

Clinical Characterization of Autosomal Dominant and Recessive Variants of Robinow Syndrome

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Robinow syndrome is a genetically heterogeneous condition characterized by mesomelic limb shortening associated with facial and genital anomalies that can be inherited in an autosomal dominant or recessive mode. We characterized these two variants clinically, with the aim of establishing clinical criteria to enhance the differential diagnosis between them or other similar conditions. The frequencies of clinical signs considered important for the discrimination of the dominant or recessive variants were estimated in a sample consisting of 38 patients personally examined by the authors and of 50 affected subjects from the literature. Using the presence of rib fusions as diagnostic of the recessive variant, and also based on the inheritance pattern in familial cases, we classified 37 patients as having the recessive form and other 51 as having the dominant form. The clinical signs

present in more than 75% of patients with either form, and therefore the most important for the characterization of this syndrome were hypertelorism, nasal features (large nasal bridge, short upturned nose, and anteverted nares), midface hypoplasia, mesomelic limb shortening, brachydactyly, clinodactyly, micropenis, and short stature. Hemivertebrae and scoliosis were present in more than 75% of patients with the recessive form, but in less than 25% of patients with the dominant form. Umbilical hernia (32.3%) and supernumerary teeth (10.3%) were found exclusively in patients with the dominant form. © 2007 Wiley-Liss, Inc.

Key words: Robinow syndrome; genetic heterogeneity; differential diagnosis

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INTRODUCTION

Robinow syndrome (RS) was first described by Robinow et al. [1969] in a family with several individuals exhibiting mesomelic limb shortening, hypertelorism, and hypoplastic genitalia, showing an autosomal dominant inheritance pattern (MIM 180700). Wadia et al. [1978] described an apparently new autosomal recessive syndrome associating mesomelic limb shortening to a pattern of facial features, hypoplastic genitalia and costovertebral segmentation defects. This syndrome received the acronym COVESDEM (*costovertebral segmentation defects with mesomelia*). In the following year, however, it was recognized that COVESDEM syndrome was a variant of RS with an alternative

inheritance mode [Wadia, 1979; MIM 238310]. Subsequently, several other patients have been

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described, most of them occurring sporadically, in which case it is impossible to determine the mode of inheritance. However, it was noticed that in reports of recessive Robinow syndrome (RRS), all affected individuals presented with costovertebral segmentation defects with rib fusions [Wadia et al., 1978; Patton and Afzal, 2002], defects that have not been observed in patients with the autosomal dominant Robinow syndrome (DRS). Hemivertebrae and scoliosis, however, were also found in DRS, including familial cases [Robinow et al., 1969; López et al., 1996]. The mutated gene responsible for RRS has been identified as *ROR2* at 9q22 [Afzal et al., 2000; Van Bokhoven et al., 2000], and encodes a tyrosine kinase receptor involved in cell growth and differentiation. The gene associated with DRS has not been identified.

The clinical diagnosis of RRS is not difficult, since there exist no other syndromes that associate its typical facial dysmorphic features, mesomelic shortening, costovertebral segmentation defects that include rib fusions, and hypoplastic genitalia. In contrast, the clinical diagnosis of DRS is difficult, particularly in the absence of mesomelic shortening. In these cases, other syndromes that commonly associate similar facial dysmorphic features (especially hypertelorism) and genital hypoplasia, such as Aarskog syndrome (MIM305400) and Opitz G syndrome (MIM300000) should be considered in the differential diagnosis.

To our knowledge, the only comprehensive study of a collection of patients with RS was performed by Butler and Wadlington [1987], and reported the frequencies of the main clinical signs and symptoms in 35 patients, including literature data. However, the authors did not distinguish DRS from RRS. Here we set out to more precisely delineate the differences in DRS and RRS as an aide to differential diagnosis.

PATIENTS AND METHODS

With a protocol for clinical examination based on previously described clinical signs and symptoms of RS, we personally evaluated a total of 38 subjects, 13 with RRS (five males and eight females) and 25 with DRS (10 males and 15 females). The diagnosis of RS was based on the presence of at least short stature and/or mesomelic limb shortening, any degree of genital hypoplasia and a subjective assessment of "fetal facies," always including hypertelorism. Measurements were taken for height, weight, head circumference, inner and outer canthal distances, arm and forearm lengths, palm and middle finger lengths, and compared to normal standards [Hall et al., 1995]. Figures were considered above standard when higher than the 97.5th centile, and below standard when lower than the 2.5th centile (outside the normal range mean \pm 1.96 SD). Fifty patients from the literature with the diagnosis of RS

and a detailed clinical description were also included in the study; 24 (14 males and 10 females) with RRS and 26 (16 males and 10 females) with DRS [Robinow et al., 1969; Vera-Roman, 1973; Wadlington et al., 1973; Kelly et al., 1975; Wadia et al., 1978; Portnoy, 1979; Petit et al., 1980; Shprintzen et al., 1982; Menon et al., 1983; Bain et al., 1986; Bhandari et al., 1988; Nájera-Martínez et al., 1988; Vila-Coro et al., 1988; Glaser et al., 1989; Kumar and Puri, 1989; Schönau et al., 1990; Webber et al., 1990; Wiens et al., 1990; Schorderet et al., 1992; López et al., 1996; Aksit et al., 1997; Guuillén-Navarro et al., 1997; Al-Ata et al., 1998; Balci et al., 1998; Soliman et al., 1998; Kantaputra et al., 1999; Criado et al., 2000; Kulkarni and Reddy, 2004]. The combined (personal + literature) sample consisted therefore of 88 patients, 37 with RRS and 51 with DRS. These patients were classified into one group (DRS or RRS) taking into account the presence of rib fusions, a sign pathognomonic of RRS, as well as the inheritance pattern in patients with familial recurrence.

Our patients were mainly Brazilian (17) or American (16). Patients or their guardians provided written informed consent, and the study was approved by the National Research Ethics Committee (CONEP # 4516; World Medical Association Declaration of Helsinki). The age at the physical evaluation of patients with RRS ranged from 6 months to 39 years (mean = 12.89 \pm SD = 11.91 years) among the patients reported here and from 2 days to 9 years (mean = 3.44 \pm SD = 3.13 years) among the literature reports. In patients with DRS, the corresponding parameters ranged from 1 month to 37 years (mean = 10.48 \pm SD = 11.09 years) and from 1 day to 23 years (mean = 4.5 \pm SD = 6.30 years). The ages at examination in our cohort and in that from the literature for both variants differ significantly at the 5% critical level, as shown by Mann-Whitney tests.

Our analyses included an assessment of the frequency of 75 clinical signs and symptoms, present in at least 5% of the 88 patients with either form of RS. Since the presence of rib fusions was considered diagnostic of RRS, this sign was excluded from the comparison of frequencies between the two forms. In regard to literature report cases, a sign or symptom that is not mentioned in the description of a given affected individual may not be present or, otherwise, may have not been investigated. If **X**, **Y**, and **Z** (with **X + Y + Z = N**) are the observed numbers of a given sign or symptom described respectively as present or absent, or non-mentioned, in a series of N cases collected from the literature, under the hypothesis that the non-mentioned characteristic was absent, its frequency estimate is given by $\mathbf{x}' = \mathbf{X} / (\mathbf{X} + \mathbf{Y} + \mathbf{Z}) = \mathbf{X} / \mathbf{N}$, with expected binomial variance $\mathbf{var}(\mathbf{x}') = \mathbf{x}'(1 - \mathbf{x}') / \mathbf{N}$; under the hypothesis that the non-mentioned sign or symptom was not investigated, its frequency estimate is given by $\mathbf{x}'' = \mathbf{X} / (\mathbf{X} + \mathbf{Y}) = \mathbf{X} / (\mathbf{N} - \mathbf{Z})$, with variance

$\text{var}(\mathbf{x}'') = \mathbf{x}''(\mathbf{1} - \mathbf{x}'')/(\mathbf{N} - \mathbf{Z})$. The true estimate of the frequency is an unknown quantity with lower and upper estimates given by \mathbf{x}' and \mathbf{x}'' . Frotta-Pessoa (personal communication) suggested heuristic criteria to enable the decision for one out of the two estimates \mathbf{x}' and \mathbf{x}'' . For instance, if the sign is important, frequent, or conspicuous, the first estimate (\mathbf{x}') should be considered as the more probable and taken instead of the weighted estimate mentioned below. Contrarily, when the sign is neither very frequent, important, nor conspicuous, the second estimate should be preferred. In the absence of further information, or in cases where one has no parameters at all in order to decide for one out of the two alternatives, an adequate estimate of the true frequency \mathbf{x} can be obtained by weighing the estimates \mathbf{x}' and \mathbf{x}'' by the reciprocal of their expected binomial variances: $\mathbf{x} = [\mathbf{x}'/\text{var}(\mathbf{x}') + \mathbf{x}''/\text{var}(\mathbf{x}'')]/[1/\text{var}(\mathbf{x}') + 1/\text{var}(\mathbf{x}'')]$, as used by Pardo et al. [2003] in their discriminant analysis of Waardenburg syndrome variants. When possible, we used this weighted estimate (\mathbf{x}) to contrast the frequencies of the clinical signs and symptoms among patients with DRS and RRS, in the set of data obtained by combining the patients reported here to those from the literature. In the few cases where the estimate \mathbf{x}'' took the value 1 and the reasoning suggested the weighted estimate as the one to be used, we assigned to \mathbf{x}'' the value 0.99 and to its variance the value $0.01/(\mathbf{X} + \mathbf{Y})$ in order to make the weighting feasible.

RESULTS AND DISCUSSION

Since in most autosomal dominant conditions there exists a positive correlation between the occurrence of de novo cases and increased paternal age [Penrose, 1955], we estimated the mean maternal and paternal ages at the birth of isolated probands with DRS and compared them to the corresponding parental ages of patients with RRS, used as control. No significant differences in the two clinical forms were observed (DRS—maternal age: 25.74 ± 5.42 , paternal age: 29.47 ± 7.44 ; RRS—maternal age: 26.66 ± 6.10 , paternal age: 27.94 ± 5.11). However, we noted that the average difference between paternal and maternal ages in the de novo patients was 3.73 years and only 1.28 years in the recessive control cases, what could suggest that our non-significant results might be ascribed to insufficient sample sizes.

We estimated the frequencies of the clinical signs in each genetic variant (see the online Supplementary Material I and II at <http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html>). The main clinical signs for the characterization of RS, present in at least 75% of the patients with either variant (Table D) were: short stature, hypertelorism, wide and depressed nasal bridge, short upturned

nose, anteverted nares, midface hypoplasia, mesomelic limb shortening, brachydactyly, clinodactyly, and micropenis. Bifid tongue was identified in 58.8% of patients with RRS and in 38.5% of patients with DRS. In addition to RS, this defect is known to be present in orofaciocigital syndrome (MIM 311200, MIM 608518, MIM 258865).

Patients with both RS variants show considerable phenotypic variability, more pronounced in patients with DRS. Twenty different signs, out of 75 (Table I), were present in more than 75% of patients with RRS, 13 of which were present in greater than 90%, while 12 clinical signs were present in more than 75% of DRS patients, although only three were present in the vast majority of them.

The differential diagnosis of RRS and DRS is based on the presence of rib fusions, which is exclusively found in patients with RRS, and, in familial cases, also by the inheritance pattern. Our analysis shows that differential diagnosis of RRS and DRS is facilitated by additional signs that have distinct frequencies in the two variants. For example, hemivertebrae and scoliosis occur with frequencies of 97.5 and 77.4%, respectively, in patients with RRS; their corresponding frequencies in patients with DRS are 22.7 and 17.6%, respectively. These defects in association with rib fusions characterize the typical costovertebral segmentation defects common in patients with RRS.

We selected additional clinical signs and symptoms that could be useful for distinguishing patients with DRS from those with RRS. These signs were present in at least 50% of the patients with either form but were widely varying in those with RRS and DRS. These included a number of features more common in patients with RRS: down-slanted mouth corners (DRS: 62.9%; RRS: 95.2%), dental malocclusion (DRS: 49.4%; RRS: 93%), gum hyperplasia (DRS: 35.8%; RRS: 71%), short hands (DRS: 61.5%; RRS: 83.9%), and hypoplastic clitoris (DRS: 45.9%; RRS: 79.4%). There were also a number of features more common in DRS: depressed nasal bridge (DRS: 77.9%; RRS: 48.7%), long philtrum (DRS: 64.7%; RRS: 38.9%), thin upper lip (DRS: 49.6%; RRS: 29%), highly arched palate (DRS: 51.5%; RRS: 13.7%), narrow palate (DRS: 45.9%; RRS: 13.7%), and macrocephaly (DRS: 64.2%; RRS: 25.5%).

Other clinical signs and symptoms can be useful in the clinical characterization, but they are not present in a majority of patients with either variant. These included: prominent eyes (DRS: 36.6%; RRS: 13.5%), epicanthal folds (DRS: 39.1%; RRS: 10%), heart defects (DRS: 28.6%; RRS: 13.5%), limited elbow supination (DRS: 7%; RRS: 36.5%), umbilical herniae (DRS: 32.3%) and supernumerary teeth (DRS: 10.3%), the latter two features being observed exclusively in patients with DRS.

For patients in whom rib fusions, which is pathognomonic for RRS, cannot be documented, other clinical signs are important for distinguishing

TABLE I. Distribution of the 75 Clinical Signs According to Their Frequencies in Patients With Autosomal Dominant (DRS) and Autosomal Recessive (RRS) Robinow Syndrome

%	DRS	RRS
75–100	Anteverted nares (95.5%) Brachydactyly (81%) Depressed nasal bridge (77.9%) Hypertelorism (100%) Mesomelic limb shortening (80.1%) Micropenis (84.1%) Midface hypoplasia (80.6%) Prominent forehead (79.0%) Short nose (81.2%) Short stature (81.2%) Upturned nose (86.7%) Wide nasal bridge (96.8%)	Anteverted nares (96.2%) Brachydactyly (91.4%) Clinodactyly (87.8%) Dental malocclusion (93.6%) Down-slanted mouth corners (95.2%) Hemivertebrae (97.5%) Hypertelorism (100%) Hypoplastic clitoris (79.4%) Hypoplastic labia minora (80.8%) Mesomelic limb shortening (100%) Micropenis (100%) Midface hypoplasia (94.2%) Prominent forehead (77.8%) Scoliosis (77.4%) Short hands (83.9%) Short nose (93.2%) Short stature (97.3%) Triangular mouth (86.2%) Upturned nose (97.0%) Wide nasal bridge (94.8%)
50–74	Clinodactyly (70%) Cryptorchidism (71.6%) Down-slanted mouth corners (62.9%) Highly arched palate (51.5%) Hypoplastic labia minora (50.4%) Long eyelashes (54%) Long philtrum (64.7%) Macrocephaly (64.2%) Micrognathia (56.7%) Short hands (61.5%) Triangular mouth (64.9%)	Bifid tongue (58.8%) Cryptorchidism (66.7%) Gum hyperplasia (71.0%) Long eyelashes (58.8%) Micrognathia (68.2%)
25–49	Bifid tongue (38.5%) Cleft lip/palate (34.7%) Dental malocclusion (49.4%) Epicanthal folds (39.1%) Gum hyperplasia (35.8%) Heart defects except murmur (28.6%) Hypoplastic clitoris (45.9%) Hypoplastic labia majora (34.9%) Large 1st toes (33.1%) Large thumbs (35.6%) Low-set ears (28.1%) Narrow palate (45.9%) Pectus excavatum (44%) Prominent eyes (36.6%) Recurrent respiratory infections (25.2%) Renal problems (26.5%) Retrognathia (44%) Rhyzomelic limb shortening (35.4%) Short neck (29.4%) Thin upper lip (49.6%) Umbilical herniae (32.3%) Up-slanted palpebral fissures (37.2%) Wide palpebral fissures (49.5%)	Depressed nasal bridge (48.7%) Hypoplastic labia majora (39.8%) Large thumbs (30.6%) Limited elbow supination (36.5%) Long philtrum (38.9%) Low-set ears (44.9%) Macrocephaly (25.5%) Nail dysplasia (35%) Pectus excavatum (30.6%) Retrognathia (36.6%) Short neck (30.7%) Thin upper lip (29%) Wide palpebral fissures (33.9%)
10–24	Accentuated cupid's bow (16.7%) Blue sclerae (17.3%) Deafness (11.9%) Development delay/mental retardation (20.5%) Down-slanted palpebral fissures (14.6%) Facial nevus (19.4%) Frontal balding (14.4%) Heart murmur (14.4%) Hemivertebrae (22.7%) Infranumerary teeth (15.8%) Inguinal herniae (16.9%)	Camptodactyly (17.4%) Cleft lip/palate (13.5%) Deafness (10%) Epicanthal folds (10%) Facial nevus (23.9%) Heart defect except murmur (13.5%) Heart murmur (20.7%) Highly arched palate (13.7%) Hip dislocation (13.7%) Hypospadias (12.5%) Infranumerary teeth (18.3%)

(Continued)

TABLE I. (Continued)

%	DRS	RRS
10–24 (cont)	Nail dysplasia (21.7%) Ptosis (14.5%) Sacral dimple (14.9%) Scoliosis (17.6%) Short philtrum (16.8%) Single palmar crease (14.5%) Small ears (14.4%) Strabismus (12.2%) Supernumerary teeth (10.3%) Syndactyly (14.4%) Wide space between 1st and 2nd toes (14.6%)	Inguinal herniae (21.3%) Large 1st toes (24.2%) Narrow palate (13.7%) Prominent eyes (13.5%) Ptosis (13.6%) Recurrent respiratory infections (18.3%) Renal anomalies (10%) Sacral dimple (13.7%) Short philtrum (13.6%) Single transversal palmar crease (13.7%) Small ears (13.8%) Strabismus (10%) Syndactyly (17.9%) Up-slanted palpebral fissures (14.5%)

Rib fusion was considered pathognomonic of RRS.

the two variants. Aiming at evaluating the importance of each sign for this differential diagnosis, we contrasted the frequencies of individuals with DRS or RRS with or without each of the 75 clinical signs (see the online Supplementary Material III at <http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html>). The sum of the logarithms (S) corresponding to signs present or absent in any patient with RS can be used to obtain the final probability [$10^S/(1 + 10^S)$] in favor of the diagnosis of DRS in a given patient.

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