Published in final edited form as:
Clin Dysmorphol. 2012 October ; 21(4): 191–195. doi:10.1097/MCD.0b013e328358243c.

VATER/VACTERL association: identification of seven new twin pairs, a systematic review of the literature, and a classical twin analysis

Enrika Bartels[a,*], **Anna C. Schulz**[b,*], **Nicole W. Mora**[i], **Daniel E. Pineda-Alvarez**[i], **Charlotte H. W. Wijers**[j], **Carlo M. Marcelis**[k], **Rüdiger Stressig**[g], **Jochen Ritgen**[g], **Eberhard Schmiedeke**[a,h], **Manuel Mattheisen**[a,c,d], **Markus Draaken**[a,c], **Per Hoffmann**[a,c], **Alina C. Hilger**[a], **Gabriel C. Dworschak**[a], **Friederike Baudisch**[a,e], **Michael Ludwig**[e], **Soyhan Bagci**[b], **Andreas Müller**[b], **Ulrich Gembruch**[f], **Annegret Geipel**[f], **Christoph Berg**[f], **Peter Bartmann**[b], **Markus M. Nöthen**[a,c], **Iris A.L.M. van Rooij**[j], **Benjamin D. Solomon**[i], and **Heiko M. Reutter**[a,b]

[a]Institute of Human Genetics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [b]Department of Neonatology, Children's Hospital, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [c]Department of Genomics, Life and Brain Center, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [d]Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [e]Department of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn [f]Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Bonn [g]Praenatal.de – Partnership of Private Practices for Prenatal Medicine and Genetics, Düsseldorf/Cologne [h]Department of Pediatric Surgery and Urology, Center for Child and Adolescent Health, Hospital Bremen-Mitte, Bremen, Germany [i]Medical Genetics Branch, National Human Genome Research Institute, Bethesda, Maryland, USA [j]Departments of Epidemiology, Biostatistics, and HTA, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [k]Human Genetics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Abstract

The VATER/VACTERL association is typically defined by the presence of at least three of the following congenital malformations: vertebral anomalies, anal atresia, cardiac malformations, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. The identification of 14 twin pairs with an initial diagnosis of VATER/VACTERL association at our clinical centers led to the performance of a classical twin study. This involved a thorough evaluation of these 14 twin pairs and a further 55 twin pairs identified from a systematic review of the literature. The zygosity, concordance, and malformation status of all 69 twin pairs were evaluated. Twenty-four twin pairs

Correspondence to Heiko M. Reutter, Department of Neonatology and Institute of Human Genetics, University of Bonn, Sigmund-Freud-Str. 25, D-53127 Bonn, Germany, Tel: +49 228 287 51012; fax: + 49 228 287 51011; reutter@uni-bonn.de.
*Enrika Bartels and Anna C. Schulz contributed equally to the writing of this article.

All supplementary digital content is available directly from the corresponding author.

Conflicts of interest
There are no conflicts of interest.

fulfilled the criteria for inclusion in a comparison of the concordance rates between monozygous (MZ) and dizygous (DZ) twin pairs. The pairwise concordance rates were 15% [95% confidence interval (CI) 4–42%] for MZ and 18% (95% CI 5–48%) for DZ twin pairs ($P = 0.53$). The probandwise concordance rates were 27% (95% CI 11–52%) for MZ and 31% (95% CI 13–58%) for DZ twin pairs ($P= 0.40$). Although based on a limited number of twin pairs, the findings of the present study are consistent with the low number of familial cases reported to date, and suggest that the role of inherited genetic factors in the majority of VATER/VACTERL cases is limited.

Keywords

concordant; discordant; dizygous; monozygous; twin study; VACTERL association

Introduction

The acronym VATER/VACTERL association (MIM #192350) refers to the rare, nonrandom co-occurrence of vertebral defects (V), anorectal malformations (A), cardiac defects (C), tracheoesophageal fistula with or without esophageal atresia (TE), renal malformations (R), and limb defects (L) (Quan and Smith, 1973). At the time of writing, no diagnostic biomarkers are available, and commonly used clinical diagnosis requires the presence of at least three major component features (CFs) (Quan and Smith, 1973; Czeizel and Ludányi, 1985). Population-based epidemiological studies in Europe and the USA have reported a prevalence among infants of one in 10 000 to one in 40 000 (Khoury *et al.*, 1983; Czeizel and Ludányi, 1985; Botto *et al.*, 1997). The involvement of environmental factors in the etiology of the VATER/ VACTERL association is suggested by both its typically sporadic occurrence (Rittler *et al.*, 1996; Botto *et al.*, 1997) and by reports of discordant monozygous (MZ) twin pairs (Koffler *et al.*, 1978; Cilento *et al.*, 1994; McNamara *et al.*, 1995; Klinger *et al.*, 1997; Cordero *et al.*, 2006; Camacho *et al.*, 2008; Solomon *et al.*, 2011a). Reported environmental factors include maternal diabetes, uterine vascular pathology, and infertility treatment (Czeizel and Ludányi, 1985; Chan *et al.*, 2002; Ornoy, 2007; Wijers *et al.*, 2010). However, the involvement of genetic factors is suggested by reports of familial occurrence (Fuhrmann *et al.*, 1958; Say *et al.*, 1971; Finer *et al.*, 1978; Auchterlonie and White, 1982; McMullen *et al.*, 1996; Nezerati and McLeod, 1999; Becker *et al.*, 2009; Solomon *et al.*, 2010), the finding of a significant increase in the prevalence of CFs among the first-degree relatives of affected individuals (Solomon *et al.*, 2010), and the presence of chromosomal (micro) aberrations in affected individuals (McNeal *et al.*, 1977; Aynaci *et al.*, 1996; Cinti *et al.*, 2001; Walsh *et al.*, 2001; Yamada *et al.*, 2009; Schramm *et al.*, 2011; Solomon *et al.*, 2011b).

Fourteen twin pairs with an initial diagnosis of VATER/ VACTERL association were identified at three participating clinical centers, and this led us to carry out the first classical twin study for this disorder. This involved a thorough evaluation of these 14 twin pairs and a further 55 twin pairs identified from a systematic review of the literature.

Materials and methods

Participants

All of the 69 twin pairs investigated in the present study were ascertained on the basis of the assignment of an initial diagnosis of a VATER/VACTERL association in at least one twin. All twin pairs were re-evaluated in terms of the precise nature of the major CFs, zygosity, and concordance status, and the presence of additional malformations or disorders beyond the spectrum of the VATER/VACTERL association or known syndromes (e.g. Goldenhar syndrome, Fanconi anemia). The twin analysis was restricted to twin pairs in which at least one twin presented with a minimum of three major CFs of the VATER/VACTERL association. Twin pairs with additional congenital anomalies or disorders that are incompatible with the spectrum of VATER/VACTERL association were excluded from the twin analysis. We also excluded twin pairs with insufficient information on their zygosity status from the twin analysis.

Twin pairs with VATER/VACTERL association identified through the participating centers

Six unreported twin pairs with an initial diagnosis of the VATER/VACTERL association were identified from two participating German centers: Bonn (n=3) and Düsseldorf/ Cologne (n=3). From June 2002 to October 2008, a total of 1130 twin pregnancies were monitored at the Department of Obstetrics and Prenatal Medicine at the University Hospital of Bonn. Similarly, from January 2002 to September 2010, a total of 3742 twin pregnancies in Düsseldorf and Cologne were monitored at ‘Praenatal.de’, a partnership of private practices for prenatal medicine and genetics. The phenotype of the affected twins was assessed retrospectively from findings at the postnatal clinical examination and documented information on general development. The zygosity status of all same-sex twins who fulfilled the clinical criteria of the VATER/ VACTERL association (n=3) was determined using the PowerPlex 16 System according to the manufacturer’s recommendations (Promega, Madison, Wisconsin, USA).

Four unreported twin pairs were identified within the context of a National Institutes of Health (Bethesda, Maryland, USA) based study on the VATER/VACTERL association. From October 2008 to August 2011, 161 unrelated families with a suspected VATER/ VACTERL association were referred or self-referred to the National Human Genome Research Institute at the National Institutes of Health. This number does not include individuals who did not fulfill the criteria for the VATER/ VACTERL association. Of these, 66 unrelated families were seen in person and/or sent samples for genetic research to our laboratory in Bethesda. The zygosity status of all same-sex twins who fulfilled the clinical criteria of the VATER/VACTERL association (n=3) was determined using the Illumina Omni1-Quad SNP micro-array (San Diego, California, USA), which analyzes ~1.2 million single nucleotide polymorphisms throughout the human genome.

Four unreported twin pairs were derived from the AGORA project (Aetiologic research into Genetic and Occupational/Environmental Risk Factors for Anomalies in Children), of the Radboud University Nijmegen Medical Centre (RUNMC) in the Netherlands. Since December 2004, the parents of children with a congenital malformation or childhood cancer

treated at the pediatric departments of the RUNMC have been asked to participate in the AGORA project, which aims to establish a databank and biobank for these disorders, comprised of questionnaire data and DNA. Diagnostic and twin data were retrieved from the medical records, following anamnestic, physical, and radiographic examinations by experienced clinicians. When unknown, the zygosity status of same-sex twins who fulfilled the clinical criteria of the VATER/VACTERL association (n=2) was determined using the Applied Biosystems Identifiler kit (Carlsbad, California, USA).

The study was approved by the respective local ethics committees, and appropriate informed consent was obtained from all parents or legal guardians.

Twin pairs with the VATER/VACTERL association identified through a review of the literature

A systematic review of the literature was carried out to identify twin pairs with an initial diagnosis of the VATER/VACTERL association. The review included electronic databases such as NCBI (http://www.ncbi.nlm.nih.gov/pubmed), and DIMDI (http://www.dimdi.de/static/de/index.html) as well as congress reports. The Medical Subject Headings used were VATER, VACTERL association, esophageal atresia, anorectal malformation, congenital heart defect, limb anomalies, renal anomalies, and vertebral anomalies. All reports were reviewed independently by two of the authors (A.C.S. and H.M.R.) to exclude duplicated reports.

Statistics

To compare the concordance rates of the MZ and dizygous (DZ) twin pairs, both pairwise and probandwise concordance rates were calculated. All concordance rates were calculated with the 95% confidence interval (CI), and the difference in the concordance rates between MZ and DZ pairs was tested using the Fisher exact test to assess one-tailed *P* values (Allen *et al.*, 1967; Risch, 2001). Probandwise concordance rates can be interpreted as the recurrence risk in the co-twin of an affected individual (Risch, 2001). Furthermore, we calculated the MZ/DZ ratio for pairwise and probandwise concordance rates.

Results

Twin pairs with the VATER/VACTERL association included in the twin analysis

We identified 14 unreported twin pairs with an initial diagnosis of the VATER/VACTERL association from our three centers and 55 twin pairs from the literature. Reevaluation of the precise nature of CFs of our 14 twin pairs showed that nine twin pairs did not fulfill the conservative clinical criteria for the VATER/VACTERL association (less than three CFs or the presence of additional malformations beyond the spectrum of the VATER/VACTERL association in the affected twin; Supplementary Table 2). Of the 55 twin pairs with an initial diagnosis of the VATER/VACTERL association reported in the literature, 38 twin pairs were excluded from the present twin study because of the presence of additional malformations and/or lack of information on phenotype, zygosity, or concordance (Supplementary Tables 1 and 2). In summary, a total of seven twin pairs from our centers and 17 twin pairs from the literature were included in the present twin study (Table 1).

Twin analysis

Analyses were carried out on two MZ concordant, 11 MZ discordant, two DZ concordant, and nine DZ discordant twin pairs. The pairwise concordance rates were 15% (95% CI 4–42%) for MZ twin pairs and 18% (95% CI 5–48%) for DZ twin pairs (P=0.53). The probandwise concordance rates were 27% (95% CI 11–52%) for MZ twin pairs and 31% (95% CI 13–58%) for DZ twin pairs (P=0.40). Concordant rates resulted in MZ/DZ ratios of 0.83 for the pairwise analysis and 0.87 for the probandwise analysis (Table 2).

Discussion

Although a systematic literature search identified a substantial number of twin pairs with the VATER/ VACTERL association, it was necessary to exclude 69% (38/55) of these from further analysis. This was either because of a lack of information on phenotype, zygosity, or concordance or the presence of additional congenital anomalies or disorders incompatible with the spectrum of the VATER/VACTERL association. The remaining twin pairs were subjected to a classic twin analysis, which showed almost equal pairwise and probandwise concordance rates for DZ and MZ twin pairs. Although this conservative approach reduced the number of patients available for analysis, such an approach is necessary in any study focusing on potentially heterogeneous conditions with a large differential diagnosis if valid results are to be obtained.

The present observation suggests that inherited genetic factors do not play a major role in the majority of VATER/ VACTERL association cases. Instead, environmental factors, postzygotic somatic or de-novo germline mutations (Kondo *et al.*, 2002), or epigenetic events occurring early in embryogenesis (Yamazawa *et al.*, 2008) may be implicated. The application of new genomic technologies such as high-resolution copy number variation studies or next-generation exome sequencing in future studies should lead to the identification of some of these causes.

No environmental risk factors such as maternal diabetes, uterine vascular pathology, and inferitlity treatment were reported in the pregnancies of the MZ discordant twin pairs ascertained through our centers. However, this information was not recorded for the MZ discordant twin pairs identified through our literature review, and thus the presence of these risk factors in these cases cannot be excluded.

Few classical twin studies of rare congenital malformations have been reported to date, and thus experience in the interpretation of such results is limited. As in all twin studies that rely on case reports from the literature, potential biases may have impacted on the present results. These include underascertainment of disease-discordant DZ twin pairs (Hamilton and Mack, 2000) and underascertainment of individuals whose co-twins had died (Hay and Wehrung, 1970). Prospective population-based ascertainment of twins is the ideal approach. However, given the rarity of the VATER/VACTERL association, the ascertainment of a sufficient number of affected twins would require a systematic surveillance of very large populations. Furthermore, the clinical phenotypes of patients with VATER/VACTERL association are often poorly delineated. This is mainly because of the imprecise phenotypic definition, and leads to the risk of the inadvertent inclusion of cases with a syndromic

diagnosis (Shaw-Smith, 2006). Hence, phenotypic evaluation of twin pairs ascertained through the literature has been restricted by the limited availabity of detailed information. Thus, affected twins with underlying syndromes that may overlap or resemble the VATER/ VACTERL association, for example Feingold syndrome, CHARGE syndrome, 22q11 deletion syndrome, etc., may have been among the cases from the literature and this may have influenced the results of our analysis.

Given the small number of twin pairs analyzed, our analysis and the generalizibility of the results are limited.

Conclusion

To our knowledge, the present study is the first to have used the twin method to assess the contribution of genetic factors to the VATER/VACTERL association. Although based on a limited number of twin pairs, our findings are consistent with the low number of familial observations reported to date, and suggest that the role of inherited genetic factors in the etiology of VATER/ VACTERL cases is limited. However, given the small sample size, our findings should be interpreted with caution.

Acknowledgments

The authors thank all the patients and their parents for their cooperation. The authors also thank the German self-help organization for people with anorectal malformations (SoMA e.V.). H.M.R., E.B., E.S., M.D., M.L., M.M., P.H., A.H., G.D., F.B., and M.M.N. are members of the ‘Network for the Systematic Investigation of the Molecular Causes, Clinical Implications, and Psychosocial Outcome of Congenital Uro-Rectal Malformations (CURE-Net),’ which is supported by a research grant (01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF). The research carried out at the National Institutes of Health was supported by the Division of Intramural Research, National Human Genome Research Institute, National Institutes of Health and Human Services, USA. Charlotte Wijers is supported by a grant from the Radboud University Nijmegen Medical Centre. GD is supported by the University of Bonn, BONFOR, grant number O-149.0096.

References

Allen G, Harvald B, Shields J. Measures of twin concordance. Acta Genet Stat Med. 1967; 17:475–481. [PubMed: 6072881]

Auchterlonie IA, White MP. Recurrence of the VATER association within a sibship. Clin Genet. 1982; 21:122–124. [PubMed: 7083612]

Aynaci FM, Celep F, Karaguzel A, Baki A, Yildiran A. A case of VATER association associated with 9qh+ Genet Couns. 1996; 7:321–322. [PubMed: 8985737]

Becker K, Howard K, Klazinga D, Hall CM. Caudal duplication syndrome with unilateral hypoplasia of the pelvis and lower limb and ventriculoseptal heart defect in a mother and features of VATER association in her child. Clin Dysmorphol. 2009; 18:139–141. [PubMed: 19474703]

Botto LD, Khoury MJ, Mastroiacovo P, Castilla EE, Moore CA, Skjaerven T, et al. The spectrum of congenital anomalies of the VATER association: an international study. Am J Med Genet. 1997; 71:8–15. [PubMed: 9215761]

Camacho AF, Schneider A, Dorsainville D, Schutzman DL. Monozygotic twins discordant for VACTERL association. Prenat Diagn. 2008; 28:366–368. [PubMed: 18382992]

Chan BW, Chan KS, Koide T, Yeung SM, Leung MB, Copp AJ, et al. Maternal diabetes increases the risk of caudal regression caused by retinoic acid. Diabetes. 2002; 51:2811–2816. [PubMed: 12196475]

Cilento BG Jr, Benacerraf BR, Mandell J. Prenatal and postnatal findings in monochorionic, monoamniotic twins discordant for bilateral renal agenesis-dysgenesis (perinatal lethal renal disease). J Urol. 1994; 151:1034–1035. [PubMed: 8126783]

Cinti R, Priolo M, Lerone M, Gimelli G, Seri M, Silengo M, Ravazzolo R. Molecular characterisation of a supernumerary ring chromosome in a patient with VATER association. J Med Genet. 2001; 38:E6. [PubMed: 11158176]

Cordero L, Franco A, Joy SD. Monochorionic monoamniotic twins: neonatal outcome. J Perinatol. 2006; 26:170–175. [PubMed: 16467856]

Czeizel A, Ludányi I. An aetiological study of the VACTERL-association. Eur J Pediatr. 1985; 144:331–337. [PubMed: 4076249]

Finer NN, Bowen P, Dunbar LG. Caudal regression anomalad (sacral agenesis) in siblings. Clin Genet. 1978; 13:353–358. [PubMed: 657575]

Fuhrmann W, Rieger A, Vogel F. Two observations on the genetics of atresia ani. Arch Kinderheilkd. 1958; 158:264–270. [PubMed: 13617965]

Hamilton AS, Mack TM. Use of twins as mutual proxy respondents in a case–control study of breast cancer: effect of item nonresponse and misclassification. Am J Epidemiol. 2000; 152:1093–1103. [PubMed: 11117619]

Hay S, Wehrung DA. Congenital malformations in twins. Am J Hum Genet. 1970; 22:662–678. [PubMed: 4253283]

Khoury MJ, Cordero JF, Greenberg F, James LM, Erickson JD. A population study of the VACTERL association: evidence for its etiologic heterogeneity. Pediatrics. 1983; 7:815–820. [PubMed: 6835768]

Klinger G, Merlob P, Aloni D, Maayan A, Sirota L. Normal pulmonary function in a monoamniotic twin discordant for bilateral renal agenesis: report and review. Am J Med Genet. 1997; 73:76–79. [PubMed: 9375927]

Koffler H, Aase JM, Papile LA, Coen RW. Persistent cloaca with absent penis and anal atresia in one of identical twins. J Pediatr. 1978; 93:821–823. [PubMed: 712494]

Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, et al. Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. Nat Genet. 2002; 32:285–289. [PubMed: 12219090]

McMullen KP, Karnes PS, Moir CR, Michels VV. Familial recurrence of tracheoesophageal fistula and associated malformations. Am J Med Genet. 1996; 63:525–528. [PubMed: 8826429]

McNamara MF, McCurdy CM, Reed KL, Philipps AF, Seeds JW. The relation between pulmonary hypoplasia and amniotic fluid volume: lessons learned from discordant urinary tract anomalies in monoamniotic twins. Obstet Gynecol. 1995; 85:867–869. [PubMed: 7724141]

McNeal RM, Skoglund RR, Francke U. Congenital anomalies including the VATER association in a patient with del(6)q deletion. J Pediatr. 1977; 91:957–960. [PubMed: 925830]

Nezerati MM, McLeod DR. VACTERL manifestations in two generations of a family. Am J Med Genet. 1999; 82:40–42. [PubMed: 9916841]

Ornoy A. Embryonic oxidative stress as a mechanism of teratogenesis with special emphasis on diabetic embryopathy. Reprod Toxicol. 2007; 24:31–41. [PubMed: 17548185]

Quan L, Smith DW. The VATER association. Vertebral defects, Anal atresia, T-E fistula with esophageal atresia, radial and renal dysplasia: a spectrum of associated defects. J Pediatr. 1973; 82:104–107. [PubMed: 4681850]

Risch N. The genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. Cancer Epidemiol Biomarkers Prev. 2001; 10:733–741. [PubMed: 11440958]

Rittler M, Paz JE, Castilla EE. VACTERL association, epidemiologic definition and delineation. Am J Med Genet. 1996; 63:529–536. [PubMed: 8826430]

Say B, Balci S, Pirnar T, Hiçsönmez A. Imperforate anus/polydactyly/ vertebral anomalies syndrome: a hereditary trait? J Pediatr. 1971; 79:1033–1034. [PubMed: 5125402]

Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology. J Med Genet. 2006; 43:545–554. [PubMed: 16299066]

Schramm C, Draaken M, Bartels E, Boemers TM, Aretz S, Brockschmidt FF, et al. *De novo* microduplication at 22q11.21 in a patient with VACTERL association. Eur J Med Genet. 2011; 54:9–13. [PubMed: 20849991]

Solomon BD, Pineda-Alvarez DE, Raam MS, Cummings DA. Evidence for inheritance in patients with VACTERL association. Hum Genet. 2010; 127:731–733. [PubMed: 20369369]

Solomon BD, Pineda-Alvarez DE, Hadley DW, Teer JK, Cherukuri PF, Hansen NF, et al. Nisc Comparative Sequencing Program . Personalized genomic medicine: lessons from the exome. Mol Genet Metab. 2011a; 104:189–191. [PubMed: 21767969]

Solomon BD, Pineda-Alvarez DE, Hadley DW, Keaton AA, Agochukwu NB, Raam MS, et al. De novo deletion of chromosome 20q13.33 in a patient with tracheo-esophageal fistula, cardiac defects and genitourinary anomalies implicates GTPBP5 as a candidate gene. Birth Defects Res A Clin Mol Teratol. 2011b; 91:862–865. [PubMed: 21608104]

Walsh LE, Vance GH, Weaver DD. Distal 13q deletion syndrome and the VACTERL association: case report, literature review, and possible implications. Am J Med Genet. 2001; 98:137–144. [PubMed: 11223849]

Wijers CH, de Blaauw I, Marcelis CL, Wijnen RM, Brunner H, Midrio P, et al. Research perspectives in the etiology of congenital anorectal malformations using data of the International Consortium on Anorectal Malformations: evidence for risk factors across different populations. Pediatr Surg Int. 2010; 26:1093–1099. [PubMed: 20730541]

Yamada K, Uchiyama A, Arai M, Kubodera K, Yamamoto Y, Orii KO, et al. Severe upper airway stenosis in a boy with partial monosomy 16p13.3pter and partial trisomy 16q22qter. Congenit Anom (Kyoto). 2009; 49:85–88. [PubMed: 19489960]

Yamazawa K, Kagami M, Fukami M, Matsubara K, Ogata T. Monozygotic female twins discordant for Silver-Russell syndrome and hypomethylation of the H19-DMR. J Hum Genet. 2008; 53:950–955. [PubMed: 18709478]

Table 1

Twin pairs with the VATER/VACTERL association included in the present twin study

	MZ twin pairs (concordant/ discordant)	DZ twin pairs (concordant/ discordant)
Literature	10 (2/8)	7 (2/5)
Present report	3 (0/3)	4 (0/4)

DZ, dizygous; MZ, monozygous.

Table 2

Pairwise and probandwise concordance rates for MZ and DZ twin pairs with the VATER/VACTERL association in the present cohort

	MZ twin pairs	DZ twin pairs	MZ/DZ ratio	*P* values*
Pairwise concordance rate (95% CI)[a]	15% (4–42%)	18% (5–48%)	0.83	0.53
Probandwise concordance rate (95% CI)[a]	27% (11–52%)	31% (13–58%)	0.87	0.40

CI, confidence interval; DZ, dizygous; MZ, monozygous.

** P* values from the Fisher exact test to assess one-tailed *P* values.

[a] Concordance rates (probandwise and pairwise) were calculated according to Allen *et al.* (1967).