Chromosome 22q11 deletions

An under-recognised cause of idiopathic learning disability

K. C. MURPHY, R. G. JONES, E. GRIFFITHS, P. W. THOMPSON and M. J. OWEN

Background Velo-cardio-facial syndrome (VCFS), a syndrome of multiple congenital abnormalities including characteristic dysmorphology, congenital heart defects and learning disability, is associated with small interstitial deletions of chromosome 22q11. We tested the hypothesis that VCFS may be significantly under-diagnosed by screening a learning-disabled population for chromosome 22q11 deletions.

Method Two hundred and sixty-five people with learning disability residing in two learning disability hospitals in South Wales were reviewed. They were selected for inclusion in the study if they fulfilled any of the following criteria: psychotic disorder (schizophrenia or affective disorder), family history of psychotic disorder, cleft palate and/or lip, congenital heart disease, broadly defined facial dysmorphism or a history of hypocalcaemia. Fluorescence *in situ* hybridisation studies were performed on 74 selected individuals.

Results Cytogenetic analysis revealed that two people demonstrated a previously undetected chromosome 22q11 deletion. A third person demonstrated a previously undetected cytogenetically visible deletion on chromosome 15.

Conclusions VCFS appears to be aetiologically significant in a proportion of individuals with idiopathic learning disability, especially in those where psychosis is associated with mild learning disability. We suggest that clinicians should consider a chromosome 22q11 deletion in people who meet selection criteria.

Velo-cardio-facial syndrome (VCFS), also termed Di George syndrome or Shprintzen syndrome, is an autosomal dominant disorder associated with small chromosomal deletions in the q11 band of chromosome 22. It has an estimated prevalence of one in 4000 births and is characterised by multiple congenital anomalies including clefts of the secondary palate, hypernasal speech, congenital heart defects, hypocalcaemia, characteristic dysmorphology, learning disability and psychosis (Shprintzen *et al*, 1978, 1992; Pulver *et al*, 1994; Papolos *et al*, 1996). We have previously suggested that the presence of cleft palate and/or lip, characteristic dysmorphology, congenital heart defects or a history of hypocalcaemia in people with learning disability and/or psychotic disorder (schizophrenia or affective disorder) should raise the suspicion of a chromosome 22q11 deletion (Murphy & Owen, 1996). As VCFS may be significantly under-reported in these people, we decided to examine the prevalence of chromosome 22q11 deletions in a population with learning disability.

METHOD

Two hundred and sixty-five people residing in two learning disability hospitals in South Wales were reviewed. Those with learning disability were selected for inclusion in the study if they fulfilled any of the following criteria: psychotic disorder (schizophrenia or affective disorder), family history of psychotic disorder, cleft palate and/or lip, congenital heart disease, hypocalcaemia or broadly defined facial dysmorphism. Seventy-four people met selection criteria (see Table 1).

Peripheral blood was cultured using standard techniques to produce cytogenetic preparations suitable for G-banding (routine demonstration of characteristic light and dark chromosomal bands) and fluorescence *in situ* hybridisation (FISH) analysis. FISH studies were carried out using a commercially available Di George chromosome region (DGCR) probe mix (Oncor Inc., Gaithersburg, MD 20877, USA). The mix contains the DGCR probe D22S75 (N25) which hybridises to chromosome 22q11.2, and a control probe S22S39 which hybridises to 22q13.3 and which allows chromosome 22 to be unequivocally identified when D22S75 is deleted. The protocol recommended by the manufacturers was used, and detection was with fluorescein isothiocyanate-labelled antibodies. The preparations were counterstained with propidium iodide and 4′,6-diamidino-2-phenylindole, and examined with a Zeiss Axioplan epifluorescence microscope. Photographs were taken using Kodak Ektachrome HC film.

RESULTS

A sample was interpreted as being non-deleted if a fluorescent signal could be seen on the chromosome 22 homologues with both the DGCR probe and the control probe. A deleted sample showed a signal on both homologues with the control probe, but on only one homologue with the DGCR probe. A minimum of 10 metaphases were examined from each person.

Two individuals were shown to demonstrate a deletion on chromosome 22q11. Another person demonstrated a previously undetected cytogenetically visible deletion on chromosome 15q11.2 consistent with Angelman's syndrome.

Subject 1

The subject was a 33-year-old Caucasian male. He had been born at term to a 25-year-old primigravida with a history of

Table 1 Characteristics of people selected for fluorescence *in situ* hybridisation

Indications for screening	*n*=74 (%)
Mild learning disability	17 (23)
Moderate/severe learning disability	57 (77)
Psychotic disorder	28 (38)
Facial dysmorphism	42 (57)
Family history of psychosis	12 (16)
Cleft palate	2 (3)
Congenital heart disease	1 (1)

https://doi.org/10.1192/bjp.172.2.180 Published online by Cambridge University Press

schizophrenia whose prenatal course had been unremarkable. After delivery, the child was noted to have a cleft lip, a ventricular septal defect and a patent ductus arteriosus, and underwent corrective cardiac surgery at age five years. He was noted to have mild learning disability and, although he initially attended ordinary school, he subsequently attended a school for the learning-disabled from the age of 10 years. He presented to the psychiatric services as a 16-year-old because of hostile and aggressive behaviour with paranoid ideation. He was treated with chlorpromazine and his full-scale IQ was found to be 56. He was readmitted aged 22 with thought disorder, aggressive and inappropriate behaviour and was treated with trifluoperazine. He has remained an in-patient for the past 11 years and during this time has experienced auditory hallucinations as well as persecutory, grandiose and bizarre delusions. On physical examination, he exhibited the characteristic facial dysmorphism observed in VCFS including inverted palpebral fissures and a bulbous nasal tip. He was diagnosed with DSM–III–R schizophrenia (American Psychiatric Association, 1987) using OPCRIT version 3.31 (McGuffin *et al*, 1991) on the basis of all available clinical information including a semi-structured clinical interview (PAS-ADD; Moss *et al*, 1993) and a review of case records. Cytogenetic analysis using FISH revealed a microdeletion at chromosome 22q11.

Subject 2

The subject was a 47-year-old Caucasian male. He was born at term to a 19-year-old primigravida whose prenatal course had been unremarkable. His developmental milestones were delayed and he attended a speech therapist as a five-year-old. He attended ordinary school and left at age 14. Initially, he presented to the psychiatric services at the age of 20 with a six-month history of auditory and visual hallucinations, delusions of persecution and passivity, and increasingly bizarre and aggressive behaviour. He was detained under the Mental Health Act and treated with chlorpromazine. At the age of 22 he was readmitted and has remained an in-patient over the past 25 years. During this period, he has exhibited auditory and visual hallucinations, thought disorder, religious and nihilistic delusions and delusions of reference and passivity. He has a full-scale IQ of 65. On physical examination, he had facial dysmorphism with inverted palpebral fissures, a bulbous nasal tip and a smooth philtrum (see Fig. 1). There were no cardiac or palatal abnormalities. He was given a diagnosis of DSM–III–R schizophrenia (American Psychiatric Association, 1987) made by OPCRIT version 3.31 (McGuffin *et al*, 1991) on the basis of all available clinical information including a semi-structured clinical interview (PAS-ADD, Moss *et al*, 1993) and a review of case notes. Cytogenetic analysis using FISH revealed a microdeletion at chromosome 22q11.

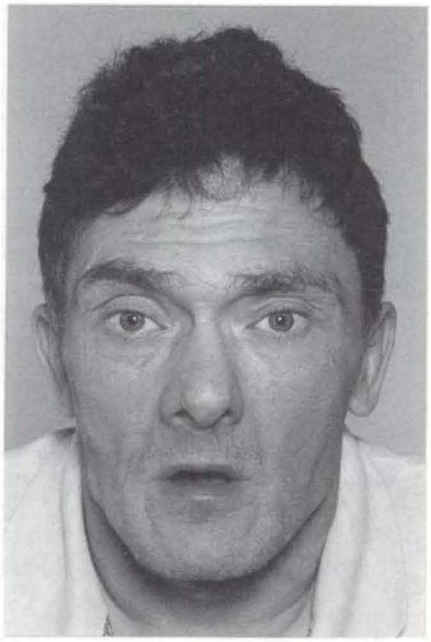


Fig. 1 Subject 2.

Subject 3

The subject was a 43-year-old Caucasian male. He had been a precipitant delivery to a 23-year-old multigravida. He developed epilepsy at an age of 14 months and was noted to have profound learning disability. He was admitted to a learning disability hospital as a four-year-old and has required continuous in-patient treatment since then. He walked at age eight and currently walks with difficulty using an aid. Although he has not developed speech, he is friendly and sociable and is reported to smile continuously. On physical examination, he has blue eyes, fair hair and an open-mouthed posture. He has a noticeable tremor with jerky incoordinate movements of both upper and lower limbs. Cytogenetic analysis revealed a visible cytogenetic deletion at chromosome 15q11 consistent with Angelman's syndrome and this was confirmed using FISH.

DISCUSSION

Learning disability is associated with a clinically and aetiologically heterogeneous range of conditions and is often subdivided on the basis of IQ test scores into mild (IQ scores between 50 and 70) and moderate or severe learning disability (IQ scores less than 50).

Aetiology of learning disability

Individuals showing mild learning disability are usually considered to represent the lower end of the normal distribution curve for IQ, and aetiological factors are thought to be primarily idiopathic. Conversely, individuals with moderate or severe learning disability are considered to differ qualitatively from the normal population, explaining the asymmetry at the lower end of the IQ distribution curve (Thapar *et al*, 1994). Discrete biological causes including both environmental and genetic factors are thought to be important in this group.

It is commonly assumed that idiopathic learning disability is transmitted multifactorially (multiple additive genetic effects and environmental influences) and evidence to support this model comes from most available data (Gottesman, 1971). In contrast, several studies of individuals with mild learning disability have shown increased rates (4–19%) of chromosomal abnormalities (Hagberg *et al*, 1981; Gostason *et al*, 1991). This suggests that at least a proportion of individuals who appear to have idiopathic learning disability will be accounted for by previously undetected or unknown chromosomal abnormalities or single-gene defects. Considering this evidence, we can therefore assume that idiopathic learning disability is aetiologically heterogeneous and can be caused by single genetic aberrations in some cases, discrete environmental hazards in others and polygenic/multifactorial influences in the remainder.

Study hypothesis confirmed

We hypothesised that VCFS is a chromosomal abnormality which may be

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aetiologically significant in a proportion of individuals with idiopathic learning disability. Consequently, we tested this hypothesis by screening a selected series of people for chromosome 22q11 deletions. Our results indicate that two people, previously diagnosed as idiopathic learning disability, had undetected VCFS. In addition, a third person was found to have previously undiagnosed Angelman's syndrome.

Prevalence of VCFS in learning disability

The prevalence of chromosome 22q11 deletions in the entire sample was low (0.7%). However, as VCFS appears to be predominantly associated with mild learning disability (Kelly, 1993), excluding those with moderate or severe learning disability from the sample reveals that 12% of people selected with mild learning disability were found to have a chromosome 22q11 deletion. Both people identified had mild learning disability and chronic schizophrenia and it is possible that chromosome 22q11 deletions are particularly common in this subgroup. In view of the small sample size, however, replication by other groups is required. Furthermore, as we screened people with mild learning disability who are long-stay in-patients, the prevalence of VCFS in people outside this treatment setting may be much lower.

Clinical implications

We have previously recommended that clinicians working in learning disability should establish close liaison with the local university department of medical genetics (Murphy & Owen, 1996). There are two main reasons for this. First, clinicians should retain a high index of suspicion for a genetic disorder in people with idiopathic learning disability who are dysmorphic or who have other physical signs suggestive of a genetic disorder. We suggest that such people should be referred to a clinical geneticist for assessment. Second, once a genetic diagnosis is made, it is necessary to ensure that appropriate genetic counselling is provided, including consideration of the relevant ethical issues, both to the person and to their family.

We suggest that clinicians should consider a chromosome 22q11 deletion in those who fulfil two or more of the following criteria: idiopathic learning disability, psychotic disorder (affective disorder or schizophrenia), facial dysmorphism, cleft palate and/or lip, a history of hypocalcaemia or congenital heart disease.

CLINICAL IMPLICATIONS

- Chromosome 22q11 deletions appear to be aetiologically significant in a proportion of individuals with idiopathic learning disability, especially in those with mild learning disability and psychosis.
- Individuals meeting selection criteria should be screened for chromosome 22q11 deletions as part of standard practice.
- Close liaison between psychiatry and medical genetics is recommended with the provision of expert genetic counselling where appropriate.

LIMITATIONS

- People in the study sample were long-stay in-patients which may have elevated the prevalence of VCFS in this sample.
- Chromosome 22q11 deletions are probably implicated in a small proportion of individuals with idiopathic learning disability.
- It may be difficult to establish the full cooperation of families in genetic counselling.

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(First received 30 April 1997, final revision 8 September 1997, accepted 11 September 1997)

ACKNOWLEDGEMENTS

This work was supported by an MRC Training Fellowship to K. C. M. Consent for publication of both the photograph and clinical material was obtained from the individuals or their relatives.

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