

## A human mosaic involving eye and hair color differences

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Mosaicism in man is a rare phenomenon. It seems therefore justified to describe a new case which involves mosaicism of eye and hair color.

### Observations

The subject, V. P., is a young woman, 21 years old, from Salinas, California. She shows a partial bilateral asymmetry of eye and hair color (Figs. 1-2). The color of the left iris is hazel with 3 brown spots while the right eye is light blue with 2 deep yellow spots. Most of the hair on the head is brown but there are two areas, one large one small, of very light blond (nearly white) hair on the right side. The large area which covers about 75 sq. cm. is toward the front while the small one, about 1 sq. cm., is toward the back of the head.

Apart from hair and eye color, the subject appears to show no mosaicism with respect to other characters. There is no difference between the color of the eyebrows and eyelashes; both are light brown. She reports that on exposure to sun her skin tans uniformly on both sides of her body.

Cotterman (1958) has described blood mosaicism in two families with heterochromia iridis. However, V. P. showed no evidence for heterogeneity for any of the erythrocyte antigens. Dr. Philip Levine, who has kindly tested her blood, reports as follows: "The blood of V. P., x-6142, who is the mosaic for both hair color and eye color, is in group O, Rh negative. Other antigens are as follows:

K-, k+, Fy<sup>a</sup>-, S-, s+, P-, MN.

All the negative reactions were examined very carefully in order to detect any clumps which would indicate a mosaic. In short, the findings with the red cell antigens were those to be expected of a normal blood".

Relevant information was also collected about the subject's family. Her mother, age 55, has dark brown eyes and hair. Her father, age 62, has pale blue eyes. His hair was blond but he is now bald. Thus it is apparent that the eye and hair colors on the left side of the subject resemble those of the mother while the colors on the

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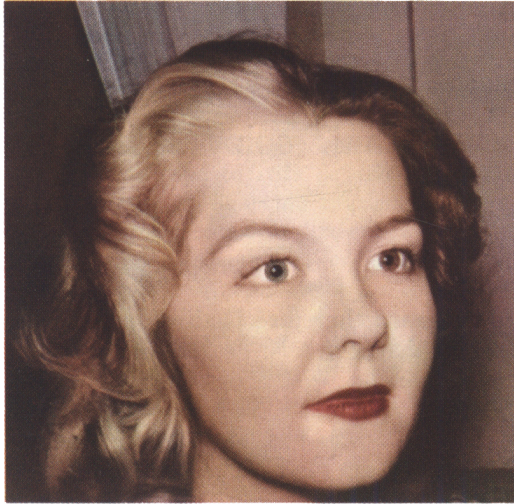


Fig. 1



Fig. 2

right side approach those of the father. The proposita also has a 28-year-old brother who has hazel eyes and light brown hair. No other relatives are reported to have mosaicism similar to that of the proposita. However, one of her relatives, a maternal aunt, age 45, has a small area of white hair at the back of her head which is otherwise covered with dark brown hair. This spot of white hair does not seem to have any relation to the mosaic described above, as such spots are not rare.

The mother of the proposita was not X-rayed during pregnancy.

### Discussion

#### INITIATION OF MOSAICISM

The subject of hair pigmentation has recently been reviewed by Fitzpatrick, Brunet, and Kukita (1958). Rawles (1947) had shown earlier that in mice the pigment of the skin and hair is derived from melanoblasts (prospective pigment cells) which in the early embryo migrate from the neural crest. This is in accordance with the origin of melanoblasts in other classes of vertebrates (Du Shane, 1935; Dorris, 1939). It has also been shown that in birds and amphibia the pigment of the iris is derived from the neural crest (Ris, 1941; Barden, 1942).

It seems safe to assume that man forms no exception to the rule that melanoblasts of skin, hair, and iris have a common origin in the neural crest. If this is granted, it may be further assumed that in the present mosaic under consideration a genetic change (to be discussed in the next section) has occurred in a neural crest cell at a stage preceding or soon after the laying down of the anlage of the embryonic head

region. The changed cell or its derivatives could have migrated outwards from the neural crest and lodged ultimately in the right side of the head region where it (they) proliferated and became responsible for limited areas of variant pigment production. Two areas of the hair on the head and the iris of one eye were affected. Alternatively, it is possible that the original changed cell proliferated into a group of cells at its site of change in the neural crest and then part of this group entered directly into the formation of the blue right iris whereas melanoblasts originating from the rest of this group migrated into affected parts of the scalp. It is of course unknown whether the two patches on the head were originally a single unit which became divided due to ingrowth of normal cells during development or whether two or more altered melanoblasts migrated independently to the two separate areas.

Still another possibility is that change might have occurred in an ectodermal cell other than a neural crest cell. Subsequently, derivatives of this changed cell formed these areas of scalp on the right side and the right iris in situ. A similar observation was made by Cohen (1957, quoted by Cock and Cohen, 1958) who stated that he obtained evidence that the whitening of feathers following X-irradiation is mediated by a change in the nature of the "cue" given by the epidermis to the pigment cells.

One can only speculate whether the change took place directly in the neural crest or in the ectoderm other than the neural crest. If one assumes that a single change might have been the cause of the entire mosaic condition, then it is hard to imagine that these three areas of lighter colored tissues, an eye and two areas on the head, were derived from a single changed ectodermal cell. On the contrary, a single change in the neural crest would explain the situation more easily because of the migratory nature of the daughter cells (melanoblasts in this case) of the neural crest.

Although the right eye is predominantly lighter in color than the left one, both the eyes have dark-colored spots in them. These colored spots may be due to irregular migration and clumping of melanoblasts.

#### GENETIC MECHANISM

Superficially, this mosaic condition resembles two different anomalies, namely, heterochromia iridis and white forelock. The eye color differences are identical with certain cases of heterochromia iridis, but the hair color pattern differs somewhat from described cases of white forelock. In the latter cases light colored areas are always median whereas in the present mosaic both light colored areas are on the right side. Furthermore, heterochromia iridis simplex and white forelock have been reported to be inherited independently, each as a monogenic dominant trait. Their association in V. P. seems likely to be due to a single, common cause.

The interrelations among the genes that control the pigmentation of hair and eye are not well understood. It is probable that some of these genes affect both hair and eyes simultaneously whereas others affect the hair alone, and still others the

eyes alone. Genes for dark or brown color of the eyes are generally dominant over those for blue color and similarly genes for dark and brown hair color are dominant over those for light hair color. Moreover, dominance is not always complete.

In the present case, as the mother of the proposita is dark-eyed and dark-haired and the father is light-eyed and light-haired, it is possible that the proposita is heterozygous at a single locus (let us call it *d*) which shows major effects on both hair and eye color; or at two loci (let us call them *a* and *b*), one affecting hair color and the other affecting eye color. In the case of two loci, *a* and *b* may be linked or unlinked. If we assume that the mosaic condition is due to a single common cause, *a-b* will have to be linked in coupling. It may further be assumed that early in development one of the neural crest cells which gave rise to the prospective pigment cells lost the dominant allele(s), *D* or *A-B*, for dark eye and hair, through gene mutation, or some chromosomal change such as a loss of a chromosome or chromosomal segment, or somatic crossing-over followed by segregation.

Among the possible mechanisms leading to the present mosaic condition, a point mutation (rather than a chromosomal mutation) seems to be the most likely. If the proposita is heterozygous at two loci, two mutations would be required to produce the asymmetry of eye and hair color. As the probability of two simultaneous mutations is extremely low, it seems logical to assume that the proposita is heterozygous (*Dd*) at a single locus with pleiotropic effects on both hair and eye color. The idea that the odds are in favor of pleiotropy, in the present case, is supported by Kloepper's (1946) studies on linkage relations in man. He failed to show any linkage between eye color and hair shade (dark-light) whereas he found evidence for genetic or non-genetic factors common to both the traits. Non-genetic factors, however, do not seem to be very likely to produce the present mosaic condition.

### Summary

An individual mosaic for eye and hair color is described. Possibly the subject is heterozygous at a single locus with pleiotropic effects on both hair and eye color. It is proposed that a genetic change, most probably a point mutation, occurred in a prospective melanoblast during early development. Migration of the derivatives of this cell from the neural crest into the affected regions would account for the light-colored hair and eye. It is not likely that the present mosaic condition will be transmitted because it is most probably a case of somatic mosaicism.

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### References

- BARDEN, R. B. 1942. The origin and development of the chromatophores of the amphibian eye. *J. exp. Zool.* 90, 479-520.
- COCK, A. G. and COHEN, J. 1958. The melanoblast reservoir available to a feather papilla. *J. Embryol. exp. Morph.* 6, 530-545.
- COHEN, J. 1957. The interaction between pigment cells and other feather germ components in the production of some color patterns in feathers. Ph. D. Thesis, Hull.
- COTTERMAN, C. W. 1958. Erythrocyte antigen mosaicism. *Symp. Genetic Approach to Somatic Cell Variation*, Suppl. 1, *J. Cell. Comp. Physiol.* 52, 69-95.
- DORRIS, F. 1939. The production of pigment by chick neural crest in grafts to the 3-day limb bud. *J. exp. Zool.* 80, 315-345.
- DU SHANE, G. P. 1935. An experimental study of the origin of pigment cells in amphibia. *J. exp. Zool.* 72, 1-31.
- FITZPATRICK, T. B., BRUNET, P. and KUKITA, A. 1958. The nature of hair pigment. Pp. 255-303 in "The Biology of Hair Growth", W. Montagna and R. A. Ellis, eds. New York: Academic Press, Inc.
- KLOEFFER, H. W. 1946. An investigation of 171 possible linkage relationships in man. *Ann. Eugen., Camb.* 13, 35-71.
- RAWLES, M. E. 1947. Origin of pigment cells from the neural crest in the mouse embryo. *Physiol. Zool.* 20, 248-266.
- RIS, H. 1941. An experimental study on the origin of melanophores in birds. *Physiol. Zool.* 14, 48-89.

### RIASSUNTO

Viene descritto un mosaico individuale per il colore degli occhi e dei capelli. Il soggetto è probabilmente eterozigotico ad un solo locus con effetti pleiotropici sul colore di occhi e capelli. Si suppone che abbia avuto luogo un cambio genetico, e probabilmente una mutazione a punta in un melanoblasto prospettivo durante il primo sviluppo embrionale. La migrazione dei derivati di questa cellula dalla cresta neurale nelle regioni affette spiegherebbe il colore chiaro dei capelli e degli occhi. Non sembra che la presente condizione mosaica potrà essere trasmessa perchè, probabilmente, è un caso di mosaicismo somatico.

### RÉSUMÉ

L'on décrit un cas mosaïque individuel pour la couleur des yeux et des cheveux. Il est probable que le sujet soit hétérozygote pour un locus qui a des effets pléiotropiques sur la couleur des cheveux et des yeux. Nous croyons qu'une mutation de points a eu lieu au commencement du développement embryonnaire dans un mélanoblaste prospectif. La migration des descendants de cette cellule de la crête neurale aux régions affectées serait la cause des cheveux blonds et de l'iris bleu. Une transmission héréditaire de cette condition mosaïque n'est pas en question, parce qu'il s'agit probablement d'un mosaïcisme somatique.

### ZUSAMMENFASSUNG

Es wird ein Fall mit Augen- und Haarfarbenmosaik beschrieben. Die Ursache dieses Mosaiks duerfte eine Heterozygotie eines einzelnen Genlokus mit pleiotroper Wirkung auf Haar- und Augenfarbe sein. Am ehesten muss eine Punktmutation eines prospectiven Melanoblasten in der fruehembryonalen Entwicklung angenommen werden. Migration der Abkoemmlinge dieser Zelle aus der Neuralleiste in die betroffenen Gebiete waere dann verantwortlich fuer das blond Haar und die blaue Iris. Es ist zu vermuten, dass sich dieses Mosaik nicht vererbt, da es sich sehr wahrscheinlich um eine somatische Mutation handelt.