*British Journal of Psychiatry* (1994), **164**, 619–624

# Imprinting and Anticipation
## Are They Relevant to Genetic Studies of Schizophrenia?

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Among 29 multiply affected pedigrees, age of onset among parents and offspring was examined for evidence of both anticipation and genomic imprinting. The results do not suggest that either mechanism is operating in schizophrenia, but only very large effects can be confidently excluded.

Recent advances in genetics have altered our perception of the gene as a unit with fixed properties. A recently described phenomenon, genomic imprinting, and a much older observation called anticipation, can effect gene expression and penetrance and appear to be explicable in molecular terms. Both these mechanisms may offer new explanations for reconciling apparently complex modes of transmission, such as that found in schizophrenia, with the existence of single genes of major effect. It is therefore pertinent to examine these processes and their underlying molecular mechanisms, and to look for evidence of them in families segregating schizophrenia.

*Historical perspective: anticipation and 'degeneration'.* It has been recognised for a long time that in some inherited disorders there is progressively earlier age of onset in successive generations (Harper *et al*, 1992). Mott (1910), who first used the term 'anticipation', states, "almost invariably in the case of insane parents and offspring, the offspring is affected earlier than the parent". He referred to this as "the law of anticipation of the insane". However, because his views were expressed alongside inflammatory statements about the degeneration of society, they were questioned by a subsequent, more liberal, generation. Penrose also noted anticipation, and referred to it in his paper, "Survey of cases of Familial Mental Illness" (Penrose, 1945). He wrote, "This finding, which in one form or another, is characteristic of mental hospital data, has in the past been attributed to a tendency for progressive degeneration or anticipation of diseases in succeeding generations. Such an explanation, which is not in accordance with the concepts of modern genetics, is unnecessary, because more likely explanations are close at hand." He then listed ascertainment biases which could give rise to the observations. This view was influential and many dismissed anticipation as an artefact.

The unwillingness of geneticists to accept anticipation as a real phenomenon is most clearly seen in myotonic dystrophy (MD). As early as 1911, Greenfield noted that cataracts alone often occurred in the earlier generations of those with MD. Age of onset was also noted to vary, and Bell (1947) carried out an analysis which strongly suggested that age of onset was lower in successive generations. Despite this, geneticists, including Penrose, Haldane and Fisher, who worked alongside Bell, persisted with the view that anticipation was due to ascertainment biases. Penrose (1948) described five points which he felt accounted for Bell's observations:

(a) selection of affected parents in whom the onset of the disease is late, because those with an early age at onset are likely to have reduced fertility
(b) selection of affected offspring in whom the onset of the disease is early, because the relationship of early age at onset with severity means that such cases present as more striking and more likely to come to the attention of the researcher
(c) selection of cases with simultaneous onset in parents and offspring; this may occur because of the short time over which most studies are carried; cases where the offspring has a late age of onset and where the parents are available for study are likely to be relatively rare
(d) weakness of real correlation of onset in parents and offspring
(e) general variability in age of onset.

*Modern analyses and concepts.* These problems of method have been overcome successfully in an analysis of the US Huntingtons's Disease Roster (Ridley *et al*, 1988). This study showed that while



https://doi.org/10.1192/bjp.164.5.619 Published online by Cambridge University Press

anticipation in the maternal line is not in excess of that predicted by normal variation and shows typical regression to the mean, anticipation in the paternal line is notably skewed and positive across all ages of onset (method discussed below).

*Genomic imprinting*. The current usage of the term 'genomic imprinting', referring to the differential expression of genes depending on whether the genetic material is derived from a maternal or paternal chromosome, has evolved over the last ten years (Hall, 1990). The existence of imprinting has probably only been recognised in recent years because it is contrary to the basic Mendelian tenet that the parental source of genetic material does not influence gene expression.

Recognition of imprinting within pedigrees is simpler than recognition of anticipation, as there are no major biases of ascertainment. Imprinting is observed when affected offspring show different phenotypic effects of genes carried on maternally-derived as compared with paternally-derived chromosomes. These differences may be in age of onset, severity, disease type or penetrance. Where imprinting affects penetrance, it may be possible to observe 'skipped' generations occurring, following transmission from the parent with low penetrance among his/her offspring (Hall, 1990). Imprinting may not occur in all cases. For example, in Huntington's disease, imprinting is only observed in a small proportion of families.

*Unstable DNA sequences*. Three single-gene disorders with variable gene expression are fragile X syndrome, myotonic dystrophy and Huntington's disease.

In fragile X syndrome, 20% of males who carry a fragile site are phenotypically normal (Turk, 1992). These normal transmitting males (NTMs) can pass the mutant X chromosome to their daughters, who are also phenotypically normal. However, the sons of these female carriers are often affected. Furthermore, it appears that mutations at the fragile site derived from NTMs are only expressed after passing through a female gamete, providing us with an example of genomic imprinting affecting gene penetrance. These observations are known as the Sherman Paradox (Sherman *et al*, 1985).

In myotonic dystrophy, there is the apparently unrelated phenomenon of anticipation, in which there is an increase in severity of symptoms and reduction in age of onset following the transmission of the mutant gene from one generation to the next. In Huntington's disease, anticipation occurs following male transmission only (imprinting), since genes derived from affected fathers tend to result in earlier age of onset, and 5–10% of cases where inheritance is through the father are of a severe early-onset type (Ridley *et al*, 1988; Hall, 1990).

It is now clear that several molecular genetic mechanisms are common to these disorders and can explain these phenomena (Brook *et al*, 1992; Huntington's Disease Collaborative Research Group, 1993). In these diseases, the size of the mutant allele varies considerably due to the expansion of a trinucleotide repeat sequence: CGG in the case of fragile X syndrome, CTG in myotonic dystrophy and CAG in Huntington's disease. These repeat sequences can become unstable and influence expression of the gene.

The fragile X syndrome gene shows variation in the number of CGG repeats among normal individuals, with 31 different-sized alleles identified in general populations. Two classes of mutation have been identified within the families (Yu *et al*, 1991). NTMs and their daughters show alleles with about 33–600 trinucleotide repeats (pre-mutations), while affected individuals and many carrier females show alleles with 600–1300 repeats (full mutation). The Sherman Paradox is explained by the expansion of pre-mutations to full mutations, which occurs during female meiosis but not male meiosis. Thus NTMs may pass on the unexpressed pre-mutation to their offspring, but only their daughters may pass on the expressed full mutation.

Anticipation in myotonic dystrophy is also explained by expansion of the trinucleotide repeat. As in fragile X syndrome, there are stable allelic variants in normal individuals. Myotonic dystrophy patients who are minimally affected have at least 50 repeats, while more severely affected patients may have an expanded repeat containing several thousand bases (Brook *et al*, 1992). Anticipation results from the instability of the repeat sequences over about 150 base pairs in length, and the tendency for mutation from a small number of repeats to a large number.

The findings in fragile X syndrome and myotonic dystrophy led some authors to postulate that the Huntington's disease gene would also contain a trinucleotide repeat sequence (Caskey *et al*, 1992). This proved to be the case and initial investigations have demonstrated a relationship between repeat length and age of onset (Huntington's Disease Collaborative Research Group, 1993).

*Present study*. Anticipation and imprinting are now known to play a role in some single-gene disorders affecting behaviour. Does either phenomenon have any bearing on psychiatric disorders that are not obviously the result of single-gene inheritance? We set out to explore this possibility in families multiply affected with schizophrenia.

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## Method

### Family sample

Families containing two or more individuals affected with schizophrenia were collected in Cardiff, London and Oxford. These were examined to determine whether age of onset was dependent on the sex of the parent through which the putative disease gene had been inherited, and whether anticipation could be observed between generations. Details of these families and their collection are described elsewhere (Andrew *et al*, 1987; Gill *et al*, 1993).

The pedigrees were originally identified for linkage studies, and selection procedures were much the same for each of the data-sets examined. Families were identified by psychiatrists being contacted and local hospitals and community services being searched for schizophrenic patients who had at least one living first-degree relative with schizophrenia or a related diagnosis. Informants were contacted from these families and information regarding first-degree, second-degree and more distant relatives was obtained. Families were selected if, as a minimum, they consisted of parents and two or more affected offspring who were living and willing to give a blood sample and be interviewed. All available first-degree relatives were interviewed, following which each pedigree was extended as far as possible to include all sibships in which the disease was known to be segregating. An attempt was made to select large families with a high density of affected individuals. These 'loaded' families are not typical of the families of schizophrenics, and the resulting Mendelian-like appearance can be misleading (Sturt & McGuffin, 1985); however, they are the most likely to be segregating single major susceptibility loci for schizophrenia.

Diagnoses were made for all three samples by use of an operational criteria checklist (OPCRIT) for psychotic illness (McGuffin *et al*, 1991). This was done by two independent raters (PA and CW). Individuals in the Welsh and Oxford families were assessed using a lifetime version of the Present State Examination (PSE), ninth edition (Wing *et al*, 1974; McGuffin *et al*, 1986), augmented with additional questions to allow diagnosis to be made according to Research Diagnostic Criteria (RDC) (Spitzer *et al*, 1978). The London families were assessed using the Schedule for Affective Disorders and Schizophrenia (SADS-L) (Spitzer *et al*, 1978). Where available, additional information was obtained from case-notes and at least one informant.

OPCRIT is a program which specifies symptom items from various operational diagnostic systems and applies these to give diagnoses according to RDC, DSM-III-R, ICD-10 and other criteria. It has been adopted as part of the minimum data-set by all major groups in this field, both in Europe and the USA, to enable a polydiagnostic approach, increase diagnostic reliability between groups and allow data from different interview schedules, in particular the SADS-L and PSE, to be combined.

It has been previously shown that using two different diagnostic interviews, the PSE (9th edition) and the Composite International Diagnostic Interview (Robins *et al*, 1988), achieves good reliability for overall diagnoses (Farmer *et al*, 1987) and for lifetime-ever diagnoses (Keller *et al*, 1981). More recently a comparison has been made between SADS-L and the PSE (10th edition; Wing *et al*, 1990), which again demonstrates broad diagnostic agreement (Farmer *et al*, 1993). However, the fact that some diagnostic differences may occur from different centres and from the use of different interview schedules is further safeguarded by the use of OPCRIT. Inter-rater reliability between PA and CW was tested on 20 cases using OPCRIT (vs. 3.2), producing a kappa score of 0.64 ($P<0.00001$).

In total, OPCRIT diagnoses and age of onset information was available from 45 male and 58 female subjects. Of these, 53 had an RDC diagnosis of narrow schizophrenia, 7 broad schizophrenia, 19 schizoaffective disorder, 12 major depression (of whom 4 had psychotic symptoms), 3 bipolar disorder and 9 unspecified functional psychosis. No cases of schizotypy had been identified.

### Imprinting

To examine the families for evidence of imprinting, the sample was divided into two groups, one with affected male parents and the other with affected female parents. Two definitions of affected status in the parental generation were used: first, a strict definition including only those parents with RDC narrow schizophrenia, and secondly, a more general definition, including those in the strict definition plus all those with RDC broad schizophrenia, schizoaffective disorder and unspecified functional psychosis. The offspring of these two groups were compared for age of onset, which was defined as the age of first medical contact for the disorder. In many cases this was the same as the age of first admission.

### Anticipation

To examine the families for evidence of anticipation, the age of onset was recorded for all affected parent-sibling pairs. Diagnosis was defined broadly as RDC schizophrenia, schizoaffective disorder and unspecified functional psychosis.

As already discussed, several ascertainment biases may be acting. The main bias is likely to be the preferential ascertainment of parents of late age of onset, since earlier age of onset would have caused diminished fertility. Preferential ascertainment of offspring with early age of onset may also occur because of the tendency to select more severe early age of onset cases and because not all unaffecteds will have passed through the age of risk (Ridley *et al*, 1988). These biases can be taken into account by plotting the size of anticipation against the age of onset of the parent, for each parent-sibling pair. Here, anticipation is defined as the difference in years between the ages of onset in parent-offspring pairs, 'positive' anticipation occurring when the offspring had an earlier age of onset than the parent, and 'negative' anticipation occurring when the offspring had a later age of onset than the parent. Under the assumption that no 'true' anticipation exists, we would expect any observed anticipation to be the result of normal variation, such that typical expression to the mean occurs; in other words, offspring of parents with

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age of onset below the mean age of onset for schizophrenia as a whole would show negative anticipation, while the offspring of parents with age of onset greater than the mean would show positive anticipation.

## Results

### Imprinting

No significant difference in age of onset is demonstrated between offspring of affected fathers and offspring of affected mothers (Table 1; Student's *t*-test and analysis of variance carried out; $P>0.05$).

### Anticipation

As in previous family studies (Penrose, 1945; Bleuler, 1978), a marked difference in age of onset was noted between parents and offspring. In this study, the parents had a mean age of onset of 33.3 years compared with 22.2 years in the offspring ($P=0.0004$).

There was a simple linear relationship between anticipation and age of onset in the parents (Fig. 1). The regression coefficient of anticipation on parental age of onset is 0.893 (ratio of variances explained by regression/error variance, $F=96.61$; $P<0.001$). Thus the line of best fit for this data is very close to that expected under the assumption that age of onset in the offspring is normally distributed around the mean, and shows typical regression to that mean. In other words, the data do not provide evidence suggestive of 'true' anticipation.

## Discussion

To date, anticipation and genomic imprinting have only been clearly identified in diseases which show unequivocal evidence of Mendelian inheritance or discrete chromosomal anomalies. There are several reasons why evidence of these phenomena should be carefully looked for in diseases with a more complex

Table 1
Age of onset in the offspring of affected mothers and affected fathers

| | Affected mother | Affected father |
|---|---|---|
| *Strict definition*[1] | | |
| *n* | 19 | 9 |
| Mean | 21.89 | 22.44 |
| s.d. | 5.97 | 6.48 |
| *General definition*[2] | | |
| *n* | 25 | 15 |
| Mean | 21.16 | 23.00 |
| s.d. | 5.69 | 5.64 |

1. Strict definition of affected status = RDC narrow schizophrenia.
2. General definition of affected status = RDC narrow schizophrenia, broad schizophrenia, schizoaffective disorder and unspecified functional psychosis.

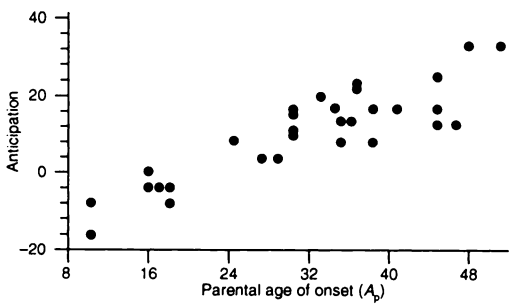



Fig. 1 Parental age of onset ($A_p$) and anticipation; affection status in the parents is defined as RDC schizophrenia, schizoaffective disorder or unspecified functional psychosis. Anticipation = $-18.5+0.893A_p$; $P<0.001$.

pattern of inheritance such as schizophrenia. Both mechanisms can bring about variability in the penetrance and expression of a gene and may result in deviations from Mendelian expectation (Hall, 1990). They may also operate in polygenic disorders to further complicate the picture and may be confounded with 'environmental' effects (McGuffin *et al*, in press).

This is relevant to schizophrenia, where the mode of inheritance remains unknown. Although single major locus inheritance seems unlikely as a general explanation (McGuffin, 1988), it has not been possible to conclude whether there is a major gene with a polygenic background or whether there are several or many genes of approximately equal and small effect. Of interest are the recent findings of single-gene inheritance in rare forms of complex diseases such as Alzheimer's disease (Harrison, 1993) and non-insulin-dependent diabetes (Hattersley *et al*, 1992) in subsets of multiply affected families with early age of onset. The possibility that this also occurs in schizophrenia gains some support from the finding that age of onset may be earlier within multiply affected families than in cases unselected for family history (Walsh *et al*, submitted).

Here we have examined a sample of multiplex families selected for use in linkage studies, as they are the most likely to be segregating major genes. However, even within this sample, the appearance of Mendelian transmission is not always seen, with a wide range of expression observed among affecteds and where some presumed obligate carriers are unaffected.

Study of this sample does not provide any evidence that either imprinting or anticipation is acting. However, we must be cautious in interpreting these results as evidence that these mechanisms have no relevance to schizophrenia. We have examined

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anticipation in age of onset only and have not looked at other phenotypic indices. The size of this sample is only adequate to demonstrate relatively large age of onset effects, and the sample contains only seven parent–offspring pairs where the parent has an age of onset below the mean age for schizophrenia as a whole. This is important since anticipation is most clearly demonstrated by finding a positive effect within this early-onset group. Recent estimates of the variance in liability to schizophrenia explained by additive genetic effects alone, are high, suggesting that these effects, if they exist, may be very modest (McGuffin *et al*, in press). This is the situation in Huntington's disease, where anticipation following transmission through the male line occurs in only about 6% of cases. The sample used to detect anticipation was very large and the age of onset was known for 1693 parent–sibling pairs (Ridley *et al*, 1988).

Genomic imprinting may also affect penetrance, and the presence of 'skipped' generations would then be expected. For this to be looked for, the sample needs to contain a large number of families, with three or more generations, containing affected individuals. The families studied here, while containing a high density of affected members, do not contain enough generations for this analysis. A further problem in the study of penetrance is that only those sibships containing at least one affected member were studied in detail, and information on 'unaffected' sibships was collected in an unsystematic way. The contribution that these sibships make to analysis of penetrance is therefore uncertain.

In summary, both genomic imprinting and anticipation can cause variability in gene expression and penetrance. Recent advances in molecular biology have now demonstrated biological mechanisms by which these epigenetic phenomena occur, in several neuropsychiatric disorders. This study provides no evidence in support of either of these possibilities, but only relatively large effects have been satisfactorily excluded. Further study of a very large data-set of multiply affected families is now required to study these and related issues further. This is now a possibility, since a large number of groups are currently carrying out linkage studies on such families (Leboyer & McGuffin, 1991). Work to collate the data required is currently under way.

### Acknowledgements

This work was funded by grants from the Medical Research Council, the Welsh Scheme for the Development of Health and Social Research, and Schizophrenia A National Emergency (SANE). The authors thank David Watt and Biddie Andrew for providing details on families collected at St John's Hospital, Aylesbury, and Peter Harper for historical details on anticipation.

### References

ANDREW, B., WATT, D. C., GILLESPIE, C., *et al* (1987) A study of genetic linkage in schizophrenia. *Psychological Medicine*, **17**, 363–370.

BELL, J. (1947) Dystrophica myotonica and allied diseases. *The Treasury of Human Inheritance*, Vol. 4, part 5. Cambridge University Press.

BLEULER, M. (1978) Translated as *The Schizophrenic Disorders* by S. Clemens. New Haven: Yale University Press.

BROOK J., MCCURRACH, M., HARLEY, H., *et al* (1992) Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell*, **68**, 799–808.

CASKEY, C., PIZZOTI, A., FU, Y., *et al* (1992) Triplet repeat mutations in human disease. *Science*, **256**, 784–789.

FARMER, A. E., KATZ, R., MCGUFFIN, P., *et al* (1987) A comparison between the Present State Examination and the Composite International Diagnostic Interview. *Archives of General Psychiatry*, **44**, 1064–1068.

———, COSYNS, P., LEBOYER, M., *et al* (1993) A SCAN–SADS comparison study of psychotic subjects and their first-degree relatives. *European Archives of Clinical Neuroscience*, **242**, 352–356.

GILL, M., MCGUFFIN, P., PARFITT, E., *et al* (1993) A linkage study of schizophrenia with DNA markers from the long arm of chromosome 11. *Psychological Medicine*, **23**, 27–44.

GREENFIELD, J. (1911) Notes on a family with myotonica atrophica and early cataract with report of an additional case of myotonia atrophica. *Reviews in Neurology and Psychiatry*, **9**, 169–181.

HALL, J. G. (1990) Genomic imprinting: review and relevance to human diseases. *American Journal of Human Genetics*, **46**, 853–857.

HARPER, S., HELEN, H., REARDON, W. *et al* (1992) Anticipation in myotonic dystrophy: new light on an old problem. *American Journal of Human Genetics*, **51**, 10–16.

HARRISON, P. (1993) Alzheimer's disease and chromosome 14: different gene, same process? *British Journal of Psychiatry*, **163**, 2–5.

HATTERSLEY, A., TURNER, R., PERMUTT, A., *et al* (1992) Linkage of type 2 diabetes to the glucokinase gene. *Lancet*, **339**, 1307–1310.

HUNTINGTON'S DISEASE COLLABORATIVE RESEARCH GROUP (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's Disease chromosomes. *Cell*, **72**, 971–983.

KELLER, M. B., LAVORI, P. W., MCDONALD-SCOTT, P., *et al* (1981) Reliability of lifetime diagnosis and symptoms in patients with a current psychiatric disorder. *Journal of Psychiatric Research*, **16**, 229–240.

LEBOYER, M. & MCGUFFIN, P. (1991) Collaborative strategies in the molecular genetics of the major psychoses. *British Journal of Psychiatry*, **158**, 605–610.

MCGUFFIN, P. (1988) Genetics of schizophrenia. In *Schizophrenia: the Major Issues* (eds P. Bebbington & P. McGuffin), pp. 107–126. London: Heinemann Medical.

———, KATZ, R. & ALDRICH, J. (1986) Past and present state examination: the assessment of 'lifetime ever' psychopathology. *Psychological Medicine*, **16**, 461–465.

———, FARMER, A. & HARVEY, I. (1991) A polydiagnostic application of operational criteria in studies of psychotic illness: development and reliability of the OPCRIT system. *Archives of General Psychiatry*, **48**, 764–770.

———, ASHERSON, P., FARMER, A. & OWEN, M. (1994) The strength of the genetic evidence – Is there room for an environmental influence in the aetiology of schizophrenia. *British Journal of Psychiatry*, in press.

MOTT, F. W. (1910) Hereditary aspect of nervous and mental diseases. *British Medical Journal*, *ii*, 1013–1020.

https://doi.org/10.1192/bjp.164.5.619 Published online by Cambridge University Press

PENROSE, L. S. (1945) Survey of cases of familial mental illness. Published (1991) in *European Archives of Clinical Neuroscience*, **240**, 314–324.

—— (1948) The problem of anticipation in pedigrees of dystrophia myotonica. *Annals of Eugenics*, **14**, 125–132.

RIDLEY, R. M., FRITH, C. D., CROW, T. J., *et al* (1988) Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *Journal of Medical Genetics*, **25**, 589–595.

ROBINS, L. N., WING, J., WITTCHEN, H. V., *et al* (1988) The Composite International Diagnostic Interview. *Archives of General Psychiatry*, **45**, 1069–1078.

SHERMAN, S. L., JACOBS, P. A., MORTON, N. E., *et al* (1985) Further segregation analysis of the fragile X syndrome with special reference to transmitting males. *Human Genetics*, **68**, 289–299.

SPITZER, R. L., ENDICOTT, J. & ROBINS, E. (1978) *Research diagnostic criteria for a selected group of functional disorders* (3rd edn). New York: New York State Psychiatric Institute.

STURT, E. & MCGUFFIN, P. (1985) Can linkage and marker association resolve the genetic aetiology of psychiatric disorders: review and argument. *Psychological Medicine*, **15**, 455–462.

TURK, J. (1992) The fragile-X syndrome: on the way to a behavioural phenotype. *British Journal of Psychiatry*, **160**, 24–35.

WING, J. K., COOPER, J. E. & SARTORIUS, N. (1974) *The Measurement and Classification of Psychiatric Symptoms*. Cambridge: Cambridge University Press.

——, BABOR, T., BURKE, J., *et al* (1990) SCAN: Schedules for Clinical Assessment in Neuropsychiatry. *Archives of General Psychiatry*, **47**, 589–593.

YU, S., KREMER, E., PRITCHARD, M., *et al* (1991) The fragile X genotype is characterised by an unstable region of DNA. *Science*, **252**, 1179–1181.

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(*First received November 1992, final revision August 1993, accepted September 1993*)

https://doi.org/10.1192/bjp.164.5.619 Published online by Cambridge University Press