

## Patterns of Dysmorphic Features in Schizophrenia

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### Abstract

Congenital dysmorphic features are prevalent in schizophrenia and may reflect underlying neurodevelopmental abnormalities. A cluster analysis approach delineating patterns of dysmorphic features has been used in genetics to classify individuals into more etiologically homogeneous subgroups. In the present study, this approach was applied to schizophrenia, using a sample with a suspected genetic syndrome as a testable model. Subjects ( $n = 159$ ) with schizophrenia or schizoaffective disorder were ascertained from chronic patient populations (random,  $n=123$ ) or referred with possible 22q11 deletion syndrome (referred,  $n = 36$ ). All subjects were evaluated for presence or absence of 70 reliably assessed dysmorphic features, which were used in a three-step cluster analysis. The analysis produced four major clusters with different patterns of dysmorphic features. Significant between-cluster differences were found for rates of 37 dysmorphic features ( $P < 0.05$ ), median number of dysmorphic features ( $P = 0.0001$ ), and validating features not used in the cluster analysis: mild mental retardation ( $P = 0.001$ ) and congenital heart defects ( $P = 0.002$ ). Two clusters (1 and 4) appeared to represent more developmental subgroups of schizophrenia with elevated rates of dysmorphic features and validating features. Cluster 1 ( $n = 27$ ) comprised mostly referred subjects. Cluster 4 ( $n = 18$ ) had a different pattern of dysmorphic features; one subject had a mosaic Turner syndrome variant. Two other clusters had lower rates and patterns of features consistent with those found in previous studies of schizophrenia. Delineating patterns of dysmorphic features may help identify subgroups that could represent neurodevelopmental forms of schizophrenia with more homogeneous origins.

### Keywords

22q11 deletion syndrome; cluster analysis; neurodevelopment; genetic subtype

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## INTRODUCTION

Schizophrenia is a complex disorder with substantial evidence for genetic causation [Jones and Murray, 1991; Waddington et al., 1999; Brzustowicz et al., 2000] and pathogenesis involving abnormal neurodevelopment [Weinberger, 1987; Murray et al., 1992]. There are undoubtedly multiple causes and mechanistic pathways to the clinical expression observable as schizophrenia. An approach based on genetic and neurodevelopmental strategies may be useful in identifying potential subgroups within schizophrenia. A similar approach has recently been advocated for the study of genetic disorders with significant behavioral components [Reiss et al., 2000]. We propose a subgrouping strategy based on the pattern of mild physical (dysmorphic) features in patients with schizophrenia to test this approach.

Dysmorphic features are defined as congenital physical features that, individually, are not associated with serious medical or cosmetic consequences [Jones, 1997]. Multiple dysmorphic features, however, often form recognizable patterns that may be associated with major organ malformations, such as congenital heart defects, and abnormal neurodevelopment manifest as learning disabilities, including mental retardation, and/or behavioral problems, including psychiatric disorders [Jones, 1997]. These patterns of physical and neurodevelopmental features may indicate the presence of specific genetic or other malformation syndromes [Jones, 1997]. There is consistent evidence for an increased prevalence of dysmorphic features (often referred to as minor physical anomalies) in schizophrenia [Gualtieri et al., 1982; Guy et al., 1983; Green et al., 1989, 1994a, 1994b; Lohr and Flynn, 1993; Murphy and Owen, 1996; Lane et al., 1997; Ismail et al., 2000]. Studies of dysmorphic features in schizophrenia have tended to focus on the number rather than the pattern of features, and these features have generally been attributed to prenatal insults to the fetus and/or birth or perinatal complications [Simonds et al., 1981; O'Callaghan et al., 1991; Cantor-Graae et al., 1994; Green et al., 1994a], rather than a possible association with underlying genetic complications. Also, despite the prevalent neurodevelopmental hypothesis of schizophrenia [Weinberger, 1987], studies of dysmorphic features in schizophrenia have generally not included subjects with learning disabilities who could help in understanding the genetics of neurodevelopment [Muir, 2000; Reiss et al., 2000].

22q11 deletion syndrome (22qDS) represents an identifiable genetic syndrome associated with specific patterns of dysmorphic features and increased rates of psychosis in adults [Murphy et al., 1999; Bassett et al., 2000]. 22qDS is characterized by a microdeletion on chromosome 22q11.2 [Scambler et al., 1992], a variable pattern of dysmorphic features (typically including long, narrow face, flat cheeks, narrow palpebral fissures, retruded jaw, and tapered fingers), hypernasal speech, sometimes congenital heart defects, and typically borderline to mild mental retardation [Cohen et al., 1999; Tobias et al., 1999]. About 25% of adults with 22qDS have schizophrenia [Pulver et al., 1994; Murphy et al., 1999], and chromosome 22q11.2 deletions are 40 to 80 times more common in schizophrenia than the general population [Bassett et al., 2000]. Increased rates of dysmorphic features, cognitive dysfunction, and structural brain abnormalities in both 22qDS [Shprintzen et al., 1978; Bingham et al., 1997; Murphy et al., 1998] and schizophrenia [Murray et al., 1992; Waddington et al., 1999] have led researchers to propose 22qDS as a model for a genetic

neurodevelopmental subtype of schizophrenia (22qDS-SZ) [Bassett et al., 1998; Bassett and Chow, 1999; Murphy et al., 1999; Reiss et al., 2000]. Identification of 22qDS in populations of patients with schizophrenia [Karayiorgou et al., 1995; Bassett et al., 1998] suggests that determining patterns of dysmorphic features may reveal this and other potential etiologic subtypes of schizophrenia.

Cluster analysis is a statistical method that can be used to help classify patients into syndromes based on patterns of features. In the clinical genetics literature, the validity of this approach has been shown using dysmorphic features in subjects with known or suspected genetic syndromes [Preus, 1980, 1984; Preus and Ayme, 1983]. Similar to factor analysis, cluster analysis attempts to delineate patterns of associations and identify subgroups within a population of interest [Rapkin and Luke, 1993], therefore a normal control group is often not employed in this study design. Instead, a testable model to assess the overall validity of the clustering methods used can be included [Preus, 1980]. In the present study, we applied a cluster analysis approach using dysmorphic features to attempt to delineate subgroups within schizophrenia that may have increased homogeneity. We used a sample representative of patients with chronic schizophrenia at provincial (state) psychiatric hospitals. Following the methodology employed previously [Preus, 1980, 1984; Preus and Ayme, 1983], we included subjects with a clinical diagnosis of 22qDS-SZ as a testable model of a genetic subtype of schizophrenia. The specific hypotheses tested were that subgroups of schizophrenic subjects identified by cluster analysis would display differing patterns and rates of dysmorphic features; they would have differing rates of mild mental retardation and congenital heart defects as well as age at onset of psychosis; and one or more of these subgroups may represent more homogeneous genetic and/or neurodevelopmental subtypes of schizophrenia. As a testable model, most of the 22qDS patients should group together if the clustering methods used are valid.

## MATERIALS AND METHODS

### Subjects and Assessments

The 159 participating subjects had chronic schizophrenia (n = 143) or schizoaffective (n = 16) disorder. All subjects provided informed consent to participate in the study. Diagnoses were confirmed by research psychiatrists (A.S.B., E.W.C.C., W.G.H.) from extensive medical records using Structured Clinical Interviews for DSM-III-R (SCID-I) criteria [American Psychiatric Association, 1987]. Information was recorded from available medical records on age at onset of psychosis, defined as age at first hospitalization, and presence or absence of mild mental retardation and congenital heart defects requiring surgery. Subjects with mild mental retardation were deliberately included in the sample because community samples of schizophrenia demonstrate there is a significant prevalence (around 13.3%) of individuals with low IQ (estimated IQ < 74) in schizophrenia [David et al., 1997] and mild mental retardation is often present in genetic or other malformation syndromes [Winter, 1996; Jones, 1997]. In the majority (n = 20) of 30 subjects diagnosed with mild mental retardation (IQ < 70), the diagnosis was based on available standardized IQ testing results; chart diagnosis based on educational history and level of functioning was used for the remaining 10 subjects.

The sample comprised two groups. Subjects in the first group (random,  $n = 123$ ) were ascertained from three provincial psychiatric hospitals, randomly ( $n = 63$  from one hospital and  $n = 30$  from another) or from consecutive admissions ( $n = 30$ ). Subjects in the second group (referred,  $n = 36$ ) were referred by clinicians from the same chronic patient population as the random sample. Thirty-one subjects were referred for evaluation of possible 22qDS and met two or more clinical referral criteria suggestive of 22qDS [Bassett and Chow, 1999]: 30 (96.8%) had two or more characteristic facial features, 27 (87.1%) had a history of learning disabilities and/or mental retardation, 23 (74.2%) had palatal abnormalities, 11 (35.5%) had other major congenital dysmorphic features (e.g., talipes), 7 (22.6%) had a history of congenital heart defects, and 1 (3.2%) had a history of hypocalcemia. The remaining five subjects were referred with known 22q11.2 deletions.

Subjects were assessed for dysmorphic features using a Standardized Physical Examination for Dysmorphic Features (SPEDF) developed by our group (A.S.B. and R.W.) to aid in the comprehensive assessment of congenital dysmorphic features in adults. Most subjects were assessed by a single physician (e.g., A.S.B. or E.W.C.C.) blind to the specific degree of any learning disability. The SPEDF was created to capture dysmorphic features in the general population rather than features associated with specific syndromes. Therefore, some dysmorphic features associated with 22qDS (e.g., nose with bulbous tip) were not specified on the original form and were not included in analyses since they were not consistently rated for all subjects. Raters were blind to cytogenetic testing results, except for the five subjects referred with known 22qDS.

The SPEDF comprises 122 directly assessed features coded as present or absent. A feature had to be rated as both congenital and dysmorphic, and the age and ethnicity of each subject were considered in all ratings. Therefore, age-related variables (e.g., prematurely gray hair) were rated as unknown in older subjects, and variables associated with specific ethnic backgrounds (e.g., narrow palpebral fissures in Asian subjects) were rated as normal. Five additional features (short stature, microcephaly, macrocephaly, hypertelorism, hypotelorism) were determined post hoc to be present or absent, based on three continuous measurement variables (height, head circumference, and inner canthal distance) [Hall et al., 1989]. Height and maximum occipitofrontal head circumference (OFC) were measured to the nearest 0.1 cm as previously described [Bassett et al., 1996]. Height was used to define short stature (height < 10th percentile, < 164.0 cm for males and < 154.5 cm for females) [Hall et al., 1989]. OFC and height were used to determine microcephaly (<3rd percentile) and macrocephaly (> 97th percentile), based on standard curves for adults [Bushby et al., 1992]. Distance between inner canthi was measured to the nearest 0.1 cm using a transparent ruler to determine hypertelorism (inner canthal distance > 2 standard deviations [SD] from the published mean, or > 3.65 cm) and hypotelorism (inner canthal distance < 2 SD from the published mean, or 2.64 cm) [Hall et al., 1989].

## Statistical Analyses

**Demographics**—Random and referred subjects were compared on basic demographic variables to evaluate possible clinical differences in the samples that could be important in the interpretation of clusters formed. All analyses were nonparametric due to nonnormal

distribution of the samples. Group differences for binary-coded variables were evaluated using the chi-square statistic. Continuous variables were assessed using the Wilcoxon two-sample z-test or Kruskal-Wallis nonparametric analysis of variance (ANOVA) for comparison between three or more samples.

**Interrater reliability**—Reliability analyses were performed on a subset of subjects ( $n = 50$ ) assessed by two or more raters. Of the SPEDF's 127 binary variables, 49 were excluded from the cluster analysis for the following reasons: 30 had low ( $< 3\%$ ) frequency of occurrence and were dropped to minimize the number of variables needed for the cluster procedure [Anderberg, 1973; Rapkin and Luke, 1993], 10 were deemed likely to be acquired, and nine were urogenital abnormalities not consistently assessed in all subjects. Of the remaining 78 variables, Cohen's kappa ( $\kappa$ ) [Cohen, 1960] was used to assess the 73 variables directly rated as binary. Reliability of the three continuous variables used to determine the five other binary variables (short stature, microcephaly, macrocephaly, hypertelorism, and hypotelorism) was assessed using the intraclass correlation coefficient (ICC) [Shrout and Fleiss, 1979]. Variables with poor interobserver agreement ( $\kappa < 0.4$ ) were excluded from further analyses [Mitchell, 1979]. Remaining variables were divided into craniofacial features and other features.

### Cluster Analyses

Cluster analyses were performed with data from all 159 subjects. Dysmorphic features used in the cluster analysis were coded as 0 (absent) or 1 (present) to ensure equal weighting of variables [Anderberg, 1973; Sneath and Sokal, 1973]. A three-step procedure was followed in order to minimize the potential biases of correlated variables and a priori investigator expectations. In step 1, a principal components analysis (PCA) transformed dysmorphic feature variables into five clustering variables to control for the possible biasing effects of correlated variables [Borgen and Weiss, 1971; Lorr, 1983]. In step 2, the Ward minimum variance and average linkage hierarchical cluster methods were performed on the five PCA-derived clustering variables in order to determine the number of target clusters for step 3 [Rapkin and Luke, 1993]. In step 3,  $k$  means iterative cluster analysis was performed using the five PCA-derived clustering variables determined in step 1 and the number of target clusters determined in step 2.

The stability of clusters formed was assessed by repeating step 3 across the range of target clusters suggested by step 2. Demographic factors (sex, age at assessment, and ethnicity) were compared across clusters. Correlations between total number of dysmorphic features and age at onset of psychosis were examined and the number and distribution of dysmorphic features were examined in the entire sample and across clusters. Between-cluster validity was examined by comparing rates of individual dysmorphic features, mental retardation, and congenital heart defects as well as median age at onset of psychosis across clusters. These validating factors were chosen as they differ between clusters, are clinically relevant to the samples under study, and were not used in the cluster analysis procedure [Rapkin and Luke, 1993]. Within-cluster validity was examined by comparing rates of dysmorphic features between males and females (to assess possible sex differences) and between early ( 21

years) and later (> 21 years) age at onset of psychosis within each cluster (to assess differences that may be related to an early age at onset).

Differences in frequencies were assessed using chi-square and continuous variables were assessed using the Kruskal-Wallis one-way analysis of variance by ranks. All analyses were performed using the SAS system for Windows, version 6.12 (SAS, Cary, NC); SAS/STAT User's Guide was consulted for analysis procedures [SAS Institute, 1990, 1997].

### Posthoc Assessments

**Specialized cytogenetic testing**—The 31 previously undiagnosed referred group subjects who met clinical screening criteria for 22qDS [Bassett and Chow, 1999] were tested in a related study [Bassett and Chow, 1999] for a 22q11.2 deletion using standard fluorescence in situ hybridization (FISH) methods and a commercially available probe (either N25 or TUPLE 1) from the commonly deleted region [Demczuk and Aurias, 1995]. Subjects from the random group who were found to meet proposed clinical criteria for 22qDS [Bassett and Chow, 1999] or other possible genetic syndromes on review of features by a medical geneticist (R.W.) also had cytogenetic testing.

## RESULTS

### Demographics

There were no significant differences between random (83 males, 40 females) and referred (19 males, 17 females) groups with respect to sex (chi-square = 2.62,  $df = 1$ ,  $P = 0.11$ ) or median age at onset of psychosis (21 years, range 13–51 years, and 19 years, range 11–36 years, respectively;  $z = -1.75$ ,  $P = 0.08$ ). The referred group had a younger median age at assessment (28.5 years, range 16–63 years, vs. 38 years, range 16–86 years;  $z = -4.27$ ,  $P = 0.0001$ ) and proportionately more Caucasian subjects (91.7% vs. 76.4%,  $df = 1$ , chi-square = 4.03,  $P = 0.05$ ) than the random group. As expected, the proportion of subjects with mild mental retardation was significantly higher in the referred group ( $n = 18$ , 33.3%) than the random group ( $n = 12$ , 14.6%; chi-square = 6.36,  $df = 1$ ,  $P = 0.012$ ).

### Dysmorphic Features and Interrater Reliability

Eight (11.0%) of 73 binary variables (asymmetrical ears, prominent nasal bridge, frontal bossing, mouth with downturning corners, large tongue, short neck, pectus excavatum, gap between first and second toes) with poor interobserver agreement were excluded from further analyses ( $\kappa < 0.4$ ) [Mitchell, 1979]. The kappa statistic could not be computed for 13 (17.8%) variables (indicated in Table I) that were rated absent by all raters. For the remaining 52 (71.2%) variables, mean interobserver agreement as assessed by the Cohen kappa was 0.63 (SD = 0.22, range 0.4–1.00). In contrast to the ICC, mean kappa values greater than 0.6 are considered good to excellent [Mitchell, 1979; Keller et al., 1995]. Reliability was also high for height (ICC = 0.997), head circumference (ICC = 0.985), and inner canthal distance (ICC = 0.926). The 70 dysmorphic features (44 craniofacial and 26 other) used for the cluster analyses are listed in Table I. The median number of dysmorphic features for the entire sample was 9 (range, 1–30). Referred subjects had more dysmorphic

features (median = 16, range 5–30) than random subjects (median = 7, range 1–20;  $z = 7.21$ ,  $P = 0.0001$ ).

### Cluster Analyses

The Ward minimum variance and average linkage cluster analyses suggested seven-cluster and four-cluster solutions, respectively. Results were essentially unchanged when the five subjects who had already been diagnosed prior to their physical examination were omitted (results not shown), therefore they were included for all analyses. The  $k$  means cluster analysis technique was performed with four, five, six, and seven target clusters to assess stability of the clusters. The most logical solution as determined by the investigators was the six-cluster solution, based on the assignment of most referred subjects to cluster 1 (Fig. 1). Clustering of subjects together was relatively consistent across four-, five-, six-, and seven-target-cluster solutions, demonstrating stability of clusters. As expected, 14 of the 18 22qDS subjects (78%) clustered together in cluster 1; the remaining subjects were allocated to clusters 2 ( $n = 1$ ), 3 ( $n = 1$ ), and 6 ( $n = 2$ ; Fig. 1). Clusters 2 and 6 were considered outliers as they contained less than 5% of the total sample size [Edelbrock, 1979] and were dropped from subsequent analyses, leaving four major clusters (1, 3, 4, and 5).

### Between-Cluster Validity

The four major clusters differed qualitatively (Table I) and quantitatively (Fig. 2) with respect to occurrence of dysmorphic features. Thirty-seven (52.9%) of the 70 dysmorphic features listed in Table I differed significantly ( $P = 0.05$  to  $P = 0.001$ ) in frequency across the four major clusters. The median number of dysmorphic features was significantly different across the clusters (medians were 16, 11.5, 8, and 6 for clusters 1, 4, 5, and 3, respectively;  $F = 60.26$ ,  $P < 0.0001$ ; Fig. 2). Clusters 1 and 4 had higher rates of craniofacial dysmorphic features than clusters 3 and 5 (medians: 11, 7.5, 5, and 4 for clusters 1, 4, 5, and 3, respectively;  $F = 74.8$ ,  $P < 0.0001$ ). Rates of other dysmorphic features were lowest for cluster 3 subjects (medians: 4, 4.5, 4, and 3 for clusters 1, 4, 5, and 3, respectively;  $F = 11.5$ ,  $P < 0.0001$ ). The distributions of rates of dysmorphic features for the total sample and each of the clusters appeared relatively normal and unimodal, with the exception of cluster 4, which appeared to be somewhat bimodal (Fig. 2).

The clusters also differed on variables not used in the cluster analysis (Table II). Sex distributions differed significantly across clusters, with an equal sex distribution in clusters 1 and more women in cluster 4 compared with male excess in clusters 3 and 5. Clusters did not differ significantly on ethnicity. Rates of mental retardation and congenital heart defects were significantly different across clusters (Table II). These features were more prevalent in cluster 1, as expected, and in cluster 4. Median age at onset of psychosis (20 years, range 11–34 years; 19 years, range 14–46 years; 22 years, range 14–45 years; and 21 years, range 13–43 years, for clusters 1, 3, 4, and 5, respectively) was not significantly different between clusters ( $F = 1.69$ ,  $P = 0.17$ ) and was not correlated with the total number of dysmorphic features ( $r = -0.06$  for all 153 subjects, and  $r = 0.13$ ,  $-0.07$ ,  $-0.19$ , and  $-0.05$  for clusters 1, 3, 4, and 5, respectively).

### Within-Cluster Validity

There were no significant differences after Bonferroni correction was applied in rates of dysmorphic features between males and females or between subjects with early and later age at onset within any of the four major clusters.

### (Post hoc) Results

**Reviews by medical geneticist and specialized cytogenetic testing**—Thirteen (41.9%) of the 31 referred subjects assessed using FISH were found to have a chromosome 22q11.2 deletion. Including the five subjects (all in cluster 1) referred with known deletions, the referred group comprised 18 22qDS subjects and 18 nondeleted subjects. Five random subjects, two in cluster 1, one in cluster 2, and two in cluster 5, were also found to meet proposed clinical screening criteria for 22qDS [Bassett and Chow, 1999]. None of these subjects was found to have a 22q11.2 deletion or other chromosomal anomaly. Three other random subjects had clinical features suggestive of other possible genetic syndromes and were assessed by a medical geneticist. A female subject from cluster 4 with mild mental retardation, short stature, minor ear anomalies, small hands and feet, cubitus valgus, and kyphosis met clinical criteria for possible Turner syndrome. Subsequent cytogenetic testing revealed a mosaic Turner syndrome variant (45,X in 10 cells; 46,XX in 19 cells; 47,XXX in one cell). A cluster 3 subject had features (tall stature, myopia, arm span greater than height, mild hypotonia, and a history of spontaneous pneumothoraces) suggestive of an unspecified connective tissue disorder. Another cluster 3 subject with multiple café-au-lait spots was assessed for possible neurofibromatosis, but did not meet criteria for a clinical diagnosis. Neither of the latter two subjects had a detectable chromosomal abnormality.

## DISCUSSION

This study found four major subgroups in a large sample of subjects with chronic schizophrenia, with differing patterns and rates of dysmorphic features and other validating factors that did not appear to be related to ethnicity or age. The results indicate the potential importance of the pattern, in addition to the number, of dysmorphic features in helping to identify possible subgroups of schizophrenia that may have relevance to a genetic neurodevelopmental pathogenesis. This study presents a complementary strategy to research involving familial (transmitted) forms of schizophrenia and risk research attempting to differentiate schizophrenia from control samples. Many genetic syndromes occur as spontaneous (not inherited) mutations that may involve structural abnormalities of chromosomes [Muir, 2000], but variability of features in syndromes may be related to random (stochastic) effects [Kurnit et al., 1987]. Thus, the overall pattern of dysmorphic features may be more indicative of common etiology than an individual feature.

### Clusters Suggestive of Genetic and/or Malformation Syndromes

Although the clusters identified in this study undoubtedly contain heterogeneous groups of subjects with schizophrenia, there is some evidence that two of the clusters may represent more homogeneous subgroups perhaps related to specific neurodevelopmentally related etiologies. Cluster 1 comprises mainly subjects with a known genetic subtype of schizophrenia, 22qDS, and/or clinical features suggestive of the syndrome. These subjects



served as a testable model that validated the cluster analysis solutions. Cluster 1 had high rates of palatal anomalies, including narrow palate and high palate that were not part of the ascertainment criteria for the referred group. This is consistent with increased rates of palatal anomalies reported in 22qDS [Cohen et al., 1999] and schizophrenia [Green et al., 1987, 1989; McGrath et al., 1995; Waddington et al., 1995; Lane et al., 1997]. Cluster 4 is the other cluster that may be more likely to contain subjects with genetic or malformation syndromes and had the second highest median number of dysmorphic features. This cluster had elevated rates of mild mental retardation and congenital heart defects, but a different pattern of dysmorphic features from cluster 1, including abnormal hair whorls, inner epicanthal folds, and sacral dimple. These features were not suggestive of any single specific genetic syndrome, and the somewhat bimodal distribution of the number of dysmorphic features in this cluster suggests that more than one neurodevelopmental syndrome is likely to be present. Interestingly, one subject in this cluster was diagnosed with mosaic Turner syndrome. Mosaic Turner syndrome occurs in women and is characterized by a normal karyotype in some cells (i.e., 46,XX) and a missing X chromosome in other cells (i.e., 45,X). Dysmorphic features in this syndrome include short stature and webbed neck, sometimes congenital heart defects, specific learning disabilities (e.g., visual-spatial deficits) [Jones, 1997], and an association with schizophrenia [Bassett et al., 2000; Prior et al., 2000].

### Clusters Consistent With Literature

The two other major clusters (clusters 3 and 5) had lower overall rates of dysmorphic features, but elevated rates of individual features found in previous studies to be relatively prevalent in schizophrenia: clinodactyly (cluster 5) [Green et al., 1989; McGrath et al., 1995], protuberant ears (cluster 5) [Lane et al., 1997], macrocephaly (clusters 3 and 5) [Green et al., 1989], and high palate (cluster 3) [Green et al., 1987; Ismail et al., 1998]. Individual dysmorphic features are usually of no significance [Jones, 1997]. However, the number and patterns of features in these clusters are consistent with generalized developmental disturbances in schizophrenia [Weinberger, 1995]. The lower rates of mental retardation and greater preponderance of males in these two clusters suggest these subjects may be more comparable to schizophrenia samples usually reported in the literature.

### Comparison of Results to Literature

Results from the present study are consistent with reports suggesting that higher rates of dysmorphic features in schizophrenia may be driven by one or more subgroups of subjects with high rates [Green et al., 1994b; McGrath et al., 1995; Griffiths et al., 1998]. Although a unimodal and relatively normal distribution of dysmorphic features has been cited as evidence for the lack of a subgroup effect in schizophrenia [Lane et al., 1997; Ismail et al., 2000], results from the present study suggest that the overall frequency distribution may conceal varying rates (Fig. 2), as well as varying patterns (Table I), of dysmorphic features in subgroups. The overlap of referred and random subjects in three of the four major clusters is consistent with previous reports of overlap among individuals with known genetic syndromes [Preus and Ayme, 1983; Preus, 1984]. This is due to both the nonspecific nature of many dysmorphic features and the considerable variability among individuals with the same genetic syndrome [Jones, 1997]. Age at onset of psychosis did not differentiate clusters, and consistent with most [O'Callaghan et al., 1991; Lohr and Flynn, 1993;

Alexander et al., 1994; McGrath et al., 1995] but not all [Green et al., 1987] studies, age at onset was not found to be correlated with the overall number of dysmorphic features. This is likely because most of the subjects had severe, chronic schizophrenia characterized by relatively early age at onset. Therefore, the present sample may represent multiple neurodevelopmental forms of schizophrenia where age at onset may not be a discriminating factor. These converging results, despite differing methodologies, suggest that dysmorphic features may be more useful than age at onset of psychosis for the identification of putative subgroups among neurodevelopmental forms of schizophrenia.

### Advantages

The current study applied a genetic approach to identifying possible subgroups in schizophrenia using dysmorphic features as markers of both abnormal development and possible genetic syndromes. The samples used ensured that a sufficient number of subjects with features of a genetic syndrome (22qDS) with known etiology would be present to act as a testable model of a genetic subtype of schizophrenia and therefore to validate the cluster analysis methods. Further, the present study included subjects with IQ < 70, an understudied group despite their clinical similarities to and prevalence in chronic populations of schizophrenia [Doody et al., 1998; Sanderson et al., 1999]. Mild mental retardation is a feature of many genetic syndromes involving abnormal neurodevelopment [Winter, 1996; Jones, 1997]. Therefore, including these subjects could have increased the likelihood of identifying genetically relevant subgroups.

The assessment tool used, the SPEDF, reliably assessed 70 dysmorphic features that may be associated with genetic syndromes in adults. Most previous studies of dysmorphic features in schizophrenia have employed varying modifications of the Waldrop scale [Waldrop et al., 1968]. Several researchers have pointed out the limitations of this scale [Alexander et al., 1994; O'Callaghan et al., 1995; Murphy and Owen, 1996], which is comprised of only 18 features and was developed to assess dysmorphic features, primarily of Down syndrome, in pediatric samples [Waldrop et al., 1968]. One study used an anthropometric approach [Lane et al., 1997], a comprehensive but labor-intensive method requiring special instruments. In contrast, the current study employed a 30-min clinical assessment of dysmorphic features.

### Study Limitations

The present study has several limitations. First, referred group subjects were ascertained partly from patterns of dysmorphic features and developmental features such as mental retardation and congenital heart defects [Bassett and Chow, 1999]. Therefore, results for cluster 1 were anticipated from the study design. However, all subjects met clinical criteria [Bassett and Chow, 1999] for a suspected genetic syndrome with known etiology; therefore, the fact that they mostly clustered together provided an initial validator of the overall cluster solutions. Second, cluster analysis techniques are somewhat arbitrary, and it is up to the researcher ultimately to decide the number of clusters that makes the most sense [Lorr, 1983]. To minimize the possible effects of a priori expectations, hierarchical and iterative methods were combined to produce discrete clusters [Milligan and Sokol, 1980]. Third, most of the features were clinically determined as present or absent. However, the current study used only reliably assessed features, and a subjective approach to assessing

dysmorphic features is commonly used for genetic and other malformation syndromes [Preus and Ayme, 1983; Jones, 1997]. This approach also predominates in the Waldrop scale, used in most other studies of dysmorphic features in schizophrenia [Gualtieri et al., 1982; Guy et al., 1983; Green et al., 1987, 1989, 1994b; O'Callaghan et al., 1991, 1995; Lohr and Flynn, 1993; Alexander et al., 1994; Cantor-Graae et al., 1994; McGrath et al., 1995; Waddington et al., 1995; Griffiths et al., 1998; Weinstein et al., 1999; Ismail et al., 2000]. Fourth, assessment of some features may have been confounded by age or ethnicity effects. For example, cluster 4 had an older median age of assessment suggesting that some dysmorphic features in this subgroup may have been acquired. However, age-related features are unlikely to be the primary reason for the clustering results, since the initial cluster analysis step should have minimized effects of correlated variables (e.g., age-related) and the common features in this subgroup (e.g., narrow/slanted palpebral fissures, flat occiput, hair whorl abnormalities) are unlikely to be age-related. Fifth, mild mental retardation was determined from chart diagnosis rather than available IQ testing results in one-third of cases. It is possible that some of these subjects could have had borderline mental retardation. Finally, subjects had a severe, chronic form of schizophrenia and a relatively high rate of mild mental retardation that is similar to rates in other unselected samples [David et al., 1997] but may be less generalizable to samples common in the research literature, which may have higher levels of education or less severe forms of the illness.

### Summary and Future Research

The value of assessing dysmorphic features in schizophrenia may lie in the pattern, as well as the number, of features. The manner in which dysmorphic features group together may sometimes offer a clue to the identification of potential underlying genetic or teratogenic abnormalities. Future research in this area should include systematic specialized cytogenetic and/or molecular testing of individuals with schizophrenia with certain patterns and elevated rates of dysmorphic and/or other features, who may be at increased risk for specific genetic syndromes [Bassett et al., 2000]. Although the phenotype of two identifiable genetic syndromes (22qDS and mosaic Turner syndrome) associated with schizophrenia is variable and may be subtle, an increased index of suspicion for these syndromes and their pattern of features may enhance their identification [Bassett et al., 2000]. Investigation of brain structure and functioning and neurocognitive deficits could help identify specific neurodevelopmental abnormalities associated with subgroups identified by patterns of dysmorphic features and/or cytogenetic or molecular abnormalities. This behavioral neurogenetics approach has recently been advocated for the multilevel investigation of genetic syndromes with significant cognitive and neuropsychiatric components, such as 22qDS [Reiss et al., 2000]. Our group has documented qualitative [Chow et al., 1999] and quantitative [Chow et al., in press] structural brain abnormalities in adults with 22qDS and schizophrenia. Further delineation of patterns of dysmorphic features and cognitive functioning and structural brain abnormalities may lead to the identification of subgroups with other, as yet unrecognized genetic or developmental etiologies for schizophrenia. Studying such etiological subtypes may improve our understanding of the pathogenesis of neurodevelopmental forms of schizophrenia that could be relevant to the illness in general.

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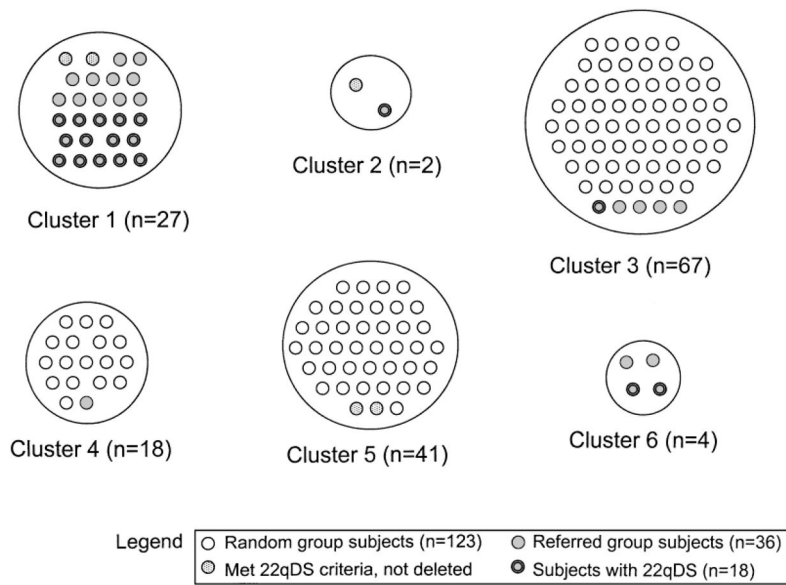
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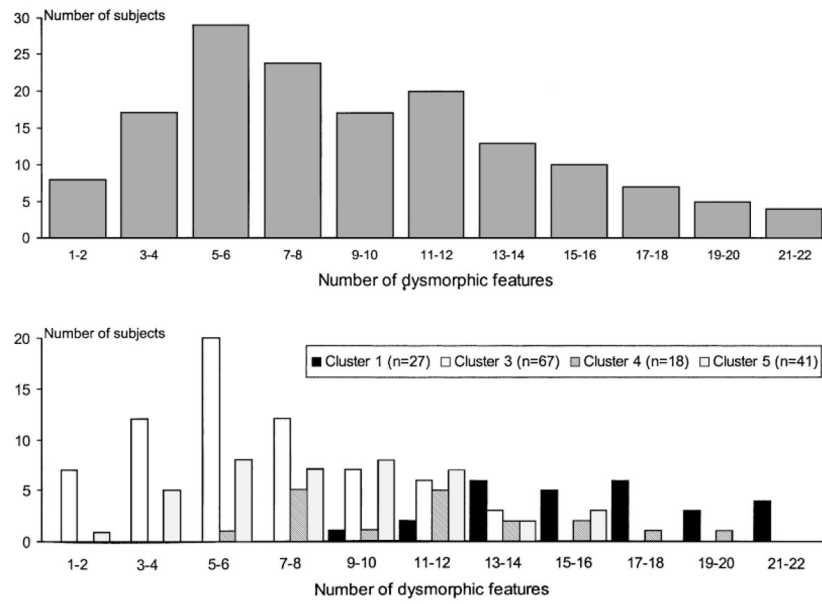
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**Fig. 1.** The six-cluster solution grouping 159 subjects with schizophrenia, as produced by the  $k$  means cluster analysis. The four major clusters (1, 3, 4, and 5) comprise 153 subjects. Clusters 2 and 6 each contained less than 5% of the sample size, therefore they were considered outliers and dropped from analyses.





**Fig. 2.** The top graph shows the distribution of number of dysmorphic features for the sample of 153 subjects from the four major clusters (1, 3, 4, and 5). The bottom graph reveals the distributions of dysmorphic features for clusters 1 (n = 27), 3 (n = 67), 4 (n = 18), and 5 (n = 41) separately.

TABLE I

Validity of Cluster Solutions Using Dysmorphic Features

	Occurrence <sup>d</sup> (%)					Chi-square (df = 3)	P value
	Cluster 1 (n = 27)	Cluster 3 (n = 67)	Cluster 4 (n = 18)	Cluster 5 (n = 41)	Cluster 5 (n = 41)		
Craniofacial dysmorphic features (n = 44)							
Hypenasal voice	92.6	4.5	0	4.9	111.0	0.001	
Flat cheeks	92.6	26.9	44.4	53.7	34.13	0.001	
Narrow/slanted palpebral fissures	85.2	9.0	55.6	12.2	66.58	0.001	
High palate	70.4	20.9	0	12.2	40.0	0.001	
Small jaw	66.7	11.9	11.1	2.4	50.16	0.001	
Large nose	66.7	16.4	27.8	12.2	30.87	0.001	
Small eyes	63.0	10.5	38.9	7.3	39.47	0.001	
Small mouth	55.6	14.9	11.1	7.3	27.8	0.001	
Broad nasal bridge	44.4	6.0	27.8	17.1	20.28	0.001	
Low-set ears	40.7	10.5	11.1	9.8	15.58	0.001	
Posteriorly rotated ears	37.0	6.0	5.6	12.2	17.54	0.001	
Narrow palate	37.0	3.0	5.6	4.9	27.7	0.001	
Lip abnormalities	37.0	13.4	22.2	2.4	15.59	0.001	
Flat occiput	33.3	11.9	50.0	41.5	16.92	0.001	
Flat supraorbital ridges	33.3	3.0	33.3	7.3	23.45	0.001	
Cleft palate	14.8	0	0	0	19.17	0.001	
Hair whorl abnormality <sup>b</sup>	7.4	11.9	50.0	17.1	16.87	0.001	
Low hair line	3.7	4.5	33.3	12.2	14.82	0.002	
Inner epicanthal folds	3.7	1.5	27.8	12.2	15.35	0.002	
Small ears	40.7	10.5	5.6	19.5	14.21	0.003	
Malformed ears	33.3	7.5	33.3	14.6	12.99	0.005	
Small nose	0	7.5	22.2	2.4	10.36	0.02	
Macrocephaly	7.4	20.9	5.6	34.2	10.08	0.02	
Low nasal bridge <sup>b</sup>	11.1	0	0	4.9	8.46	0.04	
Widow's peak	22.2	9.0	33.3	24.4	7.93	0.05	
Hypertelorism	3.7	9.0	27.8	9.8	7.27	0.06	

	Occurrence <sup>a</sup> (%)					Chi-square (df = 3)	P value
	Cluster 1 (n = 27)	Cluster 3 (n = 67)	Cluster 4 (n = 18)	Cluster 5 (n = 41)	Cluster 5 (n = 41)		
Asymmetrical face	29.6	19.4	33.3	9.8	6.20	0.10	
Iris abnormalities <sup>b</sup>	0	4.5	11.1	0	6.11	0.11	
Prominent supraorbital ridges	0	7.46	16.7	9.8	4.46	0.22	
Hypotelorism	11.1	1.5	5.6	4.9	4.15	0.25	
Long philtrum	7.4	7.5	16.7	2.4	3.82	0.28	
Asymmetrical eyes	25.9	14.9	22.2	9.8	3.67	0.30	
Short philtrum	7.4	9.0	0	14.6	3.40	0.33	
Prominent occiput <sup>b</sup>	7.4	1.5	0	4.9	3.08	0.38	
Large ears	14.8	13.4	5.6	4.9	3.01	0.39	
Missing lingual frenulum	14.8	6.0	5.6	12.2	2.59	0.46	
Eye pathology	3.7	4.5	11.1	2.4	2.24	0.52	
Ears protuberant	14.8	19.4	16.7	26.8	1.77	0.62	
Broad face	7.4	6.0	11.1	12.2	1.47	0.69	
Flat face	11.1	7.5	16.7	9.8	1.43	0.70	
Prematurely grey	7.4	6.0	0	4.9	1.34	0.72	
Microcephaly	3.7	1.5	5.6	2.4	1.07	0.78	
Triangular face	7.4	7.5	11.1	9.8	0.38	0.95	
Abnormal hair pattern <sup>b</sup>	3.7	4.5	5.6	4.9	0.097	0.99	
Other dysmorphic features (n = 26)							
Scoliosis	<b>37.4</b>	11.9	0	<b>90.2</b>	79.38	0.001	
Clinodactyly of fingers	<b>33.3</b>	10.5	0	<b>36.6</b>	18.19	0.001	
Small hands	<b>25.9</b>	6.0	<b>44.4</b>	4.9	23.85	0.001	
Cubitus valgus	<b>25.9</b>	1.5	16.7	2.4	19.55	0.001	
Sacral dimple <sup>b</sup>	3.7	3.0	<b>38.9</b>	2.4	30.76	0.001	
Sparse body hair	18.5	1.5	<b>55.6</b>	<b>22.0</b>	32.09	0.001	
Loose skin <sup>b</sup>	0	3.0	<b>33.3</b>	4.9	24.62	0.001	
Loose skin on neck <sup>b</sup>	0	1.5	<b>27.8</b>	2.4	25.38	0.001	
Kyphosis	<b>55.6</b>	<b>23.9</b>	16.7	17.1	14.59	0.002	
Short toes	<b>33.3</b>	<b>31.3</b>	0	14.6	11.06	0.01	

	Occurrence <sup>a</sup> (%)					P value
	Cluster 1 (n = 27)	Cluster 3 (n = 67)	Cluster 4 (n = 18)	Cluster 5 (n = 41)	Chi-square (df = 3)	
Skin pigmentation abnormalities	<b>37.0</b>	17.9	5.6	12.2	9.32	0.025
Long toes	<b>37.0</b>	16.4	5.6	17.1	8.23	0.04
Simian crease	3.7	5.97	0	17.07	7.33	0.062
Inguinal hernia	14.8	3.0	5.6	2.4	6.34	0.10
Webbed toes	29.6	35.8	33.3	14.6	5.82	0.12
Pectus carinatum <sup>b</sup>	0	4.5	0	9.8	4.68	0.20
Short fingers	18.5	9.0	0	12.2	4.27	0.23
Small feet	14.8	6.0	5.6	2.4	4.22	0.24
Hyperflexible joints	25.9	10.5	11.1	14.6	3.92	0.27
Short stature	14.8	14.9	33.3	14.6	3.86	0.28
Long fingers <sup>b</sup>	14.8	4.9	5.6	7.3	3.16	0.37
Asymmetrical feet <sup>b</sup>	3.7	3.0	11.1	2.4	2.87	0.41
Umbilical hernia	3.7	1.5	5.6	7.3	2.44	0.49
Longneck <sup>b</sup>	0	4.5	5.6	4.9	1.38	0.71
Winged scapula <sup>b</sup>	3.7	3.0	0	4.9	0.98	0.81
Hirsute body hair	7.4	6.0	5.6	2.4	0.98	0.81

<sup>a</sup>Frequencies in boldface are those dysmorphic features that were significantly different across clusters and occurred in at least 20% of subjects within an individual cluster.

<sup>b</sup>Dysmorphic features (n = 13) with no available kappa statistic.

**TABLE II**

Demographic and Validating Variables Not Used in Cluster Analysis

Variables not used in cluster analysis	Cluster 1 (n = 27)	Cluster 3 (n = 67)	Cluster 4 (n = 18)	Cluster 5 (n = 41)	Chi-square (df = 3)	P value
Sex (% male)	51.9	62.7	44.4	85.4	12.97	0.005
Ethnicity (% Caucasian)	96.3	76.1	88.9	73.2	7.29	0.06
Early age at onset (% < 21 years)	70.4	64.2	44.4	53.7	4.20	0.24
Congenital heart defect	22.2	1.82	7.69	0	14.39	0.002
Mild mental retardation	33.3	6.7	42.9	6.1	20.2	0.001