Velo-Cardio-Facial Syndrome and Psychotic Disorders:

Implications for Psychiatric Genetics

Eva W.C. Chow, Anne S. Bassett, and Rosanna Weksberg

Department of Psychiatry, Queen Street Mental Health Centre (E. W.C.C., A.S.B.), and
Departments of Paediatrics and Genetics, Hospital for Sick Children (R.W.), University of Toronto,
Toronto, Ontario, Canada

Abstract

Psychiatric disorders have been reported in over 10% of patients with velo-cardio-facial syndrome (VCFS) in long-term follow-up. To further explore the behavioral and psychiatric findings associated with VCFS in adulthood, detailed clinical histories of two patients—one with VCFS who developed a psychotic illness, and one with schizophrenia who was found to have dysmorphological features associated with VCFS—are described in the current report. The observed overlap of physical and psychiatric symptoms in these two patients suggests that VCFS and psychotic disorders may share a pathogenetic mechanism. This could be consistent with a contiguous gene model for VCFS and psychosis, suggesting chromosome 22q11 as a possible candidate region for genetic studies of schizophrenia.

Keywords

facial dysmorphism; schizophrenia; clinical overlap; contiguous gene

INTRODUCTION

Velo-cardio-facial syndrome (VCFS) is a congenital disorder first described by Strong [1968], and later delineated by Shprintzen et al. [1978]. An autosomal dominant mode of inheritance for VCFS has been demonstrated in some families [Williams et al., 1985]. Following recognition of the clinical overlap between DiGeorge syndrome and velo-cardio-facial syndrome, microdeletions of chromosome 22q11 were found in some VCFS patients [Scambler et al., 1992; Kelly et al., 1993]. Characteristic features of this syndrome include cleft palate, typical facies, cardiac malformations such as ventricular septal defect, and learning disabilities. However, the clinical expression of the VCFS genetic abnormality is highly variable. The phenotypic spectrum of this syndrome includes over 20 morphological features occurring at varying frequencies among patients [Shprintzen et al., 1978, 1981; Arvystas and Shprintzen, 1984; Williams et al., 1985, 1987; Wraith et al., 1985]. One author described three patients who had neither cleft palate nor cardiac defect, but exhibited other

features associated with VCFS such as typical facies, short stature, and developmental delay [Meinecke et al., 1986].

Although learning disabilities were included in the first description of the syndrome, there have been few reports on the mental and behavioral disturbances found in VCFS. Golding-Kushner et al. [1985] described the language, academic, and psychological profile of 26 VCFS patients. They found that patients generally had dull normal or lower IQ, with limited abstract reasoning skills, delayed speech onset, and immature language use. The patients also tended to have a bland affect, monotonous voice, and poor social interaction with extremes of disinhibited or shy behavior, but no identifiable psychiatric disorders in childhood. With more VCFS patients reaching adulthood in recent years, Shprintzen et al. [1992] noticed that more than 10% of their over 100 VCFS patients had developed psychiatric disorders, mostly chronic paranoid schizophrenia. However, the clinical features of these psychotic conditions in VCFS patients have not been described in the literature to the same extent as the dysmorphic features. Goldberg et al. [1993] provided a list of psychiatric diagnoses associated with some of their 120 VCFS patients, but described the behavioral and psychological profiles in detail in only two of these patients.

To further explore the behavioral and psychiatric findings associated with VCFS in adulthood, the current report describes two patients, one with VCFS who later developed a psychotic illness, and the other with chronic schizophrenia who was found to have multiple physical features suggestive of VCFS. The association between VCFS and psychotic illness and its possible significance for psychiatric genetics is discussed.

CLINICAL REPORTS

Case 1

Ms. A is a 25-year-old single woman, the first of two children born to a 28-year-old mother and 32-year-old father of unrelated Italian origin. During the pregnancy, the mother took sedative medication two or three times, and had a flu-like illness at 5 months' gestation. The patient was born full-term by forceps delivery after a long labour lasting 3 days. Because of her low birth weight of 2.3 kg, she was kept in an incubator in hospital for one month. In early infancy she had feeding problems with frequent regurgitation. At 6 months of age, she developed congestive heart failure and was found to have a moderate sized ventricular septal defect on cardiac catheterization. Later, a bicuspid aortic valve, a small atrial septal defect, mitral valve prolapse, and coronary artery-right ventricular fistula were also found. She underwent corrective surgeries for the cardiac conditions at 1 and 5½ years of age. Her speech was always hypernasal, and she was found to have velo-pharyngeal insufficiency on videofluoroscopic analysis. Her palate was high, but not cleft. Other physical features are outlined in Table I.

At age 18, a diagnosis of velo-cardio-facial syndrome was made at a medical genetic clinic based on the facial features, cardiac anomalies, and delayed development. A karyotype at 450 band resolution was normal: 46, XX. At age 25, a fluorescence in situ hybridisation (FISH) assay was performed using a cosmid probe N25 for locus D22S75 (Oncor Inc., Gaithersburg). The probe, which was previously shown to be deleted in patients with VCFS

[Driscoll et al., 1992], was hybridized to metaphase chromosomes from peripheral blood lymphocytes along with an internal control probe pH17(D22S39). The probes were digoxigenin-labelled and detected with FITC-labelled anti-digoxigenin; the chromosomes were counterstained with propidium iodide. A microdeletion was detected at the site of the N25 probe.

There was no family history of congenital cardiac or other physical abnormalities or psychiatric disorders. There was a first cousin with a mild learning disability, and a second cousin with mental retardation of unknown cause. Ms. A's sister developed a seizure disorder and severe mental retardation following DPT immunization in infancy.

Ms A's early developmental history was difficult to assess because of her poor health and frequent hospitalizations. She was a slow learner in school, eventually achieving a Grade 4 education through special classes which continued until age 21. WISC-R revealed a full-scale IQ of 54 (verbal IQ = 66, performance IQ = 49) at age 10, and similar findings on retesting at age 14. In the assessment at age 10, she was found to be especially weak in perceptual organization and had poor fine and gross motor coordination. She displayed perseverative thought processes, and could not inhibit repetitious thoughts and visual imagery.

The patient was described as shy and fearful, but pleasant and hardworking as a child. She smiled readily, but occasionally had outbursts of inappropriate laughter or crying. She was upset by changes in her environment, and easily hurt by criticism or disapproval from others. She became socially withdrawn beginning at age 7, and failed to develop any close relationships outside her family. She was reluctant to attend school and mix with other children, instead preferring solitary activities such as watching television.

Ms. A's parents first noticed a marked behavioral change in her when she was 22 years old. Over a period of few months, she gradually became more socially withdrawn and emotionally labile, with periods of crying, irritability, and shouting. She was seen talking to herself, and moving her hands as if responding to imaginary voices. For several weeks, she expressed love interest in three children she had seen in a movie, and believed that she was to go to California to marry them. She had no change in her appetite or energy level, and appeared neither depressed nor elated. However, her sleep was disrupted by agitation. Her parents, observing that Ms. A had lost touch with reality, sought medical help from her paediatrician. After two months of low dose chlorpromazine (50 mg daily), the unusual behaviors disappeared, her mood stabilized, and the anti-psychotic medication was stopped. At age 23, she was referred to one of the authors (A.S.B.) for a psychiatric consultation. A diagnosis of "psychotic disorder, not otherwise specified," using the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) [American Psychiatric Association, 1987] was made based on the history of delusions and probably hallucinations in the absence of a mood syndrome.

In the following year, after the patient's father suffered a myocardial infarction, psychotic symptoms reemerged. She displayed a thought form disorder with loosening of associations, talking continuously in a nonsensical fashion, jumping from topic to topic. She was irritable,

and had periods of agitation. Her sleep was poor, but her appetite was good. Similar grandiose delusions about marrying movie personalities recurred. Treatment with 2 mg of perphenazine daily resulted in resolution of the sleep disturbance, thought disorder, delusions, irritability, and agitation. Ms. A's limited verbal and intellectual skills unfortunately do not allow for the collection of sufficient information to determine whether her illness would fulfill the diagnostic criteria for schizophrenia or a psychotic mood disorder. Lifelong symptoms of fluctuations in mood, occasional outbursts of crying and agitation when crossed, and repetitive thinking persist. Ms. A functions at a moderately low level, living at home with her parents, and requiring assistance with basic grooming, dressing, and meal preparation.

Case 2

Mr. B is a 35-year-old, single, white man, the younger of two sons born to non-consanguineous parents of Russian-Jewish background. His mother had a flu-like illness during the pregnancy. He was a large, full-term baby at birth, weighing more than 10 pounds, and was delivered by forceps. He was physically healthy as a child, but was noticed by his parents to be "slow in all stages of development." At age 4, he was assessed by a paediatrician, and was considered to be "mildly retarded." Nonetheless, he was an average student in a regular school, and completed Grade 10 at age 16 with extra tutoring from his father and brother. Socially, he was shy, sensitive, and lonely, but did not have any behavioral problems as a child. His peer relationships were poor, and he was unable to make friends on his own. There was no family history of congenital cardiac or other physical anomalies. However, Mr. B's father noted a physical resemblance between a paternal uncle with schizophrenia and the patient. Unfortunately this uncle was unavailable for examination.

After Mr. B's mother was diagnosed with cancer when he was 16, he became socially withdrawn and "bizarre" in behavior. He refused to go to school. Instead he spent his time at home watching television or lying in bed. He began to display rhythmical rocking of his head. He became unmanageable by his family after half a year and was admitted to the psychiatric unit of a local hospital for 6 months. A diagnosis of schizoid personality was made.

Mr. B became overtly psychotic by age 18 with agitation and auditory and visual hallucinations. He reported seeing God and the devil, and hearing them talk to him. He had paranoid delusions that others were talking about him behind his back, and were trying to poison him. His thinking was disordered, with perseverative thought processes and loosening of associations. His affect was flat and inappropriate to his thoughts. On hospitalization later the same year, a diagnosis of chronic schizophrenia was made. Mr. B's psychiatric and behavioral features, including results of psychological testing at age 18, are shown in Table II. He was treated with various antipsychotic medications, with incomplete resolution of his psychotic symptoms. A course of electro-convulsive therapy at age 20 failed to provide further improvement. He had many subsequent episodes of exacerbation of his psychotic illness, resulting in six additional hospitalizations. Maintenance treatment of chlorpromazine 200 mg daily, and flupenthixol decanoate (a long-acting antipsychotic medication) 100 mg

every 2 weeks control most psychotic symptoms, but he continues to have residual symptoms, including disorganized speech, amotivation, and flat affect. His level of functioning has remained poor; he resides in a long-term care facility, and has never been gainfully employed. He meets criteria for a DSM-III-R diagnosis of chronic undifferentiated schizophrenia.

During a recent readmission, Mr. B participated in a research project and had a structured physical examination designed to detect dysmorphic features. He was found to have multiple features reported previously in VCFS patients [Shprintzen et al., 1981; Williams et al., 1985] (Table I). Other dysmorphic features noted in Mr. B included macrocephaly, large testes, and a somewhat long arm span (179 cm). Nasoendoscopy revealed mild velopharyngeal insufficiency but no clefting of the palate. Fundoscopic examination revealed mild vascular tortuosity. No cardiac anomalies were found on echocardiogram.

Cytogenetic studies, including fragile X analysis at the 450 band level were normal. FISH analysis was performed using the N25 probe for locus D22S75 as described for Ms. A. Two copies of the signal at D22S75 were visualized with fluorescent microscopy in 25/25 metaphase spreads, indicating no deletion at this site. Further delineation of the VCFS region [Driscoll et al., 1993] may clarify the issue of diagnosis for this patient.

DISCUSSION

As outlined in Tables I and II, these two patients had similar physical and psychiatric findings. Both showed many physical features consistent with VCFS. There were also many similarities in their developmental and psychiatric histories. Both patients were shy and withdrawn as children, with poor social relationships. They both had degrees of mental retardation (Mr. B had borderline mental retardation, and Ms. A had moderate mental retardation), with weaknesses in abstraction abilities and verbal reasoning. These premorbid features are consistent with the psychological profiles of the 26 paediatric VCFS patients described by Golding-Kushner et al. in 1985.

Both patients displayed similar psychiatric symptoms when ill. They suffered from auditory hallucinations, delusions, emotional irritability, and disorganized behavior, symptoms commonly found in patients with schizophrenia and other psychotic disorders. However, the manifestations of these psychotic processes were colored by the level of intellect of the patient. For example, although Ms. A was unable to describe auditory hallucinations, these were inferred from her behavior of talking to herself. The inability to obtain direct information from the patient limited the ability to make a formal DSM-III-R diagnosis of schizophrenia in her. Others have discussed the difficulty of diagnosing schizophrenia and major psychotic disorders in the mentally retarded population [Menolascino, 1988; Parsons, et al., 1984]. The prevailing opinion among clinicians supports making psychiatric diagnosis based more on changes in observed behavior than verbally reported symptoms in the mentally retarded population [Menolascino, 1988; Parsons, et al., 1984]. However, the DSM-III-R diagnostic criteria continue to rely on symptoms reported by the patient.

The course of illness, including the onset in young adulthood, precipitating stressful events, recurrent episodes of illnesses, and the low level of functioning, was similar between the two patients. Both improved on antipsychotic medications, although Mr. B did not respond to pharmacotherapy as well as Ms. A. Major physical illness in a parent preceded at least one of the psychotic episodes in both patients. These life events represented major stresses for them, since they had limited social relationships outside their immediate family, and depended on their parents for support and care. The poor functioning in both patients is typical of patients with major mental disorders, although the degree of mental retardation is also a significant contributing factor.

The major difference in these case histories is in their ascertainment. Ms. A, with many severe and life-threatening physical features of VCFS, was first seen in a cardiac clinic as an infant, and was subsequently diagnosed as having VCFS in her late teens in a medical genetic clinic before the onset of her psychotic illness. In contrast, because Mr. B had more subtle features of VCFS, recognition of his physical dysmorphism occurred much later, after the onset of his psychiatric illness, and only through a detailed physical examination designed to detect congenital anomalies. There may be more schizophrenic patients like Mr. B who have subtle features associated with VCFS that remain undetected despite routine medical examinations.

While a spectrum of psychiatric disturbances are known to occur in VCFS patients, there is little data on the precise prevalence of each of these disorders. Information available to date suggests a higher than expected overall frequency of psychotic disorders in VCFS patients [Shprintzen et al., 1992]. Schizophrenia occurs in approximately 1% of the general population, and the prevalence of psychotic disorders in the mentally retarded population is estimated to be four to six times that of the normal population [Parsons et al., 1984; Russell, 1988; Rutter, 1970]. Therefore, the observed 10% prevalence of psychiatric disorders (mostly paranoid schizophrenia [Shprintzen et al., 1992]) in a sample of VCFS patients ascertained through a craniofacial disorder clinic and not systemically screened for psychiatric illness, is likely not explicable on the basis of mental retardation alone, since only 40% of VCFS patients are mentally retarded [Goldberg et al., 1993].

A number of different mechanisms could explain an increased association between VCFS and psychotic illness. For example, one condition could cause or predispose to the development of the other. However, this appears unlikely with these two disorders. Alternatively, two medical disorders may be related to a common etiological factor. In this pathogenetic model VCFS and schizophrenia may share an overlapping developmental anomaly. In VCFS, defective development and migration of mesencephalic and cardiac neural crest cells are believed to play a significant role in the pathogenesis of mid-facial and cardiac dysmorphic features in VCFS [Thomas and Frias, 1987; Mansour et al., 1987; Scambler et al., 1992]. Schizophrenia is conceptualized by many researchers to be a neurodevelopmental disorder with structural and neurochemical abnormalities in the central nervous system [Weinberger, 1987; Murray et al., 1988]. Its pathogenesis may involve defective development and migration of brain cells prenatally, particularly in the temporal limbic structures [Bogerts, 1993]. Therefore, a mechanism disrupting cell migration could cause either disorder, schizophrenia or VCFS.

Schizophrenia has a complex inheritance pattern but there is consistent evidence of major genetic factors in its causation [Gottesman and Shields, 1982]. A contiguous gene model, in which a VCFS gene complex and a gene for schizophrenia or psychosis are adjacent to each other, could explain the occurrence of patients with varying number and severity of features of both VCFS and schizophrenia. For example, Ms. A, who has many severe physical features of VCFS but a milder psychotic disorder, may have a deletion encompassing the proximal boundary of the VCFS/DiGeorge critical region detected by the N25 probe [Driscoll et al., 1993], and extending into a neighbouring gene with expression as a psychotic illness. Whereas Mr. B, who has a severe case of schizophrenia and some mild features of VCFS, may have an overlapping deletion involving a smaller 22q11 deletion not detectable by the N25 probe, but incorporating a contiguous gene for psychosis. FISH assay on Mr. B using other 22q11 probes may detect a different microdeletion in the VCFS region.

With this contiguous gene model, chromosome 22q11 becomes a suitable candidate region to search for genes responsible for psychotic disorders and schizophrenia [Bassett, 1992]. Interestingly, a suggestive linkage result was recently reported for schizophrenia and markers from chromosome 22q12-q13, telomeric to the VCFS region [Pulver et al., 1993]. Although others have failed to replicate this result in other families using several 22q markers [Polymeropoulos et al., 1993], further genetic studies of the region are still needed.

The present report provides details of the developmental histories and psychotic illnesses of two patients to further characterize psychiatric syndromes found in patients with clinical features of VCFS. The patients were ascertained differently, one from a medical genetic clinic and the other from a psychiatric hospital, but they share many similar physical and psychiatric symptoms. Further delineation of molecular abnormalities in such patients may help clarify this interesting association. The overlap of clinical symptoms of VCFS and schizophrenia in varying degrees in these patients supports using a contiguous gene model to explain the increased association between VCFS and psychosis, and suggests chromosome 22q11 as a possible candidate gene region for future genetic studies of schizophrenia.

Acknowledgments

The authors would like to thank Dr. Teresa Costa for referring one of the patients, and Ellen Mak-Tam, Esther Capua, and Dr. Ikuko Teshima for their assistance in the FISH studies.

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington, DC: American Psychiatric Association; 1987. revised
- Arvystas M, Shprintzen RJ. Craniofacial morphology in the velo-cardio-facial syndrome. *J Craniofac Genet Dev Biol.* 1984; 4:39–45. [PubMed: 6736220]
- Bassett AS. Linkage analysis of schizophrenia: Challenges and promise. *Soc Biol.* 1992; 38:186–196.
- Bogerts B. Recent advances in the neuropathology of schizophrenia. *Schizophr Bull.* 1993; 19:431–445. [PubMed: 8322039]
- Driscoll DA, Salvin J, Sellinger B, Budarf ML, McDonald-McGinn DM, Zachai EH, Emanuel BS. Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis. *J Med Genet.* 1993; 30:813–817. [PubMed: 8230155]

- Driscoll DA, Spinner NB, Budarf ML, McDonald-McGinn DM, Zachai EH, Goldberg RB, Shprintzen RJ, Saal HM, Zonana J, Jones MC, Mascarello JT, Emanuel BS. Deletions and microdeletions of 22q11.2 in velo-cardio-facial syndrome. *Am J Med Genet.* 1992; 44:261–168. [PubMed: 1360769]
- Goldberg R, Motzkin B, Marion R, Scambler P, Shprintzen RJ. Velo-cardio-facial syndrome: A review of 120 patients. *Am J Med Genet.* 1993; 45:313–319. [PubMed: 8434617]
- Golding-Kushner KJ, Weller G, Shprintzen RJ. Velo-cardio-facial syndrome: Language and psychological profiles. *J Craniofac Genet Dev Biol.* 1985; 5:259–266. [PubMed: 4044789]
- Gottesman, Shields, J. *Schizophrenia: The Epigenetic Puzzle.* Cambridge: Cambridge University Press; 1982.
- Kelly D, Goldberg R, Wilson D, Lindsay E, Carey A, Goodship J, Burn J, Cross I, Shprintzen RJ, Scambler PJ. Confirmation that the velo-cardio-facial syndrome is associated with haplo-insufficiency of genes at chromosome 22q11. *Am J Med Genet.* 1993; 45:308–312. [PubMed: 8434616]
- Mansour A, Goldberg R, Wang F, Shprintzen RJ. Ocular findings in the velo-cardio-facial syndrome. *J Pediatr Ophthalmol.* 1987; 24:263–266.
- Meinecke P, Beemer FA, Schinzel A, Kushnik T. The velo-cardio-facial (Shprintzen) syndrome: Clinical variability in eight patients. *Eur J Pediatr.* 1986; 145:539–544. [PubMed: 3816857]
- Menolascino, FJ. Mental illness in the mentally retarded: Diagnostic and treatment issues. In: Stark, JA. Menolascino, FJ. Albarell, MH., et al., editors. *Mental Retardation and Mental Health: Classification, Diagnosis, Treatment, Services.* New York: Springer-Verlag; 1988. p. 109-123.
- Murray, RM., Lewis, SW., Owen, MJ., Foerster, A. The neurodevelopmental origins of dementia praecox. In: McGuffin, P., Bebbington, P., editors. *Schizophrenia: The Major Issues.* London: Heinemann; 1988. p. 90-107.
- Parsons, JA., May, JG., Menolascino, FJ. The nature and incidence of mental illness in mentally retarded individuals. In: Menolascino, FJ., Stark, JA., editors. *Handbook of Mental Illness in the Mentally Retarded.* New York: Plenum Press; 1984. p. 3-43.
- Polymeropoulos MH, Coon H, Byerly W, Gershon ES, Crow T, Delisi L, Merrill CR. Search for a schizophrenia locus on chromosome 22. *Psychiatr Genet.* 1993; 3:126.
- Pulver AE, Karayiorgou M, Demarchi N, Antonarakis S, Housman D, Kasch L, Kazazian H, Lamacz M, Lasseter VK, McGrath J, Meyers D, Nestadt G, Ott J, Ramu E, Wolyniec P, Childs B. A potential linkage for schizophrenia on chromosome 22q12-q13. *Psychiatr Genet.* 1993; 3:126.
- Russell, AT. The association between mental retardation and psychiatric disorder: epidemiological issues. In: Stark, JA. Menolascino, FJ. Albarell, MH., et al., editors. *Mental Retardation and Mental Health: Classification, Diagnosis, Treatment, Services.* New York: Springer-Verlag; 1988. p. 41-49.
- Rutter, M. Psychiatry. In: Wortis, J., editor. *Mental Retardation: An Annual Review.* Vol. 3. New York: Grune & Stratton; 1970.
- Scambler PJ, Kelly D, Lindsay E, Williamson R, Goldberg R, Shprintzen R, Wilson DI, Goodship JA, Cross IE, Burn J. Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet.* 1992; 339:1138–1139. [PubMed: 1349369]
- Shprintzen RJ, Goldberg RB, Golding-Kushner KJ. Letter to the editor: Late-onset psychosis in the velo-cardio-facial syndrome. *Am J Med Genet.* 1992; 42:141–142. [PubMed: 1308357]
- Shprintzen RJ, Goldberg RB, Lewin ML, Sidoti EJ, Berkman MD, Argamaso RV, Young D. A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: Velo-cardio-facial syndrome. *Cleft Palate J.* 1978; 15:56–62. [PubMed: 272242]
- Shprintzen RJ, Goldberg RB, Young D, Wolford L. The velo-cardio-facial syndrome: A clinical and genetic analysis. *Pediatrics.* 1981; 67:167–172. [PubMed: 7243439]
- Strong WB. Familial syndrome of right-sided aortic arch, mental deficiency, and facial dysmorphism. *J Pediatr.* 1968; 73:882–888. [PubMed: 5696314]
- Thomas IT, Frias JL. The heart in selected congenital malformations: A lesson in pathogenetic relationships. *Ann Clin Lab Sci.* 1987; 17:207–210. [PubMed: 3619396]
- Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry.* 1987; 44:660–669. [PubMed: 3606332]

- Williams MA, Shprintzen RJ, Goldberg RB. Male-to-Male transmission of the velo-cardio-facial syndrome: A case report and review of 60 cases. *J Craniofac Genet Dev Biol.* 1985; 5:175–180. [PubMed: 4019731]
- Williams MA, Shprintzen RJ, Rakoff SJ. Adenoid hypoplasia in the velo-cardio-facial syndrome. *J Craniofac Genet Dev Biol.* 1987; 7:23–26. [PubMed: 3597719]
- Wraith JE, Super M, Watson GH, Phillips M. Velo-cardio-facial syndrome presenting as holoprosencephaly. *Clin Genet.* 1985; 27:408–410. [PubMed: 3995791]

TABLE I

Comparison of Physical and Genetic Findings

	Ms. A	Mr. B
Head circumference	Decreased	Increased
Height (Percentile)	165 cm (65th percentile)	173 cm (65th percentile)
Malar hypoplasia	+	+
Narrow face	+	+
Broad nasal bridge	+	+
Palpebral fissures	Upslanting	Narrow
Retinal vascular tortuosity	–	+
Retruded chin	–	+
Ear anomalies	+	+
Cleft palate	–	–
Velopharyngeal insufficiency	++	+
Nasal speech	++	+
Cardiac anomalies	+++	–
Slender hands and fingers	+	+
Scoliosis	+	+
Karyotype	46, XX	46, XY
FISH analysis (N25 probe)	+	–

TABLE II

Comparison of Psychological and Psychiatric Features

	Ms. A	Mr. B
Verbal IQ	66	79
Performance IQ	49	79
Full-scale IQ	54	78
Special weaknesses	Perceptual organization Motor skills	Verbal reasoning Planning ability
Grade completed	4	10
Age of onset of psychosis	22	18
Repetitive behavior	+	++
Social withdrawal	++	++
Perseverative thoughts	++	++
Delusions	+	++
Hallucinations	+	++
Response to treatment	++	+
Recurrent episodes	+	++
Residual psychotic symptoms	–	+