Genet. Res., Camb. (1968), **12**, *pp.* 91–93
Printed in Great Britain

SHORT PAPERS

Chimerism and genetic mapping*

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(*Received* 16 *October* 1967)

In a chimera there is a mixture of cell populations which are of different origin and composition. Chimerism thus differs from mosaicism in which a mixture of cell populations are also of different genetic composition but are of the same genetic origin. Cases of blood-cell mixing and of double fertilization in man were regarded by Goodfellow, Strong & Stewart (1965) as examples of chimerism; but further subdivision is possible and several different types of chimerism, which differ in respect of genetic origin and composition, are theoretically possible. The origin varies with the type of chimerism and the composition varies also with locus position, proximal or distal, relative to the centromere. The situation is thus similar in some respects to that of recessive homozygosis in *XXY* individuals (Stewart, 1960).

In the first type of chimerism, called Zygotic Chimerism Type One or Z 1, there is fertilization by one sperm of an ovum and by another of one of the products of the first polar body, derived from the same primary oocyte as the ovum. A single individual results from this. In the second type of chimerism, called Zygotic Chimerism Type Two, or Z 2, there is fertilization by one sperm of an ovum and by another of the second polar body derived from the same primary oocyte. A single individual results from this. In the third type of chimerism, called Post-Zygotic Chimerism or PZ, there is fertilization by two sperm of two separate ova. These two zygotes fuse at a very early stage of development and a single individual results. In the fourth type of chimerism, called Twin Chimerism or TZ, there is fertilization by two sperm of two separate ova. At a relatively late stage of embryological development there is mixing of the circulation between these two individuals as a consequence of placental anastomosis and two individuals result. Additional types of chimerism are, first, foetal chimerism, in which maternal cells gain access to the circulation of the foetus and cause runting, and, second, post-natal chimerism, in which chimerism is induced artificially by transfusion following total body irradiation. There are possibly other types of chimerism, for some types of conjoined twins may be chimeras. However, these additional types are not relevant to the present study and are not discussed further.

Consider a proximal locus, with alleles PQRS, so close to the centromere that crossing-over does not occur between the locus and the centromere. Consider also a distal locus, with alleles DEFG, so far from the centromere that crossing-over is frequent and results in random distribution of the alleles at second meiosis. The phenotype of a chimeric individual (Table 1), the product of a mating between a doubly heterozygous male (RS, FG) and a doubly heterozygous female (PQ, DE), depends on the type of chimerism. In Z 1, two sperm are involved and there is independent segregation of proximal genes RS and of distal genes FG. Thus the phenotype frequencies are RR:RS:SS::1:2:1 and FF:FG:GG::1:2:1. The same phenotype frequencies occur in Z 2 and in PZ. In Z 1

* This work has been supported by a Grant from the Medical Research Council.
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and Z 2 two sperm fertilize two of the products from the same primary oocyte. In the case of proximal genes PQ, the first polar body will be 'homoallelic' for one gene and the secondary oocyte will be 'homoallelic' for the other. Thus chimeras of type Z 1 will always be maternally 'heteroallelic' for a proximal gene with phenotype frequencies PP:PQ:QQ::0:4:0 and chimeras of type Z 2 will always be maternally 'homoallelic' for a proximal gene with phenotype frequencies PP:PQ:QQ::2:0:2. In the case of distal genes in the female there is random segregation and the phenotype frequencies with respect to the mother's alleles in Z 1 and in Z 2 are DD:DE:EE::1:2:1. In chimeras of the type PZ two ova are fertilized and the phenotype frequencies with respect to the

Table 1. *Phenotype frequencies in the different types of single-born chimerism in a mating between a doubly heterozygous male (RS, FG) and a doubly heterozygous female (PQ, DE)*

(PQRS are alleles at a proximal locus and DEFG are alleles at a distal locus.)

	Phenotype frequencies	
Type of chimerism	PP:PQ:QQ	RR:RS:SS FF:FG:GG DD:DE:EE
Z 1	0:4:0	1:2:1
Z 2	2:0:2	1:2:1
PZ	1:2:1	1:2:1

Table 2. *Informative phenotype frequencies for a proximal locus in the different types of single-born chimeras*

(The mating type is defined in the text and one example of each is given.)

Mating type	Examples of mating type: female × male	Informative ratio	Expected ratio in Z 1	Z 2	PZ
1	PP × RS	None	—	—	—
2	PQ × RS	PP:PQ:QQ	0:4:0	2:0:2	1:2:1
3	PQ × PP	PP:PQ	0:4	2:2	1:3
4	PQ × PQ	PP:PQ:QQ	0:16:0	2:12:2	1:14:1
5	PQ × PR	PP:PQ:QQ	0:16:0	8:6:2	4:11:1

mother's alleles are PP:PQ:QQ::1:2:1 and DD:DE:EE::1:2:1. In twin chimerism (TZ) two separate ova are fertilized by two separate sperm and the ratios are exactly the same as in post-zygotic chimerism (PZ). It should be noted of course that the chimerism is limited in chimeric twins (TZ) to those tissues which exchange *in utero*, and that in all instances the chimerism is established on independent evidence not involving any of the genes or loci being considered.

Chimerism of types Z 1 and Z 2 can contribute to genetic mapping of the human autosomes and heterosomes. A study of phenotype frequencies will provide information about the relative frequency of Z 1, Z 2 and PZ and about the locus position of genes relative to the centromere. No information would, however, be obtained if Z 1 and Z 2 were of equal frequency and a large series would be necessary if a substantial proportion of single born chimeric individuals were of PZ type. To illustrate the principle, a mating involving four alleles at each locus has been considered, but other matings may be used. The maternal contribution in respect of distal loci and the paternal contribution in respect of

proximal and distal loci may be ignored since the distribution of genes is random and gives a 1:2:1 ratio. Thus interest is restricted to the maternal contribution of genes at proximal loci. There are five basic mating types classified according to the genes at these loci (Table 2). First, the homozygous female (PP) contributes no information. Second, the heterozygous female (PQ) with different alleles (RS) at the correspondingly paternal locus gives the ratios already noted. The heterozygous male (RS) has been considered but the situation is identical for the homozygous male (RR or SS) with alleles different from those of the female. In the subsequent types the heterozygous female (PQ) will contribute information when one or both of the same alleles are present in the male. Third, for the homozygous male (PP) the ratios expected for PP:PQ are 0:4 for Z 1; 2:2 for Z 2; 1:3 for PZ. Fourth, for the heterozygous male with the same genotype as the female (PQ) the ratios expected for PP:PQ:QQ are 0:16:0 for Z 1; 2:12:2 for Z 2; and 1:14:1 for PZ. Fifth, for the male heterozygous for one of the maternal alleles and for another independent allele (PR) the ratios expected for PP:PQ:QQ are 0:16:0 for Z 1; 8:6:2 for Z 2; and 4:11:1 for PZ.

Although few single-born chimeras have been described, and the types Z 1, Z 2 and PZ have not been established in any, yet the condition may not be so very uncommon. A search for such cases is worth while because they offer the only method of autosomal gene localization relative to the centromere at present available in man.

SUMMARY

Different types of chimerism result from double fertilization. Differences result from fertilization of first and second polar bodies and from early fusion of two zygotes. These three types of chimerism have different phenotypes or different proportions of possible phenotypes, and variation is greater in respect of gene loci close to the centromere. The phenotype frequencies in the different types of chimerism are tabulated and the phenotype frequencies expected in different mating types are shown. Studies of such cases offer the only method of autosomal gene localization relative to the centromere at present available in man.

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