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Chromosome anomalies among livebirths

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A considerable proportion of heritable disease in man is a consequence of the presence of *constitutional* chromosome anomalies. We need to distinguish between *constitutional anomalies* which are present in the germ cell or which arise during the early cleavage divisions of a zygote, so that all, or a substantial proportion, of the cells carry the abnormality, and *acquired somatic abnormalities* which are acquired later in development, or life, and which therefore affect a smaller proportion of cells. Acquired chromosome abnormalities may be important in the aetiology of certain leukaemias, lymphomas, and brain tumours, but these are not to be considered under the category of heritable changes in the newborn.

(A) Types and consequences

Individuals who have abnormal chromosome complements fall into two broad categories: (a) those who have an *abnormal number* of chromosomes and (b) those who have *abnormalities of chromosome structure*.

(1) ANEUPLOIDY

Abnormalities of chromosome number are almost all the result of new mutations and most involve an aneuploid state in which the individual possesses one or more chromosomes additional to the normal complement, i.e. 47, 48 or more chromosomes, or have one chromosome less than the normal complement, i.e. 45.

The best known example of an additional autosome (trisomy) is that associated with mongolism where an extra chromosome 21 is present. The other relatively frequent aneuploid states in man are those that involve the presence of additional sex chromosomes and among the most common are Klinefelter's syndrome, 47, XXY; the XYY male, 47, XYY; the triple X female, 47, XXX; and Turner's sydrome, 45, X.

The majority of these aneuploid states are each the result of a new mutation, that is non-disjunction, and the additional chromosome is rarely passed on to offspring. The autosomal trisomies have obvious deleterious consequences, for example Down's syndrome in the case of trisomy 21, and most, but not all, of the sex chromosome aneuploids result in a variety of physical and mental anomalies in the affected individuals.

(2) STRUCTURAL REARRANGEMENTS

Structural rearrangements arise as a result of breakage and abnormal rejoining within or between chromosomes. Unlike the aneuploid mutations, a majority of the structural rearrangements are transmitted from parent to offspring. The structural rearrangements that are mainly of concern to us today include deletions, ring formation, inversions, and translocations. Deletions and rings effectively result in partial monosomy involving the loss of a number of genes, and these aberrations may be transmitted from parent to offspring and may have serious consequences to the individual heterozygous for the deletion. Inversions may also be transmitted, are often apparently innocuous, but may be responsible for some infertility. Translocations involve an exchange of parts between chromosomes and may be considered to be of two types; balanced where the translocation results in no loss or gain of chromosome material, or unbalanced where the rearrangement does result in loss or gain of chromosome material. Translocations that are unbalanced can result in secondary trisomy, or indeed a secondary monosomy, and have the same consequences to the individual as primary trisomy or monosomy.

(B) Frequencies in the newborn

A very important question, of course, is how frequent are these major chromosome anomalies? Since a proportion of them result in a lowered fitness and

Table 1 *Chromosome analysis of newborn population, Edinburgh*

	Males	*Females*	*Total*
Number analysed 1967-1969	3800	0	3800
1970-1972	4049	3831	7880
	7849	3831	11680
Number of chromosome abnormalities	55	23	78
Incidence of all chromosome abnormalities	6·67 per 1000 (approximately 1 in 150)		
Incidence in males	7·01 per 1000		
Incidence in females	6·00 per 1000		

Table 2 *Sex chromosome abnormalities*

	Karyotype	Number	Incidence per 1000
A Males	47, XYY	10	1·45
	46, XY/47, XYY	2	
	47, XXY	9	1·58
	46, XY/47, XXY	2	
	46, XX	1	
B Females	47, XXX	5	1·41
	45, X/46, XX	1	
	45, X/46, XY	1	

Incidence of all male sex chromosome abnormalities 3·06 per 1000
Incidence of all female sex chromosome abnormalities 1·83 per 1000

Table 3 *Autosomal trisomies*

	Karyotype	Number	Incidence per 1000
A Males	47, XY, +21	14	1·78
	47, XY, +18	1	0·13
	69, XXY	1	0·13
B Females	47, XX, +21	3	0·78
	47, XX, +18	1	0·26

early death, the best estimate of frequency with which these abnormalities enter the population is obtained by determining their incidence in the live newborn. Tables 1-4 summarise the data that we have been accumulating in our laboratory in Edinburgh (Jacobs *et al.*, 1974) and Tables 5-9 summarise the information available from studies at centres outside the UK (Ratcliffe, 1975). The figures in these Tables represent information obtained on major anomalies detected with conventional staining techniques and not using the new chromosome banding methods. It may be seen from the Tables that, by and large, similar results are obtained from different centres throughout the world. In summary we can see that

Table 4 *Structural autosomal abnormalities*

Balanced	*Unbalanced and supernumerary*
*45, XX, t(13q14q)pat	
†45, XX, t(14q21q)	45, XY, −D, −D, +t(DqDq)dic
*45, XX, t(13q22q)pat	*47,XX,inv(18p+q−)+18q−mat
*45, XY, t(14q22q)pat	46, XX/47, XX, r+
*45, XY, t(13q14q)pat	
*45, XX, t(13q14q)pat	
‡*46, XY, t(1q−; 13q+)mat	†46, XY/46, XY, 16q+
‡*46, XX, t(11q−; 13q+)mat	†47, XY, +mar
*46, XX, t(3p−; 13q+)mat	
*46, XY, t(11q−; 19q+)mat	*46, XX, 15p+ mat
*46, XY, t(1q+; 14q−)mat	*46, XX, 22p+ pat
*46, XY, t(11q+; 12q−)mat	
†46, XX, t(2q−; 10q+)	
*46, XX, inv(2)pat	
*46, XX, inv(9)pat	
*46, XX, inv(1)mat	
46, XX, t(1; D)	

*=familial. †=mutation. ‡=sibs.

Table 5 *Males with abnormal sex chromosome constitution—consecutive liveborn babies*

Series	*Total males examined*	*Abnormalities*						*Total*	
		XYY		*XXY*		*Other*		*No.*	*%*
		No.	*%*	*No.*	*%*	*No.*	*%*		
Edinburgh (UK)	7849	10	0·13	9	0·11	5	0·06	24	0·30
Arhus (Denmark)	2615	3	0·11	4	0·15	3	0·11	10	0·38
Ontario (Canada)	1066	4	0·37	1	0·09	—	—	5	0·45
Winnipeg (Canada)	5828	3	0·05	6	0·10	1	0·02	10	0·17
Boston (USA)	9048	3	0·03	6	0·07	8	0·09	17	0·19
New Haven (USA)	2176	3	0·14	4	0·18	—	—	7	0·032
Total	28582	26	0·09	30	0·10	17	0·06	73	0·26

Table 6 *Females with abnormal sex chromosome constitution—consecutive liveborn babies*

Series	*Total females examined*	*Abnormalities*						*Total*	
		XO		*XXX*		*Other*		*No.*	*%*
		No.	*%*	*No.*	*%*	*No.*	*%*		
Edinburgh (UK)	3831	—	—	5	0·13	2	0·05	7	0·18
Arhus (Denmark)	2434	1	0·04	3	0·12	1	0·04	5	0·21
Ontario (Canada)	1015	—	—	—	—	—	—	—	—
Winnipeg (Canada)	5519	—	—	2	0·04	2	0·04	4	0·07
Boston (USA)	—	—	—	—	—	—	—	—	—
New Haven (USA)	2177	1	0·05	3	0·14	—	—	4	0·18
Total	14976	2	0·01	13	0·09	5	0·03	20	0·13

Table 7 *Autosomal trisomics—consecutive liveborn babies*

Series	*Total babies examined*	*+D*		*+E*		*+G*		*Other*		*Total*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Edinburgh (UK)	11680	—	—	2	0·02	17	0·15	1	0·01	20	0·17
Arhus (Denmark)	5049	1	0·02	—	—	4	0·08	—	—	5	0·10
Ontario (Canada)	2081	—	—	—	—	2	0·10	—	—	2	0·10
Winnipeg (Canada)	11347	1	0·01	1	0·01	12	0·11	1	0·01	15	0·13
Boston (USA)	9048	—	—	—	—	7	0·08	—	—	7	0·08
New Haven (USA)	4353	1	0·02	1	0·02	3	0·07	—	—	5	0·11
Total	43558	3	0·01	4	0·01	45	0·10	2	0·00	54	0·12

Table 8 *Balanced autosome structural rearrangements—consecutive liveborn babies*

Series	*Total babies examined*	*Robertsonian translocations*				*Reciprocal and insertional translocations*		*Inversions*		*Total*	
		D/D		*D/G*				*No.*	*%*	*No.*	*%*
		No.	*%*	*No.*	*%*	*No.*	*%*				
Edinburgh (UK)	11680	6	0·05	4	0.03	10	0·09	2	0·02	22	0·19
Arhus (Denmark)	5049	7	0·14	1	0·02	7	0·14	1	0·02	16	0·32
Ontario (Canada)	2081	1	0·05	—	—	—	—	—	—	1	0·05
Winnipeg (Canada)	11347	10	0·09	—	—	11	0·10	1	0·01	22	0·19
Boston (USA)	9048	5	0·06	2	0·02	5	0·06	2	0·02	14	0·15
New Haven (USA)	4353	2	0·05	1	0·02	3	0·07	—	—	6	0·14
Total	43558	31	0·07	8	0·02	36	0·08	6	0·01	81	0·19

Table 9 *Unbalanced autosomal structural rearrangements—consecutive liveborn babies*

Series	*Total babies examined*	*Robertsonian translocations*		*Reciprocal Translocations*		*Inversions*		*Deletions*		*Supernumerary*		*Other*		*Total*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Edinburgh (UK)	11680	1	0·01	—	—	1	0·01	—	—	1	0·01	2	0·02	5	0·04
Arhus (Denmark)	5049	—	—	—	—	—	—	1	0·02	2	0·04	2	0·04	5	0·10
Ontario (Canada)	2081	1	0·05	—	—	—	—	1	0·05	—	—	—	—	2	0·10
Winnipeg (Canada)	11347	—	—	1	0·01	—	—	—	—	1	0·01	1	0·01	3	0·03
Boston (USA)	9048	—	—	—	—	—	—	2	0·02	4	0·04	—	—	6	0·07
New Haven (USA)	4353	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	43558	2	0·00	1	0·00	1	0·00	4	0·01	8	0·02	5	0·01	21	0·05

around 3 per 10^3 of the newborn are sex chromosomally abnormal. A further 3 per 10^3 have autosomal abnormalities. One-third of this latter group are mongols with trisomy 21; the remainder have structural rearrangements of the autosomes, the majority seemingly being balanced rearrangements having apparently little or no effect on the individual. We should, however, note that though a cell with a balanced rearrangement appears to contain the normal full or euploid complement of chromatin, the process of exchange itself could result in a mutation at the site of exchange, as has indeed been shown to occur in Drosophila.

Recently we were able to obtain some evidence that certain so-called balanced rearrangements may indeed have phenotypic consequences to the individuals carrying them. If we look at balanced rearrangements in the mentally subnormal, excluding Down's syndrome, and compare the *proportion that are mutant* as compared with the proportion that are mutant in other non-retarded populations we have the following numbers (Table 10).

Table 10

	Number	*Number of individuals*	*Both parents examined*	*Number of mutants*
Newborn	12295	20	17	5
Other populations	18812	62	22	2
Mentally retarded (not Down's syndrome)	2426	12	7	5

There is a significantly higher proportion ($P < 0.01$) of mutant balanced rearrangements among the retarded (5 out of 7 vs 5 of 17 or 2 of22) and it will clearly be of interest to follow the development of the 5 mutant newborn individuals with respect to mental development.

What do these frequencies mean in terms of mutation rate? Before attempting to answer that question we have first to consider how many of these events that we see are really mutations and how many have been transmitted from parent to offspring.

(C) Heritability

The sex chromosome aneuploids are essentially 'one-off' events. XXY's are infertile, XYY's do not produce XYY sons in increased frequency, and XXX females do not produce similar daughters. The 45, X females are almost sterile and the autosomal trisomy 21, though fertile, because of their severe mental retardation, do not normally reproduce. The aneuploid states involving whole chromosomes, therefore, have virtually zero heritability.

Essentially, the only chromosomal abnormalities that are inherited are the structural rearrangements that arise from breakage and exchange. When we examine heritability in these cases (Jacobs *et al;* 1970) we find that where a balanced rearrangement is first found in phenotypically normal individuals, half the offspring have a normal chromosome constitution and half the balanced rearrangement. As yet, there is no evidence for the presence of unbalanced forms presumably because either they are not produced or they are selected against.

On the other hand, in families where the index case is an unbalanced carrier of a rearrangement, some 10% of the offspring in the family have the unbalanced rearrangement and half of the remainder have the balanced form and the rest are normal. The heritability here depends on a number of factors not least being the sex of the carrier.

Considering all data that we have on individuals with structural rearrangements, it appears that carriers have some 15% less liveborn offspring than their chromosomally normal sibs (Jacobs *et al.*, 1970).

(D) Mutation Rates

Since all the sex chromosome abnormalities and all the autosomal trisomies are essentially the results of fresh mutations, then the data give us the mutation rate of 14×10^{-4} per gamete per generation for numerical errors of the chromosomes which result in the birth of a live-born child.

In the case of the structural rearrangements, and adding together all the available world data, there were 56 non-mosaic babies with a structural rearrangement and in which both parents were analysed chromosomally. Fifty of these were balanced and of these 10 were new mutants; 6 were unbalanced and 2 of these were new mutants. Thus one-fifth of the balanced and one-third of the unbalanced are new mutations giving mutation rates respectively of 1.9×10^{-4} per gamete per generation and 0.46×10^{-4} per gamete per generation *where the mutants give rise to live-born babies.*

In conclusion, it should be emphasised that when we speak of mutants per gamete per generation, it should be realised that the majority of mutant gametes, and perhaps as many as 90% of them, produce inviable embryos which are lost or aborted. Thus the chromosomally abnormal liveborn really represent the tip of a very big iceberg.

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