Beyond Gómez-López-Hernández Syndrome: Recurring Phenotypic Themes in Rhombencephalosynapsis

Hannah M Tully[1,2], **Jennifer C Dempsey**[3], **Gisele E Ishak**[4], **Margaret P Adam**[3], **Cynthia JR Curry**[5], **Pedro Sanchez-Lara**[6,7], **Alasdair Hunter**[8], **Karen W Gripp**[9], **Judith Allanson**[8], **Christopher Cunniff**[10], **Ian Glass**[3], **Kathleen J Millen**[2,3], **Daniel Doherty**[2,3], and **William B Dobyns**[2,3]

[1]Division of Pediatric Neurology, Department of Neurology, University of Washington, Seattle, WA, USA

[2]Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA

[3]Division of Genetic Medicine, Department of Pediatrics, University of Washington, Seattle, WA, USA

[4]Department of Radiology, University of Washington, Seattle, WA, USA

[5]Genetic Medicine of Central California, UCSF/Fresno, CA, USA

[6]Department of Pediatrics and Pathology, Keck School of Medicine, University of Southern California, Los Angeles, USA

[7]Children's Hospital Los Angeles, Los Angeles, USA

[8]Medical Genetics PSU, Children's Hospital of Eastern Ontario, Ottawa, Canada

[9]Division of Medical Genetics, Alfred I duPont Hospital for Children, Wilmington, DE, USA

[10]Department of Pediatrics, University of Arizona College of Medicine, Tucson, AZ

Abstract

Rhombencephalosynapsis (RES) is an uncommon cerebellar malformation characterized by fusion of the hemispheres without an intervening vermis. Frequently described in association with Gómez-López-Hernández syndrome, RES also occurs in conjunction with VACTERL features and with holoprosencephaly (HPE). We sought to determine the full phenotypic spectrum of RES in a large cohort of patients. Information was obtained through database review, patient questionnaire, radiographic and morphologic assessment, and statistical analysis. We assessed 53 patients. 33 had alopecia, 3 had trigeminal anesthesia, 14 had VACTERL features and 2 had HPE with aventriculy. Specific craniofacial features were seen throughout the cohort, but were more common in patients with alopecia. We noted substantial overlap between groups. We conclude that although some distinct subgroups can be delineated, the overlapping features seen in our cohort suggest an underlying spectrum of RES-associated malformations rather than a collection of discrete syndromes.

Keywords

Contact Information: Hannah Tully, Center for Integrative Brain Research, Mailstop: C9S-10, Dobyns Lab, Phone: 206-884-1353, fax: 206-884-1353, hmtully@uw.edu.

INTRODUCTION

Rhombencephalosynapsis (RES) is an uncommon but likely under-recognized cerebellar malformation characterized by continuity of the cerebellar hemispheres across the midline without an intervening vermis. This condition usually occurs sporadically but is presumed to have genetic underpinnings (Table I), though no consistent genetic causes have been identified and no animal models exist. Disruption of dorsal-ventral patterning has been proposed as the cause of RES [Sarnat, 2000, Yachnis, 2002], but the mechanisms involved have yet to be elucidated. The prevalence of RES is unknown, but Ishak et al [2012] recently reported that 5 of 56 patients with aqueductal stenosis had unrecognized RES, suggesting that RES may be considerably more common than previously believed. Initially described as an isolated brain malformation, RES is increasingly recognized in conjunction with other anomalies.

The first syndrome to be associated with RES was described by Gómez [1979] and López-Hernández [1982], though the nature of the underlying brain malformation was not evident at the time. Key features of Gómez-López-Hernández syndrome (GLH) include RES, parietal-occipital scalp alopecia and trigeminal anesthesia, the latter often leading to recurrent corneal and facial scarring. Distinctive craniofacial features have been described in GLH, including a towering skull with short anterior-posterior and side-to-side dimensions (turricephaly)[Gómez, 1979; López-Hernández, 1982], a flat facial contour or midface retrusion, hypertelorism and low-set ears with increased posterior angulation [López-Hernández, 1982]. GLH has also been associated with variable degrees of motor developmental delay, intellectual disability, short stature, and behavioral difficulties [Brocks et al., 2000; Gomy et al., 2008].

Recently, some of the features once considered integral to a diagnosis of GLH have been called into question [Sukhudyan et al., 2010b]; the term GLH is now often applied to RES with alopecia but without trigeminal anesthesia or characteristic craniofacial features. Sporadic reports have also linked RES with holoprosencephaly (HPE) [Pasquier et al., 2009a; Ramocki et al., 2011; Siebert et al., 2005] and features of the VACTERL association [Aydingoz et al., 1997; de Jong and Kirby 2000; Pasquier et al., 2009b; Toelle et al., 2002]. Seeking to better define the full clinical spectrum of RES, we assessed a large cohort of patients with RES for associated anomalies.

METHODS

Patient acquisition

We performed a comprehensive search for patients with RES in our database of more than 6800 subjects with brain malformations or other developmental brain disorders maintained by the senior author (WBD). Most patients were referred by their families or physicians for imaging review. In some, the diagnosis of RES had been made previously, while in others it was noted upon our review of their imaging studies. Several patients in the database had previously been ascertained by reviewing MRIs of children with aqueductal stenosis in whom RES had not been recognized [Ishak et al., 2012]. Patients whose families elected to enroll in research underwent a formal consent process, supplied DNA samples and provided additional clinical information.

Assessment of RES and additional structural brain abnormalities

Imaging studies were reviewed by 4 authors (Dobyns, Doherty, Ishak, Tully) to confirm the diagnosis of RES. Scans were also assessed for major additional malformations of the forebrain and the ventricular system. Subtle abnormalities such as fusion of the colliculi and

absent mammillary bodies, which are frequently seen in conjunction with RES but often not mentioned in routine radiology reports, are described in a related article by Ishak et al [2012].

Evaluation of GLH features

Alopecia was assessed directly during clinic visits, through patient pictures and by parental questionnaire. **Trigeminal anesthesia** was assessed directly when possible (corneal swab or saline drops to elicit blink reflex), through review of medical records, or by parental questionnaire. In questionable situations, a history of repeated corneal injuries or facial scarring was considered indicative of trigeminal anesthesia. **Morphologic features** were assessed by sending photographs of patients to nine authors (Adam, Allanson, Cunniff, Curry, Dobyns, Glass, Gripp, Hunter, Sanchez-Lara) for subjective assessment of head shape (turricephaly, brachycephaly), forehead shape (high, wide), facial contour (flat contour, midface retrusion), eye placement (subjectively wide-set, telecanthus), and ear placement (low set, increased posterior angulation). Respondents could answer Yes, No, or Unable to Determine for each variable and were given the opportunity to comment on other features. A patient was deemed to have the feature in question if a majority of the 9 evaluating geneticists agreed that it was present, with a minimum consensus of 3 when some respondents were unsure. When skull shape could not be reliably assessed because of hair, a neuroradiologist made the determination based on MRI or CT images. We created a **composite morphology score** for each patient based on these responses. Patients were given 1 point for a positive finding in each of the 5 categories (head shape, forehead shape, facial contour, eye placement and ear placement). For each patient, these points became a numerator; the denominator was the total number of categories in which evaluators reached consensus. Thus, a patient who was determined to have a high forehead but no other features would receive a morphology score of 1/5. A patient who was rated as having a flat facial contour and telecanthus but in whom forehead shape and ear placement could not be determined would receive a score of 2/3.

Assessment of VACTERL features

Patient records and radiologic scans were assessed for vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, radial dysplasia, or other limb defects. Although the VACTERL association is defined as the presence of 3 or more features, we noted the presence of any VACTERL feature in our patients.

Statistical Analysis

We performed a Fisher's exact test to determine whether alopecia correlated with VACTERL features. We performed an analysis of variance (ANOVA) and a Student's t-test to determine whether mean composite morphology scores varied among specific groups of patients. We used SAS, version 9.3 (SAS Institute, Inc., Cary, NC) for all statistical analyses.

RESULTS

Overview

We assessed our cohort of 53 patients for the presence of GLH features, VACTERL features, and major additional brain anomalies (Table II). These features are seen in overlapping groups of patients (Fig 2).

GLH Features

Alopecia—In 52 patients for whom sufficient information was available, 33 (63%) had alopecia, which was bilateral in 26 patients and unilateral in seven. The degree of alopecia ranged from well-circumscribed patches of apparently hairless skin (most common) to less circumscribed areas of relatively sparse hair. We categorized patients with sparse hair as having alopecia if there was a readily appreciable difference between affected and unaffected scalp.

Trigeminal anesthesia—Trigeminal anesthesia was present in 3 of the 50 patients for whom sufficient nformation was available. In each case, there was longstanding evidence of recurrent bilateral corneal injuries and facial scarring.

Craniofacial morphology—Forty-one patients underwent morphological assessment on the basis of photographs (Fig 3). Skull shape was assessed in all 41. 3 (8%) were determined to have turricephaly. One patient had brachycephaly without turricephaly. Forehead shape was assessed in 38 patients. A high forehead was found in 22 (58%), 10 of whom were also rated as having a wide forehead (26%). A wide forehead alone was found in three patients. Facial contour was evaluated in 37 patients. Fifteen (41%) had flat facial contour or midface retrusion. Eye placement was assessed in 40 patients. Telecanthus was noted in 17 (43%); 2 also had subjectively wide-set eyes. One patient's eyes appeared wide-set without telecanthus. Ear placement was evaluated in 38 patients. Twenty-four (63%) had low-set ears, 19 of whom also had increased posterior angulation. Two patients had ears with posterior angulation that were not low-set. Based on these features, we generated a composite morphology score for each patient as described in the Methods section (Table I). Individual morphologic features can be viewed in Supplementary eTable I (See Supporting Information online).

Two patients, both with HPE, had additional dysmorphic signs: one had unilateral microtia; the other had upslanting palpebral fissures and a forme fruste cleft lip (Fig 6).

VACTERL Features

VACTERL features were seen in 14 (26%) of our 53 patients (Table II and Fig 4). 5 had a single VACTERL feature, four had two VACTERL features and five had three or more VACTERL features. Of the VACTERL features found in our cohort, vertebral segmentation defects were most common, seen in nine patients. Structural renal anomalies were seen in six patients, and structural cardiac defects in five. Four patients had pre-axial polydactyly or polysyndactyly; 2 patients had radial aplasia (one with TAR, one without). One patient had anal atresia and one patient had a retro-esophageal cyst. One patient also had thrombocytopenia-absent radius (TAR) syndrome with a confirmed 1q21.1 deletion. Though her bilateral absent radii are likely attributable to TAR, we included her in this category because of her two additional features (duplicated renal collecting system and retroesophageal cyst).

Several patients with VACTERL features also had alopecia, but there was no statistically significant association between these features (p = 0.51, Fisher's exact test).

Additional Brain Malformations

Two patients had a striking form of HPE characterized by posterior-predominant fusion of the cerebral hemispheres in conjunction with absent lateral and third ventricles (Figure 5). Another patient had what appeared to be a smaller area of hemispheric continuity across the midline resembling the middle interhemispheric fusion (MIF) variant of HPE (Fig 1, images

I–L). However, distortion from severe congenital hydrocephalus made this difficult to confirm. One other patient had bilateral perisylvian polymicrogyria.

Craniofacial differences between groups of patients (Table III)—We divided our cohort into five groups based on clinical features: 1) RES without alopecia or VACTERL Features, 2) RES with alopecia alone, 3) RES with alopecia and trigeminal anesthesia, 4) RES with VACTERL features, and 5) RES with HPE-AV (both patients in this group also had VACTERL features). We calculated an average composite morphology score for each group. Because of small numbers, Groups 2 and 3 were combined, as were Groups 4 and 5 Analysis of variance demonstrated that Groups 2 and 3 combined had a significantly higher mean composite morphology score than Group 1 (P<0.05.). Groups 4 and 5 combined had the same mean composite morphology score as categories 2 and 3 combined, but because of smaller numbers in this group, the comparison to Group 1 did not achieve statistical significance. We also compared patients solely on the basis of alopecia (patients with VACTERL features and HPE-AV were included in both groups). Patients with alopecia had a higher mean composite morphology score than those without alopecia (p=0.03).

DISCUSSION

We reviewed a series of 53 individuals with RES to delineate the full range of RES-associated phenotypes and compare them to the better-known Gómez-López-Hernández syndrome. We identified one subset of patients with features of the VACTERL association and another subset with an unusual posterior form of holoprosencephaly and aventriculy; however, only 17 of 53 patients could be classified unambiguously as having a specific malformation syndrome, including GLH itself (when defined as RES with alopecia and trigeminal anesthesia).

When we analyzed the phenotypic spectrum in more depth by dividing our cohort into five categories using easily-identified objective elements (alopecia, trigeminal anesthesia, VACTERL features and HPE-AV (Table III), substantial areas of overlap became apparent (Fig 2). To determine whether the craniofacial features reported in GLH syndrome were seen among other patients with RES, we generated a composite morphology score and found a broad range of scores in all categories, but with a statistically significant association between higher scores and alopecia. We propose that the recurrent, overlapping elements associated with RES reflect disruption of a fundamental mechanism that regulates development of the involved structures. Accordingly, we contend that RES and its associated features are best viewed as a spectrum of biologically-related malformations rather than a collection of discrete syndromes, similar to the spectrum of brain and craniofacial malformations associated with classic HPE.

GLH syndrome and the RES spectrum of anomalies

In 1979, Gómez reported a girl with trigeminal anesthesia, a band of parietal-occipital alopecia and prominent cerebellar findings on examination [1979]. Two years later, López-Hernández described 2 girls with craniosynostosis, trigeminal anesthesia and bilateral parietal alopecia [1982]. MRI scans of subsequent patients defined the associated brain malformation as RES. Though a distinctive skull shape and facial features have often been considered part of GLH syndrome, Sukhudyan et al noted that the only consistent features in GLH syndrome are RES and alopecia [Sukhudyan et al., 2010], presaging our results.

Trigeminal anesthesia—Only three patients in our cohort had trigeminal anesthesia, in contrast to the patients described in a literature review by Sukhudyan et al [2010], in which 17/21 had trigeminal anesthesia. We attribute this to differences in ascertainment: previous

patients in the literature were reported as examples of GLH syndrome, whereas the patients in our cohort were ascertained on the basis of their underlying brain malformation.

Alopecia—While few patients in our cohort had trigeminal anesthesia, 67% had alopecia, including several with VACTERL features or HPE-AV. The alopecia seen in conjunction with RES is distinctive, consisting of focal areas of hypotrichosis, often bilaterally symmetric, which may contain tufts of hair within them. On biopsy, these areas demonstrate preserved architecture with variably hypoplastic hair follicles, and no inflammation or scarring [Munoz et al., 1997; Pasquier et al., 2009a].

Interestingly, a clinically and histologically equivalent condition without neurologic abnormalities has been described in the dermatology literature as congenital triangular alopecia or temporal triangular alopecia (CTA, TTA) [Armstrong and Burrows, 1996; Assouly and Happle, 2010; Bargman, 1988; Elmer and George, 2002; Feuerman, 1981; García-Hernández et al., 1995; Kubba and Rook, 1976; Silva et al., 2010; Tosti, 1987; Trakimas et al., 1994; Yamazaki et al., 2010]. A single report linked CTA to GLH in a child with significant gross motor delay; this patient had a brother with CTA but not RES [Purvis et al., 2007]. CTA has also been described in a mother and daughter with intellectual disability and epilepsy [Ruggieri et al., 2000]. The daughter was reported to have a Dandy-Walker malformation.

Craniofacial morphology—Most patients in our RES cohort lack a distinctive skull shape. Two of the three children with turricephaly had severe congenital hydrocephalus and macrocephaly on initial imaging. Follow-up scans demonstrated acquired turricephaly in the setting of residual ventricular enlargement. Several patients also had abnormal skull shape at birth and subsequently underwent surgical correction of craniosynostosis. Follow-up scans showed normal skull contour. Taken together, this suggests that skull shape is influenced by several factors and may change over time, rendering it less useful as a diagnostic sign. In contrast to turricephaly, differences in forehead shape, facial contour, and position of ears and eyes were common among our patients. These features were seen across the entire cohort of RES patients, though on average, patients with alopecia had higher composite morphology scores than those without.

Two additional RES associations

Two additional phenotypic motifs emerged in our cohort: features of the VACTERL association (seen in 14), and HPE-AV (seen in two). We found examples of both these RES-associated phenotypes in the literature, but with limited delineation.

RES with VACTERL features—RES has occasionally been reported in association with VACTERL features [Aydingoz et al., 1997; Toelle et al., 2002]. Hydrocephalus (without known RES) has also been described in conjunction with VACTERL features, gaining the name VACTERL-H syndrome [Beemer et al., 1990; Briard et al., 1984; Corsello and Giuffre, 1994; Evans et al., 1989; Iafolla et al., 1991]. VACTERL-H syndrome is a clinically and genetically heterogeneous condition with several reports of familial recurrence. Many of these are associated with mutations in *FANCB* [McCauley et al., 2011], but others occur sporadically and lack evidence of DNA fragility [Evans and Chodirker, 1993]. In 2009, Pasquier et al. published a series of 40 fetuses with RES and linked a subset to VACTERL-H, a previously unrecognized association [2009].

Our series confirms the association of VACTERL features with RES. As the majority of our patients with VACTERL features also had hydrocephalus, we affirm the link between RES and VACTERL-H and propose the term VACTERL-R for these patients.

RES with HPE-AV—Two patients in our cohort had a striking brain malformation consisting of incompletely separated cerebral hemispheres with absent lateral and third ventricles. On the basis of undivided forebrain, this malformation can be categorized as HPE, but of a very atypical form. Most HPE demonstrates an anterior-to-posterior gradient in which the frontal lobes are most severely affected. A rare type of HPE known as the middle interhemispheric fusion (MIF) variant (or syntelencephaly) involves incomplete separation of the posterior frontal and anterior parietal lobes [Barkovich and Quint, 1993; Lewis et al., 2002]. In contrast, our patients have a posterior-predominant fusion that is maximal in the occipital lobes, suggesting that the mechanism of this malformation is distinct from that of classic anterior-predominant HPE. Ventricular anomalies can be seen in HPE, but complete aventriculy is not a feature of either the common anterior-predominant or the MIF form, underscoring the unique nature of the HPE seen in conjunction with RES.

Garfinkle described an 11-year-old girl with RES, posterior-predominant HPE and aventriculy [1996]. MRI images demonstrate a brain malformation remarkably similar to that of our two HPE-AV patients. Two subsequent patients with HPE-AV have been reported, 1 with anterior-predominant HPE and a Dandy-Walker malformation [Sener, 1998], the other with posterior-predominant HPE in whom the cerebellum appears dysplastic [Kumar et al., 2006]. Sergi reported on a 23-week fetus with RES, alobar HPE and essentially absent lateral and 3rd ventricles [1997]. The fetus also had a duplicated left thumb. Kakita described RES in a 20-week fetus with aprosencephaly (which can be considered an extreme form of HPE) [2001]. This fetus also had a cleft lip, malformed ears, rib fusion anomalies and a thoracic neural tube defect.

This novel malformation may be linked to maternal diabetes. Our two patients with HPE-AV were both born to mothers with pre-existing diabetes mellitus, as were the individuals described by Garfinkle, Sergi and Kakita. Diabetes is a well-recognized risk factor for HPE, presumably the more common anterior-predominant form. Diabetes has also been described in conjunction with the MIF variant of HPE [Robin et al., 1996]. Its role in HPE-AV needs further investigation.

Beyond GLH Syndrome

GLH syndrome was described as a clinical entity before the nature of the underlying brain malformation was recognized. With alopecia and "GLH-like" craniofacial features seen across our cohort of RES patients (including in patients with VACTERL features and HPE-AV), choosing which patients qualify for the label GLH syndrome becomes increasingly problematic. If the term GLH is used broadly to designate all patients with RES and alopecia, it lacks clinical specificity. If the term GLH is restricted to patients with RES, alopecia and trigeminal anesthesia, it becomes more clinically precise. However, the trigeminal nuclei and nerves originate from the dorsal hindbrain, so trigeminal anesthesia may simply comprise a related developmental malformation of this region. We therefore propose that alopecia, "GLH-like" craniofacial features and trigeminal anesthesia all be considered RES-associated anomalies rather than components of a named syndrome. This approach is comparable to current practice with the common form of HPE: the brain malformation itself and its associated craniofacial features are considered part of a continuous spectrum of related malformations rather than a syndrome.

VACTERL features and HPE-AV are sufficiently clinically distinctive to justify special mention, but patients in these subgroups have much in common with the rest of the cohort: several have alopecia, and their craniofacial features overlap with those seen in patients with alopecia alone. Moreover, the HPE seen in HPE-AV is posterior-predominant, suggesting that it may be a more extreme disruption of the same (unknown) mechanism that causes

RES. Although both subgroups of patients have unique clinical features, whether they differ on a genetic basis has yet to be determined.

The constellation of malformations in RES suggests that the embryologic cells of origin respond as a unit that can be disrupted by various genetic or environmental causes, a concept sometimes referred to as a developmental field defect [Martinez-Frias et al., 1998]. Since these malformations are not spatially related to each other, they presumably result from disruption of a set of interacting genes that is deployed in multiple developing regions at different times during development [Jan and Jan, 1993; Opitz et al., 2002]. The overlapping phenotypic elements seen in our RES cohort implicate a biological pathway involved in development of the cerebellum, trigeminal ganglia, skull, face and focal areas of scalp. HPE-AV suggests that this, or a related pathway, also operates in the developing cerebral hemispheres and ventricular system. VACTERL features point to a function in somitogenesis, radial ray development, and the formation of multiple organ systems. More specifically, this shared biological mechanism may play a role in pattern formation, a term used in developmental biology to describe the process by which groups of embryonic cells develop complex, spatially-oriented forms in response to genetically programmed signaling centers. Though no genes have yet been linked conclusively to RES, a number of observations support a genetic basis (Table I), although diagnostic workup in our patients did not reveal any recurrent abnormalities (Supplementary eTable II – See Supporting Information online). Our data also suggest a role for environmental influences such as diabetes.

In many ways, RES resembles classic HPE, an archetypical developmental field defect. In HPE, various genetic and environmental influences can perturb the ventral midline, resulting in a variable spectrum of characteristic forebrain and craniofacial malformations. HPE has also been seen in conjunction with VACTERL malformations [Orioli and Castilla, 2010; Siebert et al., 2005]. In contrast to HPE, however, RES involves primarily dorsal rather than ventral structures. And unlike HPE, RES is not known to occur in animals, either spontaneously or as a result of genetic or environmental manipulation. We hypothesize that RES and classic HPE are clinically analogous conditions but involve different genetic and mechanistic pathways.

CONCLUSIONS

The phenotypic profile of RES is most notable for its areas of overlap. Accordingly, the majority of patients with RES should be viewed as having RES-associated anomalies rather than a particular syndrome. Two additional phenotypic themes were seen in subgroups of patients: RES with VACTERL features (14 patients) and HPE-AV (two patients). Yet even these patients have alopecia and craniofacial features that link them to the rest of the cohort. VACTERL features and HPE-AV in the context of RES are clinically distinctive, but whether they are genetically distinct remains to be seen.

The recurring phenotypic themes observed in our RES cohort imply a fundamental biological relationship between the structures involved, most likely based upon a shared developmental pathway. Ultimately, further delineation of the RES spectrum and its key phenotypic elements will be informed by a deeper understanding of the genetic and molecular mechanisms of RES itself.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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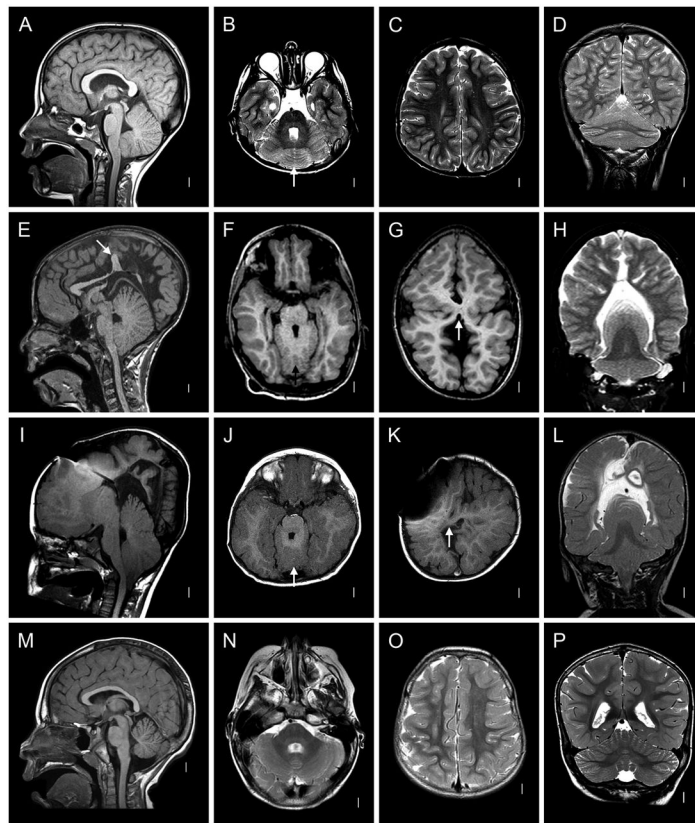
Figure 1. Radiographic Features of RES
A–D: Patient 48. Midline sagittal T1-weighted image through the cerebellum demonstrates hemispheric rather than vermian configuration (A). Axial T2 through the cerebellum shows fusion of white matter across the midline and a keyhole-shaped 4th ventricle (B). Axial T2 through though the cerebral hemispheres shows normal anatomy (C). Coronal T2 showing continuity of cerebellar folia across the midline without an intervening vermis (D). **E–H:** Patient 46. Midline sagittal T1-weighted image demonstrating a towering cerebellum with hemispheric architecture. Note the absence of a visible aqueduct. This patient had severe congenital hydrocephalus. Many of the supratentorial abnormalities (arrow) are likely a consequence of distortion from hydrocephalus and subsequent decompression (E). Axial T1 through the cerebellum demonstrating similar findings as the patient above (F). Axial T1 through the cerebral hemispheres shows an area of white matter continuity suspicious for mild HPE, but likely representing post-hydrocephalus distortion(G). Coronal T2 showing a towering cerebellum with upward displacement through the tentorial notch (H). **I–L:** Patient 14. I, Mid-sagittal and axial T1 demonstrating similar findings to Patient 46. This patient also had severe congenital hydrocephalus (J). Axial T1 showing area suspicious for HPE (arrow), though post-hydrocephalic distortion makes this difficult to confirm (K). Coronal T2 demonstrating similar findings to Patient 46 (L). **M–P:** normal brain.
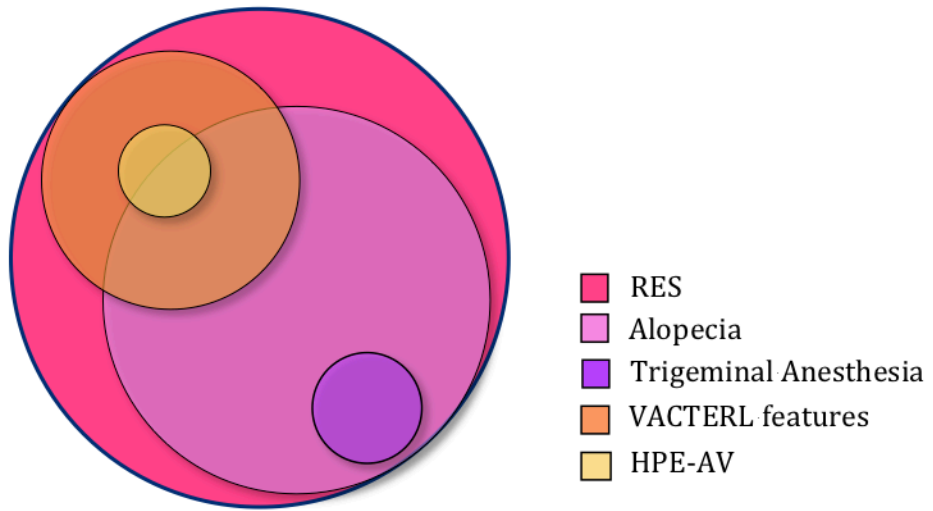
Figure 2.
Areas of overlap among patients with RES.

Figure 3. Faces of Patients with RES
A–B: Patient 39. **C–D:** Patient 28. **E–F:** Patient 26. **G–H:** Patient 17. I–J, Patient 7. **K–L:** Patient 9. **M–N:** Patient 46. **O–P:** Patient 44.
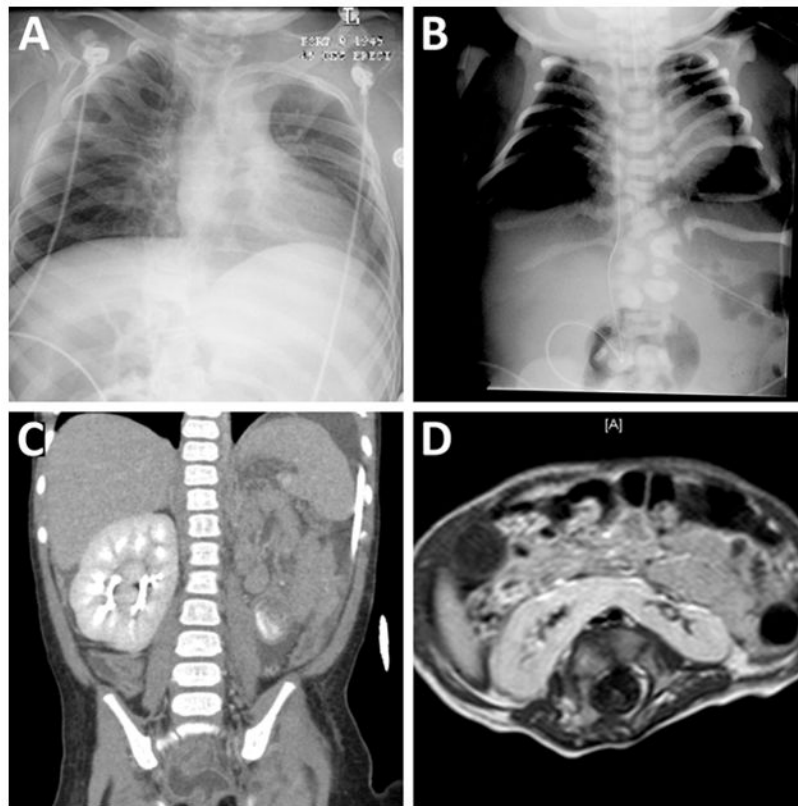
Figure 4. VACTERL Features
A: Patient 33. Radiograph demonstrating multiple fused ribs associated with vertebral segmentation defects. **B:** Patient 35. Radiograph demonstrating multiple thoracic and lumbar vertebral segmentation defects and deformed ribs. **C:** Patient 21. Coronal CT showing absent kidney on the left with partially duplicated kidney on the right (cross-fused renal ectopia). **D:** Patient 36. Axial T1-weighted image of the abdomen showing horseshoe kidney.
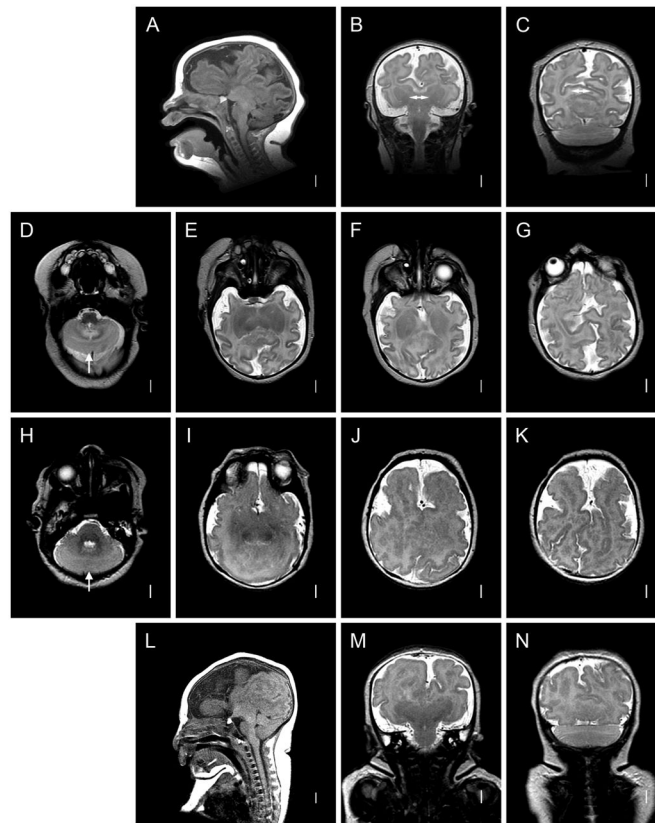
Figure 5. Holoprosencephaly-Aventriculy

A–G: Patient 15. Mid-sagittal view demonstrating dramatically infolded brain, absent 3rd ventricle and aqueduct, and mass-like fusion of the midbrain (A). Coronal T2 demonstrating gray matter continuity across the midline (HPE) and absent lateral ventricles (B). Coronal T2 demonstrating posterior predominance of HPE and continuity of cerebellar folia across the midline (C). Axial T2 demonstrating RES(D). Axial T2s showing posterior-predominant fusion, infolding and aventriculy (E–G). **H–N:** Patient 35. Multiple axial, coronal and mid-sagittal sections showing striking similarity of brain malformation to that of Patient 15.
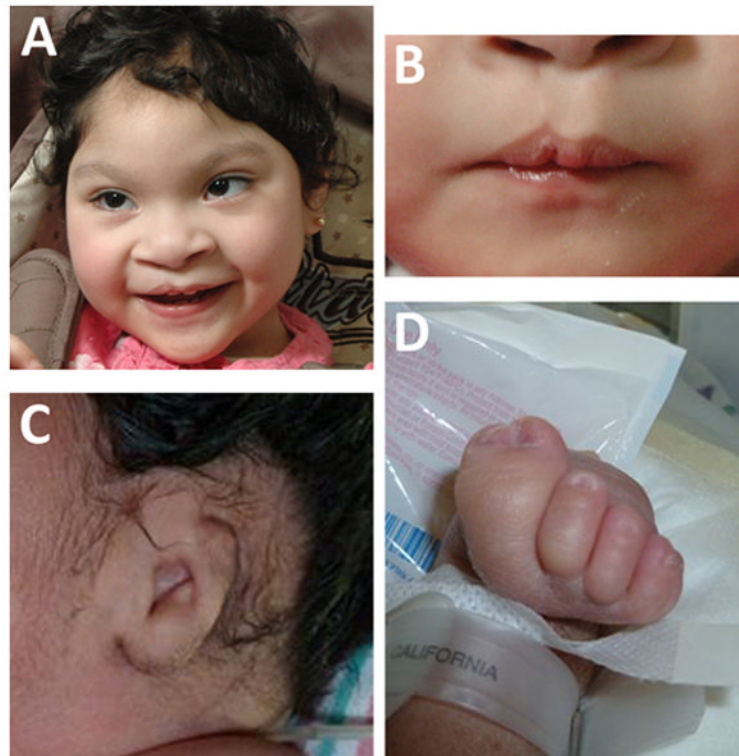
Figure 6. Additional features in patients with HPE-AV
A and B: Patient 15. Broad nose, upslanting palpebral fissures and forme fruste cleft lip (A).
Close-up of lip (B). C–D: Patient 35. Microtia (C). Partially duplicated, fused right hallux
(D).

Table I

Genetic changes described in association with RES.

Genetic changes described in association with RES	
Recurrence in two subsequent pregnancies	Pasquier et al., 2009
Consanguinity	Chemli et al., 2007
	Pasquier et al., 2009a
	Romanengo et al., 1997
	Sandalcioglu et al., 2006
	Toelle et al., 2002
Interstitial deletion of 2q	Truwit et al., 1991
Unbalanced subtelomeric translocation: t(2p:10q)	Lespinasse et al., 2004
Tetrasomy 9p	di Vera et al., 2008
Microduplication 1p	Pasquier et al., 2009
Microduplication 7q	Pasquier et al., 2009
Complex rearrangement of 22q13.3	Ramocki et al, 2011 [*]

[*] The authors also reported partial RES in conjunction with HPE in two sisters with truncating mutations of ZIC2. However, the presence of RES was disputed by Guleria [2011] and could not be confirmed by our review.

Table II

Clinical characteristics of 53 patients with RES.

Pt ID	Age	Sex	GLH Features				VACTERL Features		Other Brain Malfs	Notes
			Alo	TA	CMS	Vert SD	Cardiac/Renal/GI/GU	Limb		
RES Without Alopecia or VACTERL (13 patients)										
1	10m	F	-	-	2/5	-	-	-	-	
3	22m	F	-	-	1/5	-	-	-	-	
10	26y	M	-	-	0/5	-	-	-	-	
11	6y	F	-	-	2/4	-	-	-	-	Congenital pyriform aperture stenosis
16	44y	F	-	-	0/5	-	-	-	-	
22	7y	M	-	-	NA	-				Bilateral microtia, aural atresia, L corneal clouding attributed to infection
23	2y	M	-	-	3/5	-	-	-	-	
26	5y	F	-	-	1/5	-	-	-	-	Gestational DM
38	13m	F	-	-	NA	-	-	-	-	
40	9y	F	-	-	NA	-	-	-	-	L corneal clouding attributed to scarring from incomplete eye closure, no TA on exam
42	2y	F	-	-	NA	-	-	-	-	
46	15y	M	-	-	2/5	-	-	-		Urachal cyst
47	16y	M	-	-	0/5	-	-	-		
RES with Alopecia (23 patients)										
2	3y	F	L	-	3/5	-	-	-	-	
14	5y	M	R	-	0/5	-	-	-	Poss MIF-like HPE	
17	4y	M	L	-	3/5	-	-	-	-	
18	7y	F	L>R	-	3/5	-	-	-	-	R squamosal CSO s/p surgery, eyebrow tuft
28	4y	M	R>L	-	2/5	-	-	-	-	
41	16m	M	L	-	2/5	-	-	-	-	
4	22m	M	B	-	3/4	-	-	-	-	
6	5y	M	B	-	2/5	-	-	-	-	Gestational DM. B SN hearing loss. Chordee.

Pt ID	Age	Sex	GLH Features			Vert SD	VACTERL Features		Other Brain Malfs	Notes
			Alo	TA	CMS		Cardiac/Renal/GI/GU	Limb		
7	6y	F	B	-	4/5	-	-	-	P PMG	B SN hearing loss
9	14y	M	B	-	2/5	-	-	-	-	
12	4y	M	B	-	0/3	-	-	-	-	
13	2y	M	B	-	3/5	-	-	-	-	
24	5y	M	B	-	2/5	-	-	-	-	Idiopathic renal failure
25	27m	M	B	-	3/5	-	-	-	-	Neurofibromatosis with NF1 mutation
27	2y	M	B	-	3/5	-	-	-	-	
31	6y	F	B	-	2/5	-	-	-	-	
32	5y	M	B	-	2/5	-	-	-	-	
34	4y	M	B	-	3/5	-	-	-	-	
39	3y	M	B	-	3/5	-	-	-	-	Gestational DM
45	4y	F	B	-	3/5	-	-	-	-	CSO
48	9y	M	B	-	NA	-	-	-	-	CSO s/p surgery
51	4y	F	B	-	NA	-	-	-	-	
52	3y	F	B	-	NA	-			-	
RES with Alopecia and Trigeminal Anesthesia (3 patients)										
8	3y	F	B	B	4/5	-	-	-	-	Multi-suture CSO s/p surgery
44	31y	M	B	B	3/5	-	-	-	-	CSO s/p surgery
53	9y	F	B	B	NA				-	
RES with VACTERL Features (+/− Alopecia) (12 patients)										
5	5y	F	B	-	4/4	-	Duplicated renal collecting system, retro-esophageal cyst	Radial aplasia B	-	TAR syndrome with 1q21.1 deletion
19	6y	M	R	-	1/3	Y	ASD, VSD, bicuspid AV	Radial aplasia R	-	Posterior skull defect. Possible CSO.
20	4y	M	-	-	1/5	-	-	PPD L hand	-	Temporal tuft
21	3y	M	-	-	NA	-	Absent R kidney, fused/duplicated L kidney	-	-	
29	17y	M	R	-	0/5	Y	Absent L kidney, PUV	-	-	Gestational DM
30	3y	M	L>R	-	4/5	Y	Absent L kidney, Hypoplastic AA, VSD	-	-	

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Pt ID	Age	Sex	GLH Features			Vert SD	VACTERL Features		Other Brain Malfs	Notes
			Alo	TA	CMS		Cardiac/Renal/GI/GU	Limb		
33	12y	F	-	-	5/5	Y	-	-	-	
36	19m	F	B		3/5	Y	TOF, RSAA, horseshoe kidney	-		
37	4y	F	-	-	NA	-	TAPVR, anal atresia	-	-	
43	10m	F	B	-	2/5	Y	VSD	-	-	
49	23y	M	-		NA	-	-	PPD L hand	-	Temporal tuft, posterior skull defect
50	5y	F	NA	NA	NA	NA	Absent kidney, body wall defect	PPD R foot	-	Mother with pre-existing DM
RES with Posterior HPE, Aventriculy and VACTERL Features (+/− Alopecia) (2 patients)										
15	3y	F	R	-	1/3	Y	-	-	Post HPE, AV	Mother with pre-existing DM. Microcephaly. Forme fruste cleft lip.
35	2d	M	-	NA	2/5	Y	TOF	Fused/duplicated R hallux	Post HPE, AV	Mother with pre-existing DM. Microcephaly. Malformed ears.

Abbreviations: Alo, Alopecia. TA, trigeminal anesthesia. CMS, composite morphology score. DM, diabetes mellitus. MIF, middle interhemispheric fusion [variant of holoprsoencephaly]. HPE, holoprosencephaly. CSO, craniosynostosis. SN [hearing loss], sensorineural. P PMG, perisylvian polymicrogyria. ASD, atrial septal defect, VSD, ventricular septal defect. [Bicuspid] AV, aortic valve. PUV, posterior urethral valves. [hypoplastic] AA, aortic arch. TOF, Tetralogy of Fallot. RSAA, right-sided aortic arch. TAPVR, total anomalous pulmonary venous return.

Table III

Patient Groups and Composite Morphology Scores

Category	GLH Features			VACTERL Features	Major Additional Brain Anomalies
	Alopecia	TA	Composite Morphology Score, Mean (95% CI)		
RES without alopecia, VACTERL features or HPE-AV (13 patients)	N	N	25 (5 – 45)	N	N
RES with alopecia but without VACTERL features or HPE-AV (23 patients)	Y, ranging from unilateral sparse patch to well-circumscribed bilateral areas of alopecia	N	51 (39 – 64)	N	1 patient with possible MIF-like HPE, 1 patient with perisylvian polymicrogyria
RES with alopecia and trigeminal Anesthesia (3 patients)	Y	Y		N	N
RES with VACTERL features +/– Alopecia (12 patients)	Variably present	N	51 (31 – 71)	Y	N
RES with HPE-AV and VACTERL features +/– alopecia (2 patients)	Variably present	N		Y	Posterior HPE, aventriculy
All RES without alopecia, including patients with VACTERL features and HPE-AV (19 patients)	N	N	32 (16–50)	Y/N	Y/N
All RES with alopecia, including patients with VACTERL features and HPE-AV (33 patients)	Y	Y/N	51 (40–60)	Y/N	Y/N

Abbreviations: RES, rhombencephalosynapsis. MIF, Middle Interhemispheric Fusion [variant of holoprosencephaly]. HPE, holoprosencephaly.