

Thoughts on the behavioural phenotypes in Prader-Willi syndrome and velo-cardio-facial syndrome: a novel approach

Verhoeven W, Egger J, Tuinier S. Thoughts on the behavioural phenotypes in Prader-Willi syndrome and velo-cardio-facial syndrome: a novel approach.

Background: In both Prader-Willi syndrome (PWS) and 22q11 deletion syndrome [velo-cardio-facial syndrome (VCFS)], an increased risk for psychotic disorders is reported, which are as a rule not included in the behavioural phenotype of these two syndromes. For the description of a behavioural phenotype, the complete spectrum of physical, developmental, neuropsychological and psychiatric aspects is generally not taken into account. Moreover, psychiatric signs and symptoms often do not meet the criteria for a categorical diagnosis.

Objective: In this study, a further specification of psychotic symptoms in PWS and VCFS is shown as well as a proposal for a new model to ascertain predictors, including behavioural, for a genetic syndrome.

Methods: Over the past years, 27 patients with PWS and 19 with VCFS were referred for neuropsychiatric evaluation because of psychotic symptoms. In all the patients, a standardised psychiatric examination was performed; seven of the patients with VCFS were evaluated by means of an extensive neuropsychological battery.

Results: In both patient groups, a rather specific psychopathological profile seemed to be present, which in the case of patients with PWS showed some resemblance with bipolar affective disorder. In patients with VCFS, no formal psychiatric diagnosis could be established. Because the psychopathological profiles were rather aspecific, they are not sufficient to predict membership of a certain syndrome.

Conclusions: A quantitative probabilistic approach toward the description of a (behavioural) phenotype is suggested. For such a procedure, large data sets and international collaboration are required.

Willem Verhoeven^{1,2}, Jos Egger^{1,3}, Siegfried Tuinier¹

¹Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands; ²Department of Psychiatry, Erasmus University Medical Centre, Rotterdam, The Netherlands; and ³Department of Clinical Psychology and Personality, Radboud University, Nijmegen, The Netherlands

Keywords: 22q11 deletion syndrome; behavioural phenotype; genetic subtype; Prader-Willi syndrome; probabilistic analysis; psychosis

Prof. Dr Willem Verhoeven, Vincent van Gogh Institute for Psychiatry, Stationsweg 46, 5803 AC Venray, The Netherlands.
Tel: +31 478 52733;
Fax: +31 478 527110;
E-mail: wverhoeven@vvgi.nl

Introduction

The explosion of knowledge in the field of molecular and quantitative genetics over the past decades has stimulated research into the so-called behavioural phenotypes. At the same time, this has led to a feeling of discomfort in psychiatry, especially with respect to the validity of the current taxonomies and their relevance to genetic research. In fact, there is an ongoing debate on the composition of symptoms to construct the ideal phenotype (1).

The term behavioural phenotype in patients with intellectual disabilities (IDs) was originally introduced by Nyhan in 1972, who hypothesised a causal relationship between a chemical abnormality in

an identified genetic disorder and an unusual behavioural profile, especially with respect to motor dysfunctions like self-injuries, stereotypes and aggression (2). Later, this concept was further elaborated by Flint and Yule who formulated two essentials: first, it should include a distinctive behaviour that occurs in almost every case of a genetic or a chromosomal disorder and rarely if at all in other conditions and second, the behaviour has a direct relationship to the genetic or chromosomal anomaly (3). They recognised the disadvantages of questionnaires and diagnostic criteria to describe behavioural abnormalities and the element of chance depending on the skills and preferences of the investigator.

Behavioural phenotypes in Prader-Willi syndrome and 22q11 deletion syndrome

This quite rigid definition was amended by several authors who stressed the importance of the inclusion of physical and motor aspects (4), the probabilistic nature of behaviours, the within-syndrome variability (5) and the longitudinal fluctuations of behavioural patterns (6). Since then, the definition of a behavioural phenotype includes a characteristic pattern of motor, cognitive, linguistic and social abnormalities and comprises developmental aspects too (7).

There is some consensus about the existence of behavioural phenotypes in certain genetic syndromes such as fragile X syndrome, Williams syndrome, Prader-Willi syndrome (PWS) and velo-cardio-facial syndrome (VCFS). In general, however, somatic anomalies, dysmorphias and developmental issues are not included in the description of the behavioural phenotype (8). This might be an expression of the Cartesian mind-body dualism that was recently criticised by Kendler, who stressed that dualistic thinking and vocabulary remain deeply anchored in clinical practice and research programs and stated, 'to reject Cartesian dualism means to no longer consider the mental (or functional) to be a fundamentally different thing from the biological (or organic)' (9). This dualistic approach is reflected in the delineation of behavioural phenotypes, with its focus on some nosological categories like bipolar disorder, attention-deficit disorder and psychoses in VCFS and obsessive-compulsive disorder and psychosis in PWS (10). Such a procedure does not contribute to the ultimate goal: linking behaviour to genes. The shortcomings of the current endeavors are shown by means of two series of patients suffering from psychotic disorders, who were known with a diagnosis of either PWS or VCFS. In addition, a proposal for a more appropriate delineation of a phenotype including behaviours is shown.

Prader-Willi syndrome

PWS is a multisystem disorder, accompanied by a variable degree of ID and arising from the lack of expression of genes on the paternally derived chromosome q15.11–q13 as a result of a paternal deletion or a uniparental maternal disomy (UPD).

With respect to the behavioural phenotype of PWS, a broad array of psychopathology with a prevalence of 5–25% is described, which, depending on the orientation of the investigator, ranges from (atypical) psychotic and bipolar affective disorders (11,12) to obsessive-compulsive disorder (13) and attention-deficit/hyperactivity disorder (14). Concerning psychotic disorders, an association has been suggested with UPD (15–17).

Velo-cardio-facial syndrome

VCFS (also known as Shprintzen syndrome, 22q11 deletion syndrome) is associated with interstitial deletions, with a variable size, on chromosome 22q11.

The behavioural phenotype in childhood and adolescence comprises social withdrawal, a special attachment to mother or other caregivers, poor social skills, emotional instability, affective problems, anxieties and attention deficits (18,19). The neuropsychological profile comprises mild ID and impairments in problem solving and planning as well as in abstract and social thinking (20). Magnetic resonance imaging has shown widespread deficits in white matter and reduced brain volumes (21,22). After adolescence, a high prevalence of psychiatric illness is reported, including psychotic disorders, especially schizophrenia and bipolar spectrum disorders (23–30).

Materials and methods

Over the past years, 27 patients with PWS and 19 with VCFS were referred for neuropsychiatric evaluation because of persisting or relapsing psychotic symptoms. In all the patients, a standard psychiatric examination including the behavioural aspects of psychopathology was performed, and additional data about history and course were collected from all available sources. The diagnostic procedure comprised the elements of the Comprehensive Psychiatric Rating Scale (31) and followed the format of the diagnostic criteria for psychiatric disorders for use with adults with learning disabilities/mental retardation (DC-LD) (32). Individual symptoms were rated on a symptom checklist targeted at observable signs and symptoms according to the policy as described elsewhere (33). Tentative formal psychiatric diagnoses were established according to the clinical descriptions and diagnostic guidelines of the International Classification of Diseases (ICD)-10. In seven of the patients with VCFS, an extensive neuropsychological examination was performed.

Results

Prader-Willi syndrome

Of the group of 27 patients with PWS, reports on 23 were published previously (11,17,27,28). The age range of the patients (15 females and 12 males) was 16–43 years (mean: 24 years), and the level of ID was mild to moderate in 24 and severe in 3. All but two patients (insufficient data in the medical record) had a history of affective instability, paralleled by fluctuating behavioural problems.

With respect to the actual psychopathology, six patients met the criteria for a bipolar affective disorder in that they showed an episodic pattern of euphoria, hyperactivity and sleep disturbances or depressed mood and inactivity. In the other 21 patients, the psychiatric symptomatology included emotional turmoil, anxieties, irritability, confusion, (rapid) mood swings, hallucinatory experiences and paranoid ideation, with a variable intensity and a subacute onset. Therefore, a diagnosis of cycloid psychosis was considered to be most appropriate in the acute phase (Table 1).

Concerning the genetic etiology, three patients had a deletion, and in four, only a clinical diagnosis was made. Three patients were genetically confirmed but not differentiated. In the remaining 17 patients, an UPD was shown.

Velo-cardio-facial syndrome

Of the group of 19 patients, reports on 8 were published previously (29). All cases were confirmed by fluorescence in situ hybridization. The main characteristics including somatic anomalies and family history are shown in Table 2. In the seven patients who had a (neuro)psychological examination, a discrepancy between verbal and performal IQ was shown as well as an impaired visuo-perceptual ability and a diminished comprehension of abstract and symbolic language. In terms of personality constructs, it was observed that most patients scored high on neuroticism and low on agreeableness, a profile associated with adjectives like shy, moody, irrational and unempathetic (Table 3).

The behavioural profile of the patients included oppositional behaviour, social withdrawal, clinging to mother or caregiver, aggression and compulsive behaviours. The psychopathological syndrome comprised both affective and obsessive-compulsive symptoms as well as psychotic symptoms (Table 4). Eight patients reported preoccupation with death

without, however, suicidal ideas or attempts. In six patients (patients 2, 3, 6, 7, 11 and 12), a functional decline over time was observed. None of the patients showed Schneider's first-rank symptoms or negative symptoms and disorganised speech, nor did they meet the criteria for a manic episode.

Discussion

In this study, the psychiatric symptoms in a group of patients with PWS and VCFS are shown. With respect to PWS, the clinical picture of most of the patients in the acute phase meets the criteria for a cycloid psychosis (ICD-10: F23). The psychiatric symptomatology in VSFC does not meet the criteria for a distinct psychiatric disorder. With respect to genetic analysis, all but four patients with PWS were genetically confirmed. Genetic analysis in the VCFS sample did not include the estimation of the deletion size.

In the reported 21 of 27 patients with PWS in this study, the psychosis was characterised by symptoms like confusion, auditory hallucinations and paranoid behaviour on the one hand and an increase of obsessive rituals, anxieties and mood swings on the other hand and was preceded by affective instability for many years. Even though the actual psychopathology justifies the diagnosis of cycloid psychosis, longitudinal evaluation points toward an atypical bipolar disorder (ICD-10: F31.9). It can therefore be hypothesised that the psychopathological phenotype of PWS patients with an UPD etiology comprises an increased risk for an atypical bipolar affective disorder (17).

In the group of 19 patients with VCFS, psychotic symptoms emerge from adolescence, mostly after separation from the major caregiver, of which 'auditory hallucinations' and exaggeration of the preexistent paranoid attitude are the most prominent. As already mentioned by Shprintzen, there is a close relationship between the psychological dysfunctions and the behavioural and psychiatric symptoms (19). In fact, the auditory hallucinations may be a description by the patients of their own thoughts and paranoid ideation may be the result of an impaired capacity to estimate intentions, emotions and behaviours of others. In older patients, a functional decline is observed, which was also reported by Baker and Skuse (30). Furthermore, the endocrine dysfunctions, particularly hypoparathyroidism, may mimic the psychotic features described above.

The results shown in this study typically suggest a psychiatric syndrome in a subclass of two genetic disorders; but the psychiatric symptoms as such

Table 1. Psychiatric symptoms in 21 PWS patients with cycloid psychoses

Symptoms and course	Number	%
Auditory hallucinations	10	48
Perceptual disturbances	4	19
Paranoid ideation	16	76
Confusion	19	90
Anxieties	20	95
Mood swings	20	95
Emotional turmoil	17	80
Increased obsessive rituals	18	85
Hyperactivity/agitation	13	62
Subacute onset	21	100

Behavioural phenotypes in Prader-Willi syndrome and 22q11 deletion syndrome

Table 2. Main characteristics of the patients with VCFS

Patient number	Age (in years)/sex	Age at diagnosis (in years)	Level of ID	Somatic anomalies	Age at first psychosis (in years)	Family history	History of epilepsy	Functional decline
1	58/M	57	Mild	Thyroid adenoma, recurrent upper airway infections, cataract, auditory impairment	29	ID: n = 1	-	-
2	45/M	42	Moderate	Thrombocytopenia, VSD, pulmonic stenosis, left-side hydronephrosis, hepatic cysts, frequent otitis	20	-	+	+
3	23/M	22	Mild	Thrombocytopenia, MRI: polymicrogyria	16	-	+	+
4	21/M	21	Mild	Hypoparathyroidism, recurrent upper airway infections, thrombocytopenia	17	ID: n = 1	-	-
5	38/M	37	Mild	Thrombocytopenia, velopharyngeal insufficiency, cleft palate, recurrent upper airway infections; MRI: slight atrophy	23	-	-	-
6	36/M	31	Mild	Recurrent upper airway infections, right-sided aorta, keratoconus	18	-	-	+
7	25/M	25	Mild	Recurrent upper airway infections	21	-	-	+
8	25/F	25	Mild	Thrombocytopenia, cleft palate, recurrent upper airway infections	23	-	-	-
9	35/M	35	IQ: 80	Hypothyroidism, agenesis right kidney, reduced T-cell populations; MRI: white matter hyperintensities	34	ID: n = 1; congenital abnormalities: n = 2; depression: n = 1	-	-
10	20/M	19	Mild	Cleft palate, hypernasality; MRI: white matter hyperintensities	18	VCFS: n = 4 (brother patient 14)	-	-
11*	70/F	70	Mild	Cleft palate, velopharyngeal insufficiency, hypernasality, scoliosis; CT: mild cortical atrophy	25	-	-	+
12*	45/M	45	Mild	Intrathoracic goiter, velopharyngeal insufficiency, recurrent upper airway infections	20	-	-	+
13*	20/M	18	Mild	Velopharyngeal insufficiency, recurrent upper airway infections	18	-	-	-
14*	17/F	17	IQ: 75	-	17	VCFS: n = 4 (sister patient 10)	-	-
15*	16/F	7	IQ: 80	Velopharyngeal insufficiency, thrombocytopenia	15	-	-	-
16*	29/F	27	Mild	Falot's tetralogy	16	-	-	-
17*	31/F	31	Mild	Cleft palate, hypoparathyroidism, scoliosis	21	ID: several family members; cleft palate: n = 1	+	-
18*	22/F	22	Mild	Recurrent upper airway infections, VSD?	21	-	-	-
19	23/M	23	IQ: 75	Hypoparathyroidism, recurrent upper airway infections, thrombocytopenia	21	Congenital abnormalities: n = 1; schizophrenia: n = 1	-	-

CT, computer tomography; F, female; M, male; MRI, magnetic resonance imaging; VSD, ventricular septal defect; +, present; -, absent.

*Includes patients, who were reported in *Annales de Génétiques* (See reference 29).

Table 3. Neuropsychological characteristics of seven patients with VCFS

Measurement domain	Patient number						
	8	9	10	14	15	16	19
Intelligence*							
Total IQ	-	-	-	--	+	--	-
Verbal IQ	-	-	-	--	+	-	-
Perfomal IQ	--	-	-	--	-	--	--
Cognitive functions†							
Concept formation	-	--	--	--	-	--	-
Speed of information processing	--	-	-	-	-	--	--
Verbal memory	-	-		+	+	--	-
Visual memory	-	-		+	-	--	-
Visuospatial/perceptual functioning	-	-	-	+	-	--	-
Attention	--	-		-	-	-	+
Executive functioning	-	-	+	+	-	-	-
Social interpretation and social adequacy	-	-	-	-	--	--	-
Personality dimensions‡							
Neuroticism	4	4	4	4	5	1	4
Extraversion	3	1	2	2	2	3	4
Agreeableness	2	2	3	1	2	1	3
Conscientiousness	3	4	1	2	3	2	3

Because of variation in the test-taking abilities of the patients with VCFS, neuropsychological examination of the cognitive domains was conducted using different tests per patient. Apart from clinical observation, personality dimensions were rated using the Five-factor Personality Inventory (FFPI) (34) or Ten Item Personality Inventory (TIPI) (35).

*'+', IQ ≥ 90; '- ', 70 < IQ < 90; '-- - ', IQ < 70.

†'+', normal; '- ', mild/moderate disorders; '-- - ', severe disorders.

‡1, very low; 2, low; 3, neutral; 4, high; 5, very high.

have by no means a predictive diagnostic value with regards to the genetic syndrome. In fact, this 'forward' approach ignores the diagnostic relevance of the whole range of developmental and behavioural characteristics for the identification of a syndrome. The PWS comprises among others a variable degree of ID, neonatal hypotonia, obsessive-compulsive disorder (OCD)-like symptoms, overeating, skin picking, stubbornness and hypothalamic dysfunctions, whereas in VCFS, severe separation anxiety, phobias, OCD-like symptoms, social withdrawal, language problems and level of ID are excluded.

Because it is generally accepted that several indicators that are either consistently or occasionally

Table 4. Psychiatric symptoms in 19 patients with VCFS

Symptoms	Number of patients	Percentage
Anxieties	18	95
Affective instability	16	84
Depressed mood	13	68
Obsessive rituals/perseverations	17	89
Preoccupation with death	8	42
Paranoid ideation and delusions	18	95
'Hallucinations'	13	68
Aggressive behaviour	15	79
Confusion	14	74

associated with the syndrome, such as somatic anomalies, level of ID, motor behaviour, developmental characteristics, neuropsychological variables and psychiatric signs and symptoms, are to a variable degree capable of predicting the presence of a syndrome, the discussion on behavioural phenotypes should be reoriented toward a quantitative, probabilistic approach. This can be achieved by a *feature-based* model, which assumes that certain entities are best represented in terms of sets of qualitative features (36). According to this model, a behavioural phenotype should be considered as a set of hypothetical abstractions or components (eg OCD-like symptoms, motor abnormalities, social dysfunctions) that are constituted by various features (eg overeating, skin picking, ruminating). The linkage between the features and the hypothetical abstractions can be quantified in terms of their *cue validity*. Cue validity can be understood as the level to which the features contribute to the different components, that is the (conditional) probability that, given a component, the feature is present (37). Consequently, the likelihood of the presence of a behavioural phenotype can be estimated and a possible connection with genetic abnormalities or a genetic subtype investigated. This approach is to a certain extent comparable with that suggested by McGuffin et al. in their search for the genetic etiology of functional psychoses (1). In case of PWS, for instance, the prevalence of a set of features and symptoms can be enumerated and subsequently analyzed for latent classes as described by Maris (38). Such a method may elucidate clusters of behaviours not easily visible, which are more relevant for behavioural genetics but can only be performed with very large data sets that require international collaboration.

Several genetic subtypes have been described in the two syndromes shown in this study. In PWS, two types of paternal deletion have been shown, of which type I results in the loss of more material than type II. The behavioural and psychological problems are most pronounced in patients with a type I deletion or UPD (39). No information is available so far about the behavioural profiles in the UPD subtypes. In VCFS, two large community studies have shown a prevalence of congenital cardiac and great vessel malformations of 75 (40) and 76% (19), respectively. In the patients with psychoses, on whom reports are published so far ($n = 73$), the percentage of these conotruncal heart defects is 33, a remarkably lower figure (Table 5). Interestingly, in the patients shown in this article, only three (patient 2,6 and 16) had cardiac or vascular malformations. This low percentage was

Behavioural phenotypes in Prader-Willi syndrome and 22q11 deletion syndrome

Table 5. Reports about VCFS patients (aged >16 years) with psychoses (p) and conotruncal heart defects (cd)

Author(s), year	Number (p/cd)	Diagnosis	Heart defect
Chow et al., 1994*	1/1	Psychotic disorder	VSD, ASD, cardiac valve abnormalities
Karayiorgou et al., 1995*	5/0	Schizophrenia	None
Jönsson et al., 1997*	1/1	Psychotic disorder	VSD
Carlson et al., 1997*	9/6	Bipolar affective or schizoaffective disorder	VSD, ASD
Chow et al., 1998*	1/0	Schizophrenia	None
Murphy et al., 1998*	2/1	Schizophrenia	VSD, patent ductus arteriosus
Bassett et al., 1998,2003*	16/5	Schizophrenia	VSD, ASD, cardiac valve abnormalities
Gothelf et al., 1997, 1999*	4/3	Schizophrenia	ADS, Fallot's tetralogy
Murphy et al., 1999 (26)	15/4	Schizophrenia and bipolar affective disorder	VSD, ASD, aberrant artery
Usiskin et al., 1999*	3/0	Schizophrenia	None
Vogels et al., 2002 (29)	16/3	Psychiatric phenotype	Fallot's tetralogy, aorta abnormalities

VSD, ventricular septal defect; ASD, atrial septal defect.

*See reference 29.

also present in the series of VCFS patients with psychosis as published by Murphy et al. (26). These observations suggest that patients who develop psychotic symptomatology may have a different deletion, most likely a smaller one as was reported in a group patients with an early-onset form of schizophrenia (41). It cannot, however, be excluded that these results are influenced by an ascertainment bias.

In conclusion, the behavioural phenotypes of PWS and VCFS can be ascertained almost definitive if a cluster of physical, developmental and behavioural characteristics is taken into account. It should be stressed that behaviour and mental processes are not domains separate from the physique. The search for the genetic underpinnings of behaviour should acknowledge this (9). Furthermore, a psychiatric disorder is by no means an ideal phenotype, despite the consensus about its definition. Because the diagnostic vignettes are not at all composed with the objective to find relevant genes, a polydimensional approach is possibly more fruitful (1,42).

References

1. MCGUFFIN P, FARMER A, HARVEY I. A polydiagnostic application of operational criteria in studies of psychotic illness. *Arch Gen Psychiatry* 1991;**48**:764–770.
2. NYHAN WL. Behavioral phenotypes in organic genetic disease. *Pediatrics* 1972;**6**:1–9.
3. FLINT J, YULE W. Behavioral phenotypes. In: RUTTER M, ed. *Child and adolescent psychiatry: modern approaches*. Oxford, UK: Blackwell Science, 1994: 666–687.
4. TURK J, HILL P. Behavioural phenotypes in dysmorphic syndromes. *Clin Dysmorphol* 1995;**4**:105–115.
5. DYKENS EM. Measuring behavioral phenotypes: provocations from the “New genetics”. *Am J Ment Retard* 1995;**99**:522–532.
6. FINEGAN JA. Study of behavioral phenotypes: goals and methodological considerations. *Am J Med Genet* 1998;**81**: 148–155.
7. O'BRIEN G, YULE W. Why behavioural phenotypes. In: O'BRIEN G, YULE W, eds. *Clinics in developmental medicine*. Cambridge, UK: Cambridge University Press, 1995: 1–23.
8. CASSIDY SB, ALLANSON JE. *Management of genetic syndromes*. New York: Wiley-Liss Inc., 2001.
9. KENDLER KS. Toward a philosophical structure of psychiatry. *Am J Psychiatry* 2005;**162**:433–440.
10. CASSIDY SB, MORRIS CA. Behavioral phenotypes in genetic syndromes: genetic clues to human behavior. *Adv Pediatr* 2002;**49**:59–86.
11. VERHOEVEN WMA, TUINIER S, CURFS LMG. Prader-Willi syndrome: cycloid psychosis in a genetic subtype? *Acta Neuropsych* 2003a;**15**:32–37.
12. VERHOEVEN WMA, TUINIER S. Prader-Willi syndrome: atypical psychoses and motor dysfunctions. *Int Rev Neurobiol* 2006;**72**:119–130.
13. CLARKE D, BOER H, WHITTINGTON J, HOLLAND A, BUTLER J, WEBB T. Prader-Willi syndrome, compulsive and ritualistic behaviours: the first population-based survey. *Br J Psychiatry* 2002;**180**:358–362.
14. WIGREN M, HANSEN S. ADHD symptoms and insistence on sameness in Prader-Willi syndrome. *J Intellect Disabil Res* 2005;**49**:449–456.
15. BOER H, HOLLAND A, WHITTINGTON J, BUTLER J, WEBB T, CLARKE D. Psychotic illness in people with Prader-Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* 2002;**359**:135–136.
16. VOGELS A, MATTHIJS G, LEGIUS E, DEVRIENDT K, FRYNS JP. Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. *J Med Genet* 2003;**40**: 72–73.
17. VERHOEVEN WMA, TUINIER S, CURFS LMG. Prader-Willi syndrome: the psychopathological phenotype in uniparental disomy. *J Med Genet* 2003b;**40**:112.
18. SWILLEN A, DEVRIENDT K, LEGIUS E et al. The behavioural phenotype in velo-cardio-facial syndrome (VCFS): from infancy to adolescence. *Genet Couns* 1999;**10**:79–88.
19. SHPRINTZEN RJ. Velo-cardio-facial syndrome: a distinctive behavioural phenotype. *Ment Retard Dev Disabil Res Rev* 2000;**6**:142–147.
20. HENRY JC, VAN AMELSVOORT T, MORRIS RG, OWEN MJ, MURPHY DGM, MURPHY KC. An investigation of the neuropsychological profile in adults with velo-cardio-facial syndrome (VCFS). *Neuropsychologia* 2002;**40**: 471–478.
21. CHOW EWC, MIKULIS DJ, ZIPURSKY RB, SCUTT LE, WEKBERG R, BASSETT AS. Qualitative MRI findings in adults with 22q11 deletion syndrome and schizophrenia. *Biol Psychiatry* 1999;**46**:1436–1442.
22. VAN AMELSVOORT T, DALY E, HENRY J et al. Brain anatomy in adults with velocardiofacial syndrome with and without schizophrenia. *Arch Gen Psychiatry* 2004;**61**:1085–1096.
23. SHPRINTZEN RJ, GOLDBERG R, GOLDING-KUSCHNER KJ, MARION RW. Late-onset psychosis in the velo-cardio-facial syndrome. *Am J Med Genet* 1992;**42**:141–142.
24. PAPOLOS DF, FAEDDA GL, VEIT S et al. Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial

- syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry* 1996;**153**:1541–1547.
25. BASSETT AS, CHOW EWC, ABDELMALIK P, GHEORGHU M, HUSTED J, WEKSBERG R. The schizophrenia phenotype in 22q11 deletion syndrome. *Am J Psychiatry* 2003;**160**:1580–1586.
 26. MURPHY KC, JONES LA, OWEN MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 1999;**56**:940–945.
 27. VERHOEVEN WMA, CURFS LMG, TUINIER S. Prader-Willi syndrome and cycloid psychoses. *J Intellect Disabil Res* 1998;**42**:455–462.
 28. VERHOEVEN WMA, TUINIER S, CURFS LMG. Prader-Willi psychiatric syndrome and velo-cardio-facial psychiatric syndrome. *Genet Couns* 2000;**11**:205–213.
 29. VOGELS A, VERHOEVEN WMA, TUINIER S et al. The psychopathological phenotype of velo-cardio-facial syndrome. *Ann Genet* 2002;**45**:89–95.
 30. BAKER KD, SKUSE DH. Adolescent and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. *Br J Psychiatry* 2005;**186**:115–120.
 31. ÅSBERG M, PERRIS C, SCHALLIG D, SEDVALL G. The CPRS-development and applications of a psychiatric rating scale. *Acta Psychiatr Scand* 1978;(Suppl.):**271**:5–27.
 32. Royal College of Psychiatrists. DC-LD. Diagnostic criteria for psychiatric disorders for use with adults with learning disabilities/mental retardation. London, UK: Gaskell, 2001.
 33. VERHOEVEN WMA, SIBEN AES, TUINIER S. Psychiatric consultation in intellectual disability; dimensions, domains and vulnerability. *Eur J Psychiatry* 2004;**18**:31–43.
 34. MEULDERS M. Probabilistic feature models for psychological frequency data: a Bayesian approach. PhD Thesis, University Leuven, Belgium, 2000.
 35. DE FRUYT F, McCRAE RR, SZIRMAK Z et al. The Five-factor Personality Inventory as a measure of the Five-factor Model: Belgian, American, and Hungarian comparisons with the NEO-PI-R. *Assessment* 2004;**11**:207–215.
 36. GOSLING SD, RENTFROW PJ, SWANN WB. A very brief measure of the big five personality domains. *J Res Pers* 2003;**37**:504–528.
 37. EGGER JIM, MARIS E, DE MEY HRA. Multiple classification latent class models in the assessment of personality psychopathology: item decomposition of MMPI-2 PSY-5 scales. In: Abstracts 38th Annual Symposium on Recent Developments of the MMPI-2/MMPI-A. Fort Lauderdale, USA, 2003.
 38. MARIS E. Estimating multiple classification latent class models. *Psychometrika* 1999;**64**:187–212.
 39. BUTLER MG, BITTEL DC, KIBIRYEVA N, TALEBIZADEH Z, THOMPSON T. Behavioural differences among subjects with Prader Willi syndrome and type I or type II deletion and maternal disomy. *Pediatrics* 2004;**113**:565–573.
 40. RYAN AK, GOODSHIP JA, WILSON DI et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 1997;**34**:798–804.
 41. LIU H, HEATH SC, SOBIN C et al. Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl Acad Sci USA* 2002;**99**:3717–3722.
 42. STEYAERT J, FRYNS JP. Psychiatric genetics: the case of single gene disorders. *Eur Child Adolesc Psychiatry* 2002;**11**:201–209.