Hum Genet (2010) 127:731–733
DOI 10.1007/s00439-010-0814-7

SHORT REPORT

Evidence for inheritance in patients with VACTERL association

Benjamin D. Solomon · Daniel E. Pineda-Alvarez · Manu S. Raam · Derek A. T. Cummings

Received: 29 December 2009 / Accepted: 19 March 2010 / Published online: 6 April 2010

Abstract VACTERL/VATER association is typically a sporadic disorder. We present data on inheritance in 78 probands with VACTERL association, and show that 9% of probands have a primary relative with at least one component feature of VACTERL association. The prevalence of component features in first-degree relatives is significantly higher than expected in the general population, which has implications for counseling of affected families and for research into possible etiologies.

Introduction

VACTERL association is relatively common, though the causes remain unknown (Czeizel and Ludányi 1985). The condition, sometimes termed VATER association depending on which features are included, is an acronym for the major component features, not all of which may be present in patients: vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheo-esophageal fistula (TE); renal abnormalities (R), and limb anomalies (L); other features (e.g., genitourinary anomalies) are not uncommon. Diagnostic criteria are controversial, and the many overlapping conditions make accurate diagnosis challenging (Rittler et al. 1996; Källén et al. 2001). Though there is some evidence for inheritance of component features, the condition is usually sporadic (in this context, meaning occurring in an isolated fashion), with low risk of having an affected relative (Weaver et al. 1986; Brown et al. 1999). We present inheritance data on 78 patients with VACTERL association and demonstrate evidence for inheritance in at least a subset of patients.

Methods

We collected data through our National Human Genome Research Institute IRB-approved protocol on VACTERL association. Patients were diagnosed with VACTERL/VATER association prior to inclusion, were included only if they had at least two major component features, and were excluded if alternate diagnoses were felt to be likely. No patient had an identified genetic etiology. We saw 10 probands and 25 total relatives at the National Institutes of Health. For patients who did not come to the NIH, we reviewed available medical records, with medical histories provided directly from patients, relatives, and referring clinicians.

Results

Seven of 78 probands (9.0%) had first-degree relatives with at least one major component feature of VACTERL association (Fig. 1; see supplemental material for detailed

Electronic supplementary material The online version of this article (doi:10.1007/s00439-010-0814-7) contains supplementary material, which is available to authorized users.

B. D. Solomon (✉) · D. E. Pineda-Alvarez · M. S. Raam
Medical Genetics Branch, National Human Genome Research Institute, NIH MSC 3717, Bethesda, MD 20892, USA
e-mail: solomonb@mail.nih.gov

M. S. Raam
National Institutes of Health Research Scholars Program, Howard Hughes Medical Institute, Bethesda, MD, USA

D. A. T. Cummings
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

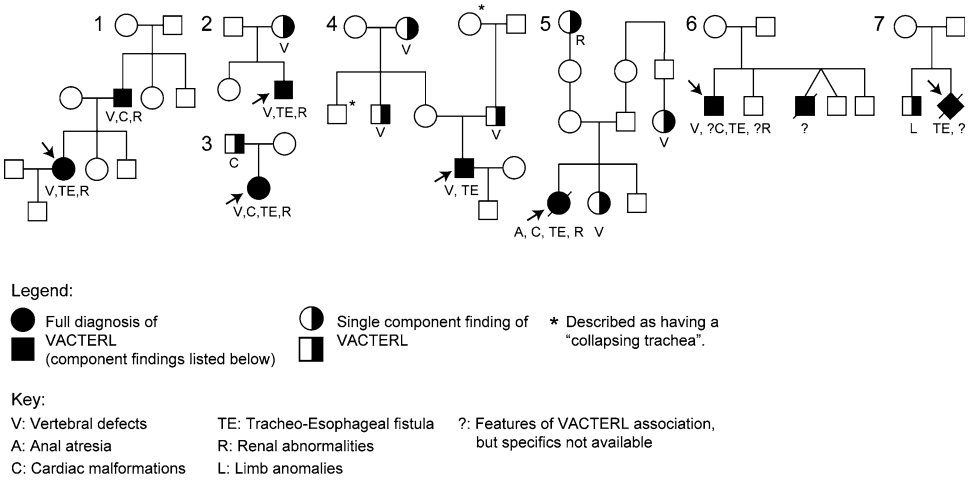

Fig. 1 Pedigrees indicating major component features in probands diagnosed with VACTERL association, as well as findings in affected first-degree relatives. Other, more distant relatives are shown for the sake of completeness, though the presence of major component features in these individuals was not used for analysis

information). This is not significantly higher than the 5.8% prevalence of affected first-degree relatives of patients with tracheo-esophageal fistula/esophageal atresia (with or without other anomalies) reported by Brown et al. (1999) ($p = 0.3074$). For pedigrees in which detailed family data were available, 7 of 141 first-degree relatives (5.0%) had at least one major component finding of VACTERL association.

The proportion (0.0496, 95% Confidence Interval [CI], 0.0224–0.1007) of first-degree relatives with features of VACTERL association is significantly higher than in the general population. We compared our data to: (1) the proportion (0.00248, CI, 0.00241–0.00255) of approximately 2.5 million infants in a Latin American registry with major component features of VACTERL association (Rittler et al. 1996): $\chi^2_{(1)} = 127.9, p < 0.0001$; (2) the proportion (0.0160, CI 0.01598–0.0161) of these features among approximately 11 million infants in a United States registry (Population-based Birth Defects Surveillance 2008): $\chi^2_{(1)} = 10.08$, $p = 0.0015$. Comparing the prevalence of major component features of VACTERL association in first degree relatives of probands (not including those with insufficient evidence, such as features in individual II.1 in pedigree 6) to the general population (Rittler et al. 1996), we find the following odds ratios (OR) V: OR = 216.0, CI, 79.5–587.2; C: OR = 12.9, CI, 3.2–52.1; R: OR = 44.8, CI, 11.1–181.4. The severity, type of findings, and presence of other anomalies did not appear to differ between probands with affected relatives and probands without affected relatives. The one exception might be family 7: the proband had hydrocephalus and a brother had ectrodactyly. While VACTERL with hydrocephalus has an inherited component, only one of our seven families had a member with hydrocephalus.

Discussion

Our results show that there is an increased risk of major component features in probands' first-degree relatives, which suggests a genetic basis for the condition in at least some families. Brown et al. (1999) showed evidence that tracheoesophageal fistula/esophageal atresia has an inherited component. Participants in that study were ascertained because of the presence of that specific feature, not the broader diagnosis of VACTERL association.

Just as in patients with a full diagnosis of VACTERL association, the major component features we observed in first-degree relatives, varied widely. It is unclear why vertebral anomalies were the most prevalent finding in first-degree relatives in our cohort, though the small sample size makes it difficult to generalize. However, while scoliosis was common, it does appear that more severe vertebral anomalies were also present in most patients with scoliosis. Several patients (including the proband in pedigree 5) appear to have urogenital anomalies and/or urorectal septal malformation sequence. This is unsurprising, as the embryology and developmental biology of the genitourinary (GU) tract is closely connected to that of the hindgut and renal systems; in addition, previous studies have provided statistical evidence that GU anomalies may be a "secondary" feature of VACTERL association (Rittler et al. 1996).

Acknowledgments The authors would like to express gratitude to the participating patients and families, and would also like to thank Dr. Maximilian Muenke for his support and mentorship. This research was supported by the Division of Intramural Research, National Human Genome Research Institute, National Institutes of Health and Human Services, USA.

References

Brown AK, Roddam AW, Spitz L, Ward SJ (1999) Oesophageal atresia, related malformations, and medical problems: a family study. Am J Med Genet 85:31–37

Czeizel A, Ludányi I (1985) An aetiological study of the VACTERL-association. Eur J Pediatr 144:331–337

Källén K, Mastroiacovo P, Castilla EE, Robert E, Källén B (2001) VATER non-random association of congenital malformations: study based on data from four malformation registers. Am J Med Genet 101:26–32

Population-based Birth Defects Surveillance data from selected states, 2001–2005 (2008) Birth Defects Res A Clin Mol Teratol 82:831-961

Rittler M, Paz JE, Castilla EE (1996) VACTERL association, epidemiologic definition and delineation. Am J Med Genet 63:529–536

Weaver DD, Mapstone CL, Yu PL (1986) The VATER association. Analysis of 46 patients. Am J Dis Child 140:225–229