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Clinical Geneticists' Views of VACTERL/VATER Association

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Abstract

VACTERL association (sometimes termed "VATER association" depending on which component features are included) is typically defined by the presence of at least three of the following congenital malformations, which tend to statistically co-occur in affected individuals: Vertebral anomalies, Anal atresia, Cardiac malformations, Tracheo-Esophageal fistula, Renal anomalies, and Limb abnormalities. Although the clinical criteria for VACTERL association may appear to be straightforward, there is wide variability in the way clinical geneticists define the disorder and the genetic testing strategy they use when confronted with an affected patient. In order to describe this variability and determine the most commonly used definitions and testing modalities, we present the results of survey responses by 121 clinical geneticists. We discuss the results of the survey responses, provide a literature review and commentary from a group of physicians who are currently involved in clinical and laboratory-based research on VACTERL association, and offer an algorithm for genetic testing in patients with this association.

Keywords

VACTERL association; VATER association

INTRODUCTION

VATER association was originally named in the early 1970s with the description of seven patients as including at least three of the following features: Vertebral defects, Anal atresia, Tracheo-Esophageal fistula, Radial and Renal dysplasia [Quan and Smith, 1973]. Shortly thereafter, additional features, such as Cardiac malformations and additional Limb abnormalities, were added, and the condition was called VACTERL association, which remains the more prevalent term according to our survey (we will use this term in the remainder of this article) [Quan and Smith 1973; Nora and Nora, 1973; Temtamy and

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Miller, 1974; Nora and Nora, 1975; Khoury et al., 1983; Czeizel and Ludányi, 1985, Rittler et al., 1996]. As described in detail below, the precise definition has remained uncertain, at least partially because of a lack of uniform population-based studies that support the early descriptions.

VACTERL association is estimated to occur in approximately 1 in 10,000 to 1 in 40,000 live-born infants, depending on the exact criteria and the type of ascertainment used [Khoury et al., 1983; Czeizel and Ludányi, 1985; Botto et al., 1997]. Despite the original descriptions almost four decades ago, relatively little is known about the etiology of VACTERL association [reviewed in Solomon, 2011].

The authors of this article comprise a group of physicians who are all currently involved in clinical and laboratory-based research on VACTERL association and related conditions. We are aware that a wide range of opinions exists with regards to howVACTERL association is defined and what diagnostic genetic tests should be requested in patients with this association. In order to determine how practicing clinical geneticists view this condition and what genetic tests are typically ordered, we surveyed a cohort of clinical geneticists who provide medical services to individuals with VACTERL association. In this article, we present and discuss data obtained from 121 respondents. The results of this survey demonstrate a wide variability in the way physicians approach the diagnostic evaluation and genetic testing of individuals with VACTERL association. In some cases, these results can be used to determine the “mainstream” approach. In addition to commenting on the results of the survey, we provide in the Discussion, a review of the literature on certain salient issues raised in this study, as well as a detailed differential diagnosis of testable conditions that may be considered when encountering an affected patient.

MATERIALS AND METHODS

An invitation to participate in this study, containing a link to a free online survey, was sent via email to a cohort of practicing physician clinical geneticists. The survey consisted of a combination of open and closed-ended questions (see Supplementary material in Supporting Information online for an exact transcript of the questions in the online survey). The email was sent to current and previous participants of the David W. Smith Workshop on Malformations and Morphogenesis, and participants were told that they could also forward the invitation to their physician clinical geneticist colleagues. Additionally, each of the article’s co-authors sent the invitation to physician colleagues at their institutions and other potential respondents.

RESULTS

The results of the survey responses are presented in tabular format, and are summarized here as well. The data have been divided into the following tables: demographic data (Table I); definitions and diagnostic criteria (Table II); testing approach (Table III); information related to Fanconi anemia testing (Table IV).

We analyzed results from 121 respondents; although most (61%) are based in the United States, the remainder (39%) represents 14 different countries. Approximately 10% are physicians still in genetics-training programs. The experience of the remaining 90% of respondents ranges from immediate post-training to over 20 years of medical genetics experience; the latter category represents the single largest group of respondents (26% of the total) (Table I).

As expected, there was a wide range of responses in terms of how the condition is termed, defined, and what testing is offered (Table II). Most respondents call the condition

"VACTERL" association (64%) and require at least three component features to be present (79%). Among component features, vertebral anomalies, anal atresia, and tracheo-esophageal fistula were included as defining in at least 90% of respondents. Cardiac malformations, renal anomalies, and limb abnormalities were all considered to be defining features by less than 90%. In addition to the core component features, some respondents consider other features to be defining, including other anomalies (eg, genitourinary) and the presence of spatially disparate malformations. A majority of respondents indicated that the presence of non-classic features, such as dysmorphic facial features (79%), or unexplained cognitive impairment (80%), would alter the diagnostic impression.

Just as there is great variability in the definition and diagnostic features used, there is a wide spectrum in terms of genetic work-up typically initiated when clinical geneticists encounter a patient with VACTERL association (Table III). Microarray analysis is the single most common test used in both the prenatal (56%) and postnatal (86%) settings, followed by routine karyotype, Fanconi anemia testing, and single-gene testing.

As Fanconi anemia can be associated with significant medical complications, we inquired about how often respondents test for this condition, and what typically leads to such testing (Table IV). Unsurprisingly, many different responses were given related to what triggers Fanconi anemia testing. Interestingly, approximately two-thirds of respondents either never test for this condition, or test for this condition less than 25% of the time.

DISCUSSION

The results of this survey demonstrate the wide range of opinions held by clinical geneticists who care for patients with VACTERL association. Using data from both our survey and the literature, we address several key issues.

How should the condition be described and defined?

In terms of the number of component features required, the presence of at least 3 component features of VACTERL association is still most commonly used. However, our study (as well as some publications) shows that this requirement is not universally accepted [Weaver et al., 1986; Wheeler and Weaver, 2005; Aguinaga et al., 2010; Källén et al., 2001; Solomon et al., 2010a]. Seventy-nine percent of respondents required at least three component features (7% required at least four), while 15% required only at least two component features. An alternate approach mentioned by several survey respondents, which may have some credence, is the requirement of a "core" feature, in which the presence of certain component features would be weighted more heavily in the others. In the literature, this approach has been suggested for anorectal malformations or tracheo-esophageal fistula as such core features [Jenetzky et al., 2011].

It should be noted that in terms of the specific component features included in the definition, the presence of congenital heart malformations as well as other "vascular" anomalies such as single umbilical artery, were added shortly after the initial description based on further cohorts of analyzed patients and studies of possibly associated teratogens and [Nora and Nora, 1973; Temtamy and Miller, 1974; Nora and Nora 1975]. However, later statistical analyses of larger cohorts cast doubt about the inclusion of some features, such as cardiac malformations or renal anomalies, and provided some evidence that only certain types of limb abnormalities (such as upper limb radial/preaxial reduction abnormalities) should be included [Rittler et al., 1996; Botto et al., 1997; Källén et al., 2001].

As our survey results indicate, cardiac malformations, renal anomalies, and limb abnormalities are less frequently considered to be defining component features (these are

considered to be defining features by 82%, 85%, and 71% of respondents, respectively, versus vertebral anomalies, anal atresia, and tracheo-esophageal fistula, all of which were considered to be defining features by at least 90% of respondents), reflecting the uncertainty in the literature.

To further complicate the picture, there is also evidence that other component features not traditionally included in the VACTERL acronym can be supportive, such as single umbilical artery, genitourinary anomalies, or spatially disparate findings, as mentioned by some respondents [de Jong et al., 2008; de Jong et al., 2010a; Solomon et al., 2010a; Solomon et al., 2011c].

Much of the confusion in terms of exactly what should be incorporated in the definition is likely due to the fact that a high level of etiological heterogeneity is likely to be present among individuals with VACTERL association [Evans et al., 1985; Evans et al., 1992; Botto et al., 1997; Solomon et al., 2010a]. As our ability to identify the underlying etiologies of individuals with VACTERL association improves, it is likely that patients will be subdivided into molecularly-defined groups representing discrete disorders. As that occurs, concerns over the exact number and type of malformations that should be used to define an individual as having VACTERL association will become less important than the identification of specific signs could be used to guide physicians in their choice of diagnostic tests.

What genetic tests should be considered in a patient with VACTERL association?

Our results show that just as there is a wide range in how VACTERL association is defined, there is also high variability in terms of the clinical approach to genetic testing. This variability may be due, at least in part, to the variation in medical experience and familiarity with this disorder seen in our cohort as well the variation in the availability of various testing modalities available to respondents.

Prenatal setting—As in the postnatal setting, the first step in the evaluation of a patient involves a thorough clinical work-up to determine the number and type of congenital malformations. While detailed examination is naturally more challenging in the prenatal setting, clues for alternative diagnoses should be carefully sought at the outset, with testing directed accordingly. A careful family and medical history (including questions related to potential teratogens, including maternal hyperglycemia, as several survey respondents mentioned) is key, and may best be conducted by a clinical geneticist [reviewed in Solomon, 2011; de Jong et al., 2010b].

Though overall becoming less prevalent in many situations, due to the availability of newer techniques, the karyotype can be a useful, and relatively inexpensive, test to identify aneuploidy, large, cytogenetically-detectable copy number variations, and chromosomal rearrangements that can cause malformations seen in VACTERL association. Over half of survey respondents suggested that they would request a karyotype in the prenatal work up of a fetus with anomalies suggestive of VACTERL association. However, the majority of these respondents would also use other testing modalities including copy number analyses by microarray.

The use of microarrays to detect copy number abnormalities is becoming more common in the prenatal setting, and some series describe clinically relevant findings in setting of prenatal patients with congenital anomalies [Tyreman et al., 2009]. In the prenatal setting, variants of unknown significance can raise complex issues related to reproductive decision making. Indeed, our survey shows that 56% of respondents would use microarray analyses in prenatal setting with 28% of respondents using microarray analyses as the only genetic

test. Another strategy that some survey respondents indicated was the use of targeted testing for deletion 22q11.2, especially in the context of cardiac anomalies.

Postnatal testing—From our experience with the clinical work-up of patients with VACTERL association, we suggest the algorithm presented in Figure 1, along with Table V, for the work-up of patients with features of VACTERL association who present to the clinic (Figure 1). In all such situations, the first step is a thorough and careful clinical work-up - including family history - to determine the presence and type of anomalies that may suggest a particular genetic disorder [Solomon et al., 2010a; Solomon et al., 2010b].

In the absence of a clinically or molecularly identifiable syndrome, copy number analysis by microarray should be considered a first-tier test in patients with congenital anomalies [Miller et al., 2010]. By way of etiological explanation, VACTERL association includes several relatively severe malformations. These malformations were associated with a high rate of lethality in the newborn period until relatively recently, such that affected individuals often did not survive to reproduce. Thus, for the disorder to recur in the population, causes may include highly penetrant *de novo* events (such as array-detectable aberrations), rare recessive mutations, as well as a multifactorial etiology involving multiple interacting genetic and environmental insults. Thus, array-based testing appears warranted (as does research examining recessive and *de novo* mutations) as a way to test for one of these explanations. In fact, reports of patients with VACTERL-type anomalies secondary to genomic imbalances supports this recommendation [Walsh et al., 2001; reviewed in Felix et al., 2009; Arrington et al., 2010; de Jong et al., 2010a; de Jong et al., 2010b; Schramm et al., 2011; Solomon et al., 2011c]. Survey respondents indicate this general trend, with 44% of respondents typically performing microarray only, with an additional 42% indicating the selection of a microarray along with other genetic testing.

In cohorts followed by the authors, the use of microarray analysis has been shown to reveal potentially pathogenic aberrations in a small but significant number of individuals, some of whom have been previously reported [de Jong et al., 2010a; Solomon et al., 2011b]. From estimates from several currently-followed cohorts (including over 100 well-phenotyped individuals with VACTERL association) high-density single nucleotide polymorphism (SNP) microarray (>1 million SNPs) showed *de novo* aberrations likely associated with disease in 3–5% of tested individuals. However, as the inheritance of VACTERL association remains unclear, it is also highly possible that familial array-detected copy number variations may also contribute in a more complex disease model involving incomplete penetrance and multiple interacting factors [Solomon et al., 2010b; Bartels et al., 2012], As with other etiological aspects, when the causes of VACTERL association are further unraveled, reanalysis of existing microarray data sets may be informative.

Unusual features or Mendelian inheritance patterns may provide impetus for single gene testing. For example, alveolar capillary dysplasia should prompt testing of the *FOXF1* gene [Stankiewicz et al., 2009]. Approximately 80% of survey respondents indicated that dysmorphic facial features or otherwise unexplained neurocognitive impairment would alter the diagnostic impression. These “red flags” (as well as other findings not usually seen in VACTERL association) may serve as clues for the presence of conditions that include features of VACTERL association (see Table V). For each overlapping condition, many of which have testing available, clinical clues can help determine the likelihood of each, and testing may be important for prognostic discussions and reproductive decision-making.

As an interesting side note, it is clear that VACTERL association is heterogeneous, and it is likely that more identified causes will emerge in the near future. Known etiologies of VACTERL association and overlapping conditions, in conjunction with biological models,

have long implicated several key signaling pathways and gene families, such as the Sonic Hedgehog signaling pathway, WNT signaling, and the HOX gene clusters [Mortlock and Innis, 1997; Kim et al., 2001; Biason-Lauber et al., 2004; Johnston et al., 2005; Garcia-Barcelo et al., 2008; Person et al., 2010]. Indeed, genes implicated in related conditions (as shown in Table V) reinforce this observation, and indicate that these signaling pathways may be fruitful to interrogate further. However, it is important to point out in this context that both observed patterns of inheritance and epidemiological factors as well as recent studies showing the plausibility of an environmental insult imposed on a genetic susceptibility indicate that the etiologies contributing to VACTERL association may in many situations be complex [de Jong et al., 2008; Solomon et al., 2010b; Bartels et al., 2012; Sparrow et al., 2012]

Fanconi anemia appears to be a rare cause of features observed in VACTERL association, but it is an important part of the differential diagnosis. This condition deserves special attention because of testing availability and associated morbidity and mortality of the disease. Our survey shows that Fanconi anemia testing is not frequently performed in patients with VACTERL association, with almost two-thirds of responders indicating they never ordered Fanconi anemia testing or ordered it in less than 25% of cases. In one review of over 200 patients with Fanconi anemia, approximately 5% were judged to have VACTERL association [Faivre et al., 2005]. More importantly, another report of 370 patients showed that, at diagnosis, over 16% of patients manifested with congenital malformations but no hematologic abnormalities [Giampietro et al., 1993]. There is little data describing the converse, and more central, question in this context: the prevalence of Fanconi anemia in cohorts of patients ascertained because of the presence of VACTERL association. Data from our cohorts reveal an extremely low rate of positive testing for Fanconi anemia in individuals ascertained primarily because of the cause of VACTERL association In over 100 patients tested via chromosomal breakage assays (e.g., DEB assay), no patients had Fanconi anemia, though one had a myelodysplastic phenotype greatly heightening the index of suspicion, and further testing (from skin biopsy) is currently being performed to test for mosaicism.

As is evident from Table V, while Fanconi anemia is often immediately considered in patients with VACTERL association findings and hematologic and/or oncologic manifestations, other conditions can include both groups of features. Important conditions in the differential diagnosis include both Diamond-Blackfan anemia and Thrombocytopenia-absent radius syndrome [Greenhalgh et al., 2002; Griesinger et al., 2005; Doherty et al., 2010; Vlachos and Muir, 2010; Albers et al., 2012].

Nevertheless, testing for Fanconi anemia is relatively efficient and economical, and the diagnosis is especially important as Fanconia anemia can result in severe hematologic anomalies and predisposition to malignancy. For the purposes of review, findings in patients with Fanconi anemia include any physical anomaly (60%), microsomia (40%), skin anomalies (40%), unilateral or bilateral upper limb abnormalities (35%), microcephaly or hydrocephalus (20%), ocular anomalies (20%), renal anomalies (20%), cognitive impairment (10%), and ear anomalies (10%) [reviewed and much more completely presented in Shimamura and Alter, 2010]. We would, however, suggest that Fanconi anemia testing be considered more often than is currently the case according to our survey results.

As a technical note, there are two cytogenetic assays that can be used to test for Fanconi anemia (using either or both diepoxybutane or mitomycin C, as the latter tends to result in more variable background results) [Cervenka et al., 1981; Auerbach, 1993]. Logistically, the choice of assay type may be limited by availability. Targeted molecular testing is challenging due to locus heterogeneity, but might be considered after cytogenetic diagnosis

or in certain situations, such as the case in a known family mutation. Array-based diagnosis has also been described in an instance of X-linked Fanconi anemia manifesting as classic VACTERL-association findings in a neonate [Umaña et al., 2011].

This study has several limitations. First, analysis of results from 121 respondents offers only a small proportion of the opinions of practicing clinical geneticists, and does not include others who may be involved in the early diagnosis and medical management, such as obstetricians, neonatologists, and surgeons. Additionally, emphasizing participants in a specific genetics workshop may skew the results. Second, the survey was relatively short (in order to help maximize respondents' willingness to participate), and did not explore issues in depth. Finally, while the use of both open and close-ended questions can be helpful in order to capture responses, this can cause challenges in terms of tabulating and considering the overall results of the survey.

In conclusion, modern genomic techniques coupled with the ability to perform complex dissections of environmental insults acting on a background of genetic/genomic susceptibility do offer promise for a better understanding of VACTERL association in the near future. In order to expedite knowledge regarding this condition, we recommend that clinicians avail themselves of publicly accessible databases, such as www.clinicaltrials.gov, in order to find appropriate research referrals (as several survey respondents mentioned) when the etiology remains elusive.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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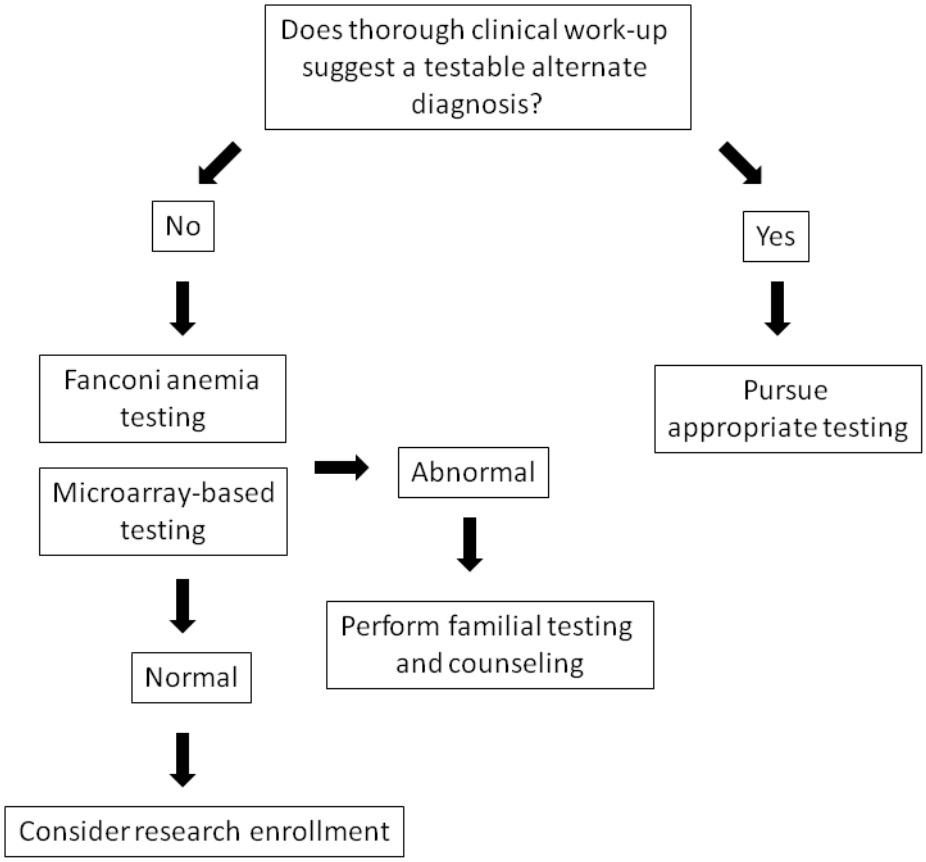

Figure 1.

Suggested algorithm for the molecular work-up of patients with features of VACTERL association seen in the postnatal setting (see also Table V). The first step involves thorough medical and family history and a detailed physical examination, as well as imaging studies, in order to determine the presence and type of congenital malformations. Clinicians must keep in mind the differential diagnosis, especially those conditions for which testing is available. If there is no evidence for a specific overlapping condition (see Table V for a list of conditions and features), and the features of VACTERL association are classic, the two tests that might be performed for all patients are a microarray and Fanconi anemia testing (to be clear, ruling-out cytogenetic disorders and Fanconi anemia might also be better considered to be part of a thorough differential-diagnosis related work-up). A positive result would lead to familial testing, counseling, and further referrals as necessary. In the instance of a negative test, referral to an appropriate research center for discussion of further research-based testing may be considered.

Table I

Demographic information for 121 survey respondents.

Location of Practice	
United States	74 (61%)
Non-United States *	47 (39%)
Experience	
Currently in training	12 (10%)
0–5 years post-training	25 (21%)
5–10 years post-training	18 (15%)
10–15 years post-training	18 (15%)
15–20 years post-training	17 (14%)
>20 years post-training	31 (26%)
Work Setting	
Almost all clinical	46 (38%)
Mostly clinical, some research	38 (31%)
Approximately equal clinical/research	10 (8%)
Mostly research, some clinical	25 (21%)
All research	2 (2%)

* Representing a total of 14 different countries.

Table II

Definitions and diagnostic criteria.

Term used	
VACTERL	78 (64%)
VATER	43 (36%)
Component features considered to be defining features[a,b]	
V	112 (93%)
A	109 (90%)
C	99 (82%)
TE	116 (96%)
R	103 (85%)
L	86 (71%)
Number of component features considered to be defining	
At least 2	18 (15%)
At least 3	95 (79%)
At least 4	8 (7%)
Other diagnostic criteria used besides the number of component features[a]	
Absence of signs of overlapping conditions	23 (19%)
Absence of chromosomal anomalies[c]	13 (11%)
Normal cognitive development	10 (8%)
Absence of dysmorphic features	10 (8%)
Use of a “weighted” score[d]	7 (6%)
Spatially disparate malformations	6 (5%)
Limb malformations only used if radial	3 (2%)
Presence of genitourinary anomalies	2 (2%)
Single umbilical artery	2 (2%)
Absence of brain malformations	2 (2%)
Presence of tracheo-esophageal fistula or esophageal atresia	2 (2%)
Presence of both vertebral and gastrointestinal anomalies	2 (2%)
Maternal/gestational diabetes mellitus	1 (1%)
Would the presence of dysmorphic facial features alter the diagnostic impression?	
Yes	95 (79%)
No	26 (21%)
Would the presence of otherwise unexplained neurocognitive impairment alter the diagnostic impression?	
Yes	97 (80%)
No	24 (20%)

[a]Each individual component feature could yield a result of up to 121 (100% of respondents).

[b] When asked to list whether any other component features were used (see also below), 3 (2%) listed single umbilical artery, 2 (2%) listed radial anomalies as part of limb abnormalities, and 1 each (1% each) listed genitourinary anomalies and spatially disparate (eg, occurring “above and below the diaphragm”) anomalies.

[c] By karyotype or microarray.

[d] By “weighted”, respondents indicated that certain features “count” more than others, such as tracheo-esophageal fistula being weighted more heavily than cardiac malformations.

Table III

Testing approach.

Genetic testing offered prenatally	
Microarray[a] only	34 (28%)
Karyotype only	23 (19%)
Karyotype and microarray[a,b]	14 (12%)
No testing offered	12 (10%)
No response or is not involved in prenatal care	12 (10%)
Karyotype and/or microarray and Fanconi anemia testing	8 (7%)
Karyotype and deletion 22q11.2 testing[c]	7 (6%)
Karyotype and/or microarray and specific gene testing[d]	4 (3%)
Karyotype and/or microarray and Fanconi anemia testing and specific gene testing[d]	3 (2%)
Karyotype and deletion 22q11.2 testing and Fanconi anemia testing	2 (2%)
Specific gene testing[d] only	1 (1%)
Fanconi anemia testing only	1 (1%)
Genetic testing offered postnatally	
Microarray only[e]	53 (44%)
Karotype and/or microarray and Fanconi anemia testing[f]	29 (24%)
Karyotype and microarray	13 (11%)
No testing	9 (7%)
Microarray and single gene testing[d]	3 (2%)
Microarrray and Fanconi anemia testing and single gene testing[d]	3 (2%)
Research enrollment only	2 (2%)
Karyotype and microarray and single gene testing[d]	1 (1%)
Karyotype and deletion 22q11.2 testing	1 (1%)
Fanconi anemia testing and single gene testing[d]	1 (1%)
Karyotype and microarray and research testing	1 (1%)
Microarray and Fanconi anemia testing[e] and mitochondrial testing[g]	1 (1%)
Would the presence of dysmorphic facial features alter the diagnostic impression?	
Yes	95 (79%)
No	26 (21%)
Would unexplained neurocognitive impairment alter the diagnostic impression?	
Yes	97 (80%)
No	24 (20%)

[a] Some respondents additionally indicated the type of array they would use, such as “high-density SNP array”, though most simply indicated the choice of performing a microarray.

[b] One respondent additionally ascertaining family history of breast cancer.

[c] Of these, three mentioned deletion 22q11.2 testing only in the context of cardiac malformations.

[d] Genes mentioned as examples include *SALL1*, *SALL4*, and *PTEN* (the latter in the context of hydrocephalus).

[e] Several respondents mentioned an array would only be done in the case of cognitive delay, but since this can be hard to ascertain in an infant or young child, they would tend to request a microarray in any infant/young child.

[f] Several respondents mentioned Fanconi anemia testing only in the presence of limb abnormalities.

[g] Mitochondrial testing would be done only in the context of clinical signs such as hypotonia.

Table IV

Data related to Fanconi anemia testing attitudes.

Frequency of Fanconi anemia testing	
Never	21 (17%)
< 25%	59 (49%)
25–50%	12 (10%)
50–75%	10 (8%)
>75%	11 (9%)
Always	8 (7%)
What prompts Fanconi anemia testing[a]?	
Radial/limb abnormalities	80 (66%)
Poor growth	29 (24%)
Hematologic anomalies	21 (17%)
Microcephaly	20 (17%)
Pigmentary anomalies	14 (12%)
Family history (pertaining to consanguinity and/or ethnic origin)	8 (7%)
Developmental delay/cognitive impairment	7 (6%)
Dysmorphic facies	4 (3%)
Non-VACTERL type anomalies[b]	3 (2%)
Family history of breast cancer	2 (2%)
Age[c]	2 (2%)
Presence of esophageal anomalies	2 (2%)
Absence of esophageal anomalies	1 (1%)
Malignancy	1 (1%)
Recurrent infections	1 (1%)
Symmetrical malformations	1 (1%)

[a] Each response could yield a result of up to 121 (100% of respondents); some respondents listed multiple findings that would prompt Fanconi anemia testing.

[b] Examples given included cleft lip/palate and ocular anomalies.

[c] One respondent wrote that young age would prompt Fanconi anemia testing, while the other wrote that old age would prompt testing.

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Table V

Specific conditions in which mutations have been identified that may cause features that overlap VACTERL association. The degree of overlap with "classic" VACTERL association (if such a term might be used) is highly variable, and certain conditions may frequently be readily recognizable. VACTERL-type features, either isolated or in combination have additionally been reported in a number of other conditions, and the differential diagnosis may extend further depending on specific characteristics present.

Condition	Associated gene(s)	Features in common with VACTERL association (in individuals with proven mutations)	Features not typically observed in conjunction with VACTERL association	Reference(s)
Alagille syndrome	*JAG1*, *NOTCH2* (heterozygous)	Vertebral anomalies, cardiac anomalies, renal anomalies	Characteristic dysmorphic facies, hepatic anomalies including bile duct paucity and cholestasis, ophthalmologic anomalies (e.g., posterior embryotoxon), neurological anomalies	Li et al., 1997; Oda et al., 1997; Krantz et al., 1999; McDaniell et al., 2006; Kamath et al., 2012
Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome; Fuhrmann syndrome	*WNT7A* (homozygous/compound heterozygous)	Vertebral anomalies, genitourinary anomalies, limb anomalies	Pelvic and limb anomalies tend to be more severe than typically described in VACTERL association, and primarily affect the lower limbs	Woods et al., 2006; Lonardo et al., 2007; Kantaputra et al., 2010; Eyaid et al., 2011
Andersen syndrome	*KCNJ2* (heterozygous)	Skeletal anomalies (including vertebral and limb anomalies), cardiovascular anomalies, renal anomalies	Characteristic dysmorphic facies, severe arrhythmias, hypokalemic periodic paralysis	Andelfinger et al., 2002; Tristani-Firouzi et al., 2002; Davies et al., 2005
Anopthhalmia-esophageal atresia-genital syndrome	*SOX2* (heterozygous)	Tracheo-esophageal fistula, limb anomalies, genitourinary malformations	Specific ocular anomalies (anophthalmia/ microophthalmia), neurocognitive impairment	Williamson et al., 2006
Baller-Gerold syndrome	*RECQL4* (heterozygous)	Limb anomalies (radial ray), anorectal anomalies in some individuals	Craniosynostosis, skin anomalies	Van Meldergem et al., 2006
Beals syndrome	*FBN2* (heterozygous)	Vertebral anomalies, cardiac anomalies, esophageal atresia, single umbilical artery	Contractures, arachnodactly, other GI atresia,	Wang et al., 1996

Condition	Associated gene(s)	Features in common with VACTERL association (in individuals with proven mutations)	Features not typically observed in conjunction with VACTERL association	Reference(s)
Cat-eye syndrome	Tetrasomy 22q11.1q11. 21 (typically supernumerary)	Anorectal malformations cardiac malformations, renal anomalies, genitourinary anomalies	Eye anomalies (e.g., coloboma, microphthalmia), ear anomalies, clefting	Rosias et al., 2001; Knijnenburg et al., 2012
Caudal regression syndrome	*VANGL1* (heterozygous)	Vertebral malformations, anorectal malformations	Classic (including severe) neural tube defects	Kibar et al., 2007
Cenani-Lenz syndactyly syndrome	*LRP4* (homozygous/compound heterozygous)	Renal anomalies, limb anomalies	Characteristic dysmorphic facies, limb malformations including syndactyly	Li et al., 2010
CHARGE syndrome	*CHD7* (heterozygous)	Cardiac malformations, genitourinary anomalies; may also include TEF	Colobomata, choanal atresia, neurocognitive and growth impairment, ear anomalies, cranial nerve dysfunction, characteristic facial features	Vissers et al., 2004; Zentner et al., 2010
Ciliopathies: Bardet-Biedl syndrome; McKusick-Kaufman syndrome; Meckel-Gruber syndrome	Multiple genes, including *MKKS* (homozygous/ compound heterozygous, though more complex models of inheritance have been described)	Cardiac malformations, renal anomalies, genitourinary malformations	Retinitis pigmentosa, obesity, neurocognitive impairment, characteristic polydactyly as part of limb malformations	Kaufman et al., 1972; Slavotinek and Biesecker, 2000; Smith et al., 2006; Deveault et al., 2011
Cornelia de Lange syndrome	*NIPBL* (heterozygou s); *SMC1A* (X-linked); *SMC3* (heterozygou s) (mutations in the latter 2 genes may be less likely to be associated with VACTERL- like features)	Renal anomalies, limb anomalies	Characteristic facial appearance; characteristic limb anomalies	Krantz et al., 2004; Tonkin et al., 2004; Selicorni et al., 2005; Deardorff et al., 2007; Pié et al., 2010
Currarino syndrome	*MNX1* (heterozygous)		Presacral mass (e.g., teratoma, lipoma), anterior meningocele	Ross et al., 1998; Hagan et al., 2000; Urioste et al., 2004; Wang et al., 2006
Diamond-Blackfan anemia	Multiple Ribosomal protein genes: *RPL5*, RPS7, RPS10, *RPS11, RPS17, RPS19, RPS24, RPS 26, RPL35A* (heterozygous)	Cardiac malformations, renal anomalies, limb anomalies, genitourinary anomalies	Dysmorphic facial features (including clefts), Hematologic anomalies, oncologic complications	Doherty et al., 2010; Vlachos and Muir, 2010
Diarrhea 3, secretory sodium, congenital, syndromic	*SPINT2* (heterozygous)	Anal atresia, renal anomalies, limb anomalies	Congenital sodium diarrhea, ocular anomalies (including corneal erosions), choanal atresia	Heinz-Erian 2009

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Condition	Associated gene(s)	Features in common with VACTERL association (in individuals with proven mutations)	Features not typically observed in conjunction with VACTERL association	Reference(s)
22q11.2 deletion syndrome (also known by other names, such as DiGeorge syndrome or velocardiofacial syndrome)	22q11.2 deletion (heterozygous)	Cardiac malformations, renal anomalies, numerous other VACTERL-type anomalies have been additionally described	Characteristic dysmorphic facies, specific palatal anomalies, learning difficulties, immune dysfunction, neuropsychiatric disturbances, hypocalcemia	Kobrynski and Sullivan, 2007
Duane radial ray syndrome; IVIC syndrome; Okihiro syndrome	*SALL4* (heterozygous)	Anorectal malformations, renal anomalies, limb anomalies	Ocular anomalies (Duane syndrome), hearing impairment, hematologic anomalies	Al-Baradie et al., 2002; Kohlhase et al., 2002; Kohlhase et al., 2003
Fanconi anemia	Multiple genes (homozygous/compound heterozygous or X-linked); Testing is usually via chromosomal breakage studies	Limb (radial) anomalies, though any VACTERL association-related feature may occur	Skin pigmentation anomalies; hematologic anomalies	Alter et al., 2007; Auerbach 2009
Feingold syndrome	*MYCN* (heterozygous)	Gastrointestinal atresias, cardiac malformations, renal anomalies	Characteristic dysmorphic facies, syndactyly (toe), brachymesophalangy microcephaly, neurological impairment,	van Bokhoven et al., 2005; Marcelis et al., 2008
FOXF1 mutations	*FOXF1* (heterozygous)	Vertebral anomalies, cardiovascular malformations, trachea-esophageal fistula, renal anomalies	Alveolar capillary dysplasia, additional GI anomalies (e.g., pancreatic anomalies)	Stankiewicz et al., 2009
Fraser syndrome	*FRAS1* or *FREM2* (homozygouss/compound heterozygous)	Cardiopulmonary anomalies, renal anomalies, genitourinary malformations	Crypophthalmos, syndactyly	McGregor 2003; Jadeja 2005; Van Haelst 2008
GDF6 mutations	*GDF6* (heterozygous)	Vertebral malformations, renal anomalies, genitourinary anomalies	Ophthalmologic anomalies	Asai-Coakwell et al., 2009
Hand-foot-genital syndrome	*HOXA13* (heterozygous)	Genitourinary malformations, limb anomalies	Limb anomalies including dysmorphic first digits	Stern et al., 1970; Mortlock and Innis, 1997; Goodman et al., 2000

Condition	Associated gene(s)	Features in common with VACTERL association (in individuals with proven mutations)	Features not typically observed in conjunction with VACTERL association	Reference(s)
Holt-Oram syndrome	*TBX5* (heterozygous)	Cardiac malformations, limb anomalies	Cardiac conduction disease (also reported in VACTERL association)	Basson et al., 1997; McDermott et al., 2005
HOXD13 mutations	*HOXD13* (heterozygous)	Anal atresia, cardiac malformations, vesicoureteric reflux	Fusion of distal interphalangeal joints	Garcia-Barcelo et al., 2008
Mitochondrial mutations	Mitochondrial DNA mutations (and/or clear biochemical evidence of mitochondrial dysfunction)	Individual or multiple component features	Signs/symptoms consistent with mitochondrial disease	Solomon et al., 2011a
Mullerian aplasia and hyperandrogenism	*WNT4* (heterozygous)	Renal anomalies, genitourinary anomalies	Hyperandrogenism	Biason-Lauber et al., 2004
Opitz G/BBB syndrome	*MID1* (X-linked); deletion 22q11.2 (heterozygous)	Anorectal malformations, cardiac malformations, tracheo-esophageal fistula, genitourinary malformations (hypospadias)	Hypertelorism, syndactyly	McDonald-McGinn 1995; Quaderi 1997; De Falco 2003
Pallister-Hall syndrome	*GLI3* (heterozygous)	Anorectal malformations, renal anomalies, limb anomalies	Hypothalamic hamartoma, clefting (including bifid epiglottis), nail hypoplasia, postaxial polydactyly as limb anomaly	Kang et al., 1997; Killoran et al., 2000; Johnston et al., 2005
Robinow syndrome	*WNT5A* (heterozygous)	Vertebral anomalies, limb anomalies, genitourinary anomalies	Characteristic dysmorphic facial appearance, dental anomalies	Robinow et al., 1969, Vera-Roman 1973; Person et al., 2010
STAR syndrome; Toe syndactyly, telecanthus, and anogenital and renal malformations	*FAM58A* (X- linked)	Anogenital malformations, renal anomalies	Characteristic dysmorphic facial appearance, toe syndactyly	Unger et al., 2008
Thrombocytopenia-absent radius syndrome	*RBM8A* (Homozygous/compound heterozygous, typically involving 1q21.1 deletion in one allele)	Radial anomalies; many VACTERL-associated findings have been described	Unaffected thumbs; thrombocytopenia	Greenhalgh et al., 2002; Griesinger et al., 2005; Albers et al., 2012
Townes-Brocks syndrome	*SALL1* (heterozygous)	Anorectal malformations, cardiac malformations, limb (radial) anomalies,	Dysmorphic ears, hearing impairment	Kohlhase et al., 1998; Powell and Michaelis 1999

Condition	Associated gene(s)	Features in common with VACTERL association (in individuals with proven mutations)	Features not typically observed in conjunction with VACTERL association	Reference(s)
		renal anomalies, limb (radial) anomalies,		
Ulnar-Mammary syndrome	*TBX3* (heterozygous)	Cardiac malformations, limb anomalies, genitourinary malformations	Apocrine and endocrine anomalies, characteristic ulnar anomalies as part of limb anomalies	Bamshad et al., 1997; Wollnik et al., 2002; Linden et al., 2009
VACTERL/VACTERL-H	*ZIC3* (X-linked)	All features of VACTERL association	May include situs abnormalities, hydrocephalus	Wessels et al., 2010; Chung et al., 2011

GI: gastrointestinal; GU: genitourinary; H: hydrocephalus; TEF: tracheo-esophageal fistula