes are held together at first metaphase, not by the formation of chiasmata, but by these remnants of the sex vesicle, and/or an end-to-end adhesion between the X and Y.

The meiosis of the sex chromosomes in man is thus of a special type which is quite different from that of the autosomes. In the autosomes chiasma formation during meiosis takes place in the normal way. But, there is no evidence of chiasma formation between the X and Y at any stage of the meiotic process. And, in the absence of chiasma formation during meiosis there can be no genetical crossingover between the X and Y.

" The meiosis of the X and Y thus presents no possibility for the existence of partial sex-linkage due to crossing-over between genes located on the sex chromosomes. Since there is no evidence that genetical crossing-over can take place without chiasma formation, genes located on the X- and Y-chromosomes of man therefore cannot undergo genetical recombination by crossing-over at meiosis. Partial sex-linkage, if it exists, therefore cannot be in the form of crossing-over between genes actually located on the X and Y. " (Sachs 1954).

Hence, it may be inferred that chiasmata do not occur in male sex chromosomes, and hence no genetical crossingover. However, both the studies of Koller and Sachs provide enough cytological evidence in favour of some sort of homology between the X and Y chromosomes. Keller's finding that there correspond homologous pairing segments in both X and Y, and Sach's observation that the two sex chromosomes in man are confined either in the same sex vesicle or in different vesicles lying close to one another, seem to suggest that there may be a segment in the Y chromosome which is homologous to a segment of the X chromosome, homologous in the sense that genes located on these segments possess alleles on both the segments corresponding to X and Y. However, between loci on these homologous segments, crossingover does not take place.

## JUSTIFICATION FOR THE TWO-GENE HYPOTHESIS

With this as the basis, a new hypothesis called the Two-Gene Hypothesis was proposed by the author (Rao 1970*a*), involving two nonallelic genes for the inheritance of hypertrichosis of the ear rims. Of the two corresponding loci, one is assumed

to be situated on the nonhomologous segment of the Y chromosome and the other on the homologous segment. The above discussion on the sex chromosomes in man appears to support the particual location of the two loci of the two-gene hypothesis. It should be noted, however, that all this constitutes one of the many possibilities, and no pretence is made here to the effect of having proved or disproved anything.

## SINGLE-CASE LONGITUDINAL STUDY

No longitudinal study of the trait seems to have been ever reported in the literature. In this short section, growth of hypertrichosis on the author's own ear rims is reported.

At the onset of the trait, the author was 22-years old (early 1968), and ever since observations were regularly taken. At the time of onset, there was a single strand on each of the two ear rims which grew to three strands on each by April 1970. There upon no further growth took place. The exact pattern of the growth is shown in Fig. 1. The author's father, now aged 60 years, shows the trait with grade-1 intensity (see Rao 1970*b*). The purpose of reporting this observation is to show that an affected individual may start with one strand (or a few strands) at the time of onset, and the intensity may grow numerically over time, until such growth *stabilises*. Evidence to this effect may also be found in Gates et al. (1962). Thus, whenever the grade (numerical

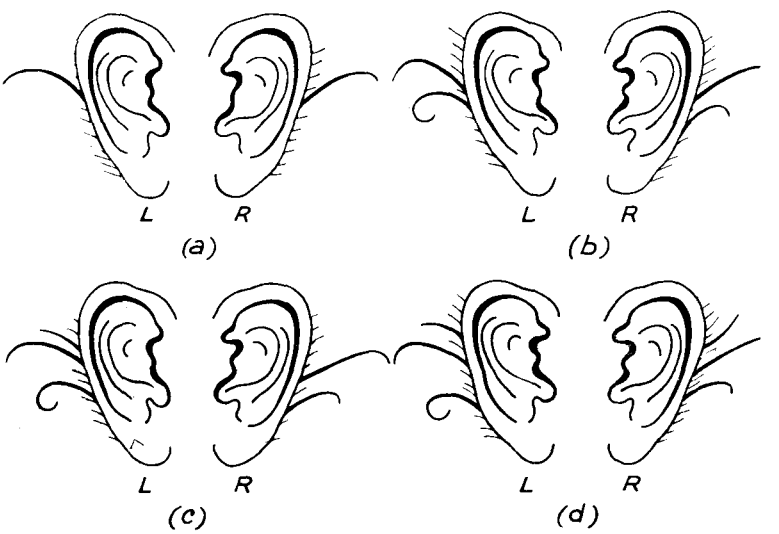


Fig. 1. *Growth of hypertrichosis of the ear rims in D.C. Rao during 1968-72.*



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intensity) of the trait is important in a study, observations should not be made on individuals below the expected age of stabilisation. These age limits are, probably, higher for higher grades of intensity. It follows, therefore, that the two-gene hypothesis may be tested on the basis of family data, where all the subjects (fathers and their sons) are above the critical age.

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RIASSUNTO

Vengono presentate due note riguardanti l'ipotesi di Rao su di un'eredità digenica dell'ipertricosi dei padiglioni auricolari. La prima fornisce una giustificazione della localizzazione dei loci NH ed H sui cromosomi sessuali nell'uomo. Viene quindi riferito uno studio longitudinale su di un singolo caso, il quale dà luogo alla possibilità di una verifica dell'ipotesi digenica su dati familiari.

RÉSUMÉ

Deux notes sont présentées sur l'hypothèse de Rao concernant une hérédité digénique de l'hypertrichose des pavillons de l'oreille. La première offre une justification de la localisation des locus NH et H sur les chromosomes sexuels chez l'homme. Ensuite, une étude longitudinale sur un seul cas est rapportée, qui rend possible un test de l'hypothèse digénique sur des données familiales.

ZUSAMMENFASSUNG

Zwei Bemerkungen zur Vermutung von Rao bezüglich der digenischen Vererbung der Ohrmuschelhypertrichose. Die erste rechtfertigt die Lokalisation der Loci NH und H in den männlichen Geschlechtschromosomen; die andere berichtet über eine Longitudinalforschung an einem einzigen Fall, der den Nachweis für die digenische Hypothese bei Familienerhebungen gestatten würde.



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