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Deletion of *JAM-C*, a Candidate Gene for Heart Defects in Jacobsen Syndrome, Results in a Normal Cardiac Phenotype in Mice

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The 11q terminal deletion disorder (11q-) is a rare chromosomal disorder caused by a deletion in distal 11q. Fifty-six percent of patients have clinically significant congenital heart defects. A cardiac "critical region" has been identified in distal 11q that contains over 40 annotated genes. In this study, we identify the distal breakpoint of a patient with a paracentric inversion in distal 11q who had hypoplastic left heart and congenital thrombocytopenia. The distal breakpoint mapped to *JAM-3*, a gene previously identified as a candidate gene for causing HLHS in 11q-. To determine the role of JAM-3 in cardiac development, we performed a comprehensive cardiac phenotypic assessment in which the mouse homolog for *JAM-3*, *JAM-C*, has been deleted. These mice have normal cardiac structure and function, indicating that haplo-insufficiency of *JAM-3* is unlikely to cause the congenital heart defects that occur in 11q- patients. Notably, we identified a previously undescribed phenotype, jitteriness, in most of the sick or dying adult *JAM-C* knockout mice. These data provide further insights into the identification of the putative disease-causing cardiac gene(s) in distal 11q, as well as the functions of JAM-C in normal organ development.

Key words: Jacobsen syndrome; heart; JAM-3; hypoplastic left heart; mouse model; 11q deletion

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INTRODUCTION

The 11q terminal deletion disorder (11q-) is a rare chromosomal disorder caused by deletions in distal 11q [Jacobsen et al., 1973]. We previously performed a prospective genotype/phenotype study on 110 11q- patients. We defined "critical regions" for 14 clinical phenotypes, consistent with a contiguous gene model for the constellation of clinical problems that occur in 11q- [Grossfeld et al., 2004].

Congenital heart malformations are the most common birth defects, occurring in 0.7% of liveborn infants [Ferencz, 1990]. Fifty-six percent of 11q- patients have clinically significant heart defects, and there is no correlation between deletion size and the presence, or type, of congenital heart defect. Of the 56% of patients with congenital heart defects, two-thirds have so-called cardiac flow defects, involving either the ventricular septum and/or left-sided structures. Remarkably, we found that hypoplastic left heart (HLH), one of the most severe congenital heart defects, occurs in about 5% of all 11q- patients, higher than for any other known chromosomal disorder. In addition to flow defects, one-third of 11q- patients with congenital heart disease have many other common severe heart defects. These defects include double outlet right ventricle, d-transposition of the great arteries, pulmonary atresia with intact ventricular septum, tricuspid atresia, type B interruption of the aortic arch, truncus arteriosus, atrial septal defects, total anomalous pulmonary venous connections, and complete atrioventricular canal. Taken together, understanding the genetic basis of the congenital heart defects in 11q- should provide critical and

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novel insights into the pathogenesis of many of the major congenital heart defects that occur in the general population.

We [Grossfeld, 2008, unpublished work] and Phillips et al. [2002] have identified the smallest size terminal deletion in 11q- in association with congenital heart defects to be about 7 Mb. This cardiac "critical region" contains over 40 annotated genes. Based on mapping and gene expression data, Phillips, et al., proposed junction adhesion molecule (JAM)-3 as a candidate gene for causing at least a subset of the congenital heart defects in 11q-, including HLHS.

JAM-3 is a member of the IgG superfamily of molecules [Ebnet et al., 2003]. Previous studies have demonstrated that the JAM-3 protein is on the surface of platelets [Santoso et al., 2002], and that haplo-insufficiency of *JAM-3* might contribute to the platelet disorder in 11q- (Paris–Trouseau syndrome). In mice, the JAM-3 homolog, JAM-C, is also required for normal motor neuron function [Scheiermann et al., 2007]. The role of *JAM-3* in heart development is unknown. Previous studies [Phillips et al., 2002] have demonstrated that *JAM-3* is expressed in the human embryonic heart, specifically the aorta, aortic valve, and left ventricle. Immunostaining using a JAM-C-specific antibody demonstrated robust expression of JAM-C in the epicardium of the atria, ventricles, and outflow tract, by ED11 in mice. JAM-C expression was also detected in the myocardium, by ED11 [Grossfeld, unpublished work]. Interestingly, up to 90% of homozygous *JAM-C* knockout mice die on the first day of life, appearing cyanotic and in respiratory distress [Praetor et al., 2009].

In this report, we mapped the distal breakpoint of a paracentric inversion in 11q in a patient with HLH and thrombocytopenia, two common problems in patients with 11q [Grossfeld et al., 2004]. The distal breakpoint mapped to the *JAM-3* gene, suggesting that disruption of *JAM-3* was disease-causing in this patient. Our data, combined with previous studies, implicate *JAM-3* as a strong candidate gene for causing at least a subset of the congenital heart defects that occur in 11q-. Towards that end, we performed a comprehensive cardiac phenotypic analysis on *JAM-C* gene-targeted knockout mice. In a BL6/129 mixed genetic background, *JAM-C* knockout mice have structurally normal hearts. We discuss the implications of these findings with respect to the identification the disease-causing gene(s) for congenital heart defects in distal 11q.

METHODS

(1) All human studies were performed in compliance with the UCSD Internal Review Board protocol.
(2) FISH mappingHuman BAC clones were used to perform FISH on metaphase chromosomes as described previously [Grossfeld et al., 2004]. At least ten metaphase cells were analyzed for each probe used.
(3) Embryo dissection and histological analysisFemales with copulation plugs were considered to be at embryonic development day 0.5 (E0.5) of gestation. Pregnant females were euthanized at E18.5 of gestation, and embryos were dissected for histological analysis as described previously [Liang et al., 2007]. Adult mice were euthanized and the heart was dissected for histological analysis.
(4) Mouse echocardiographyTransthoracic echocardiograms to assess cardiac structure and function were performed as described previously [Bose et al., 2007].

RESULTS

Identification of a Patient With Hypoplastic Left Heart, Congenital Thrombocytopenia, and, a Paracentric Inversion (inv11q23.3-q25)

The proposita was full-term female infant born by natural delivery after an uncomplicated pregnancy to a 21-year-old mother and 27-year-old father. Immediately after birth, she was noted to be cyanotic. A cardiac evaluation revealed HLH. In addition, she was found to have severe thrombocytopenia, with a platelet count of ~20 K. Karyotype analysis was performed and revealed the presence of a paracentric inversion in 11q (inv11q23.3-25). Parental karyotypes were normal, indicating that the inversion was a de novo event. The patient underwent a Norwood procedure as a neonate, and had a prolonged and complicated postoperative course. At age 5 months, she developed multiple thrombi, including in her heart and coronary arteries, resulting in myocardial infarction. The parents elected to withdraw support and she expired shortly thereafter.

Mapping of the Distal Breakpoint of the Paracentric Inversion

Consent to obtain blood was obtained through a UCSD Internal Review Board approved protocol. Metaphase chromosomes were prepared from peripheral blood lymphocytes. Mapping of the distal translocation breakpoint was performed by fluorescence in situ hybridization (FISH) using commercially available human BAC clones, as described previously [Grossfeld et al., 2004]. The distal breakpoint was found to be within a 70 kb region spanning exon 1 of the *JAM-C* gene (Fig. 1).

Genomic Structure of the *JAM-C* Gene and Generation of Gene-Targeted JAM-C Knockout Mice

The human *JAM-3* gene consists of 9 exons spanning an 83 kb region in distal 11q, approximately 1 Mb from the telomere. The gene encodes a 355 amino acid protein that has a predicted signal sequence at the amino terminus, followed by two immunoglobulin-binding domains. It is conserved in humans and mice. In mice, the *JAM-3* homolog, *JAM-C*, encodes a 310 amino acid protein that is 87% identical to the human gene. The shorter form in the mouse is due to a shorter exon 1 sequence, the exon that encodes the predicted signal sequence. In the mouse genome, *JAM-C* also consists of nine exons spanning a 58 kb region. The *JAM-C* gene is located on chromosome 9 in the region syntenic to the Jacobsen syndrome region in distal 11q, and the order of the genes in this region has been completely conserved (Dr. Charles Shaw Smith, personal communication). Gene-targeted *JAM-C* knockout mice were kindly provided by Dr. Sherman Fong (Genentech), which were purchased from Lexicon Genetics (Houston, TX) [Praetor et al., 2009]. The mice were bred into a BL6/129 mixed background.

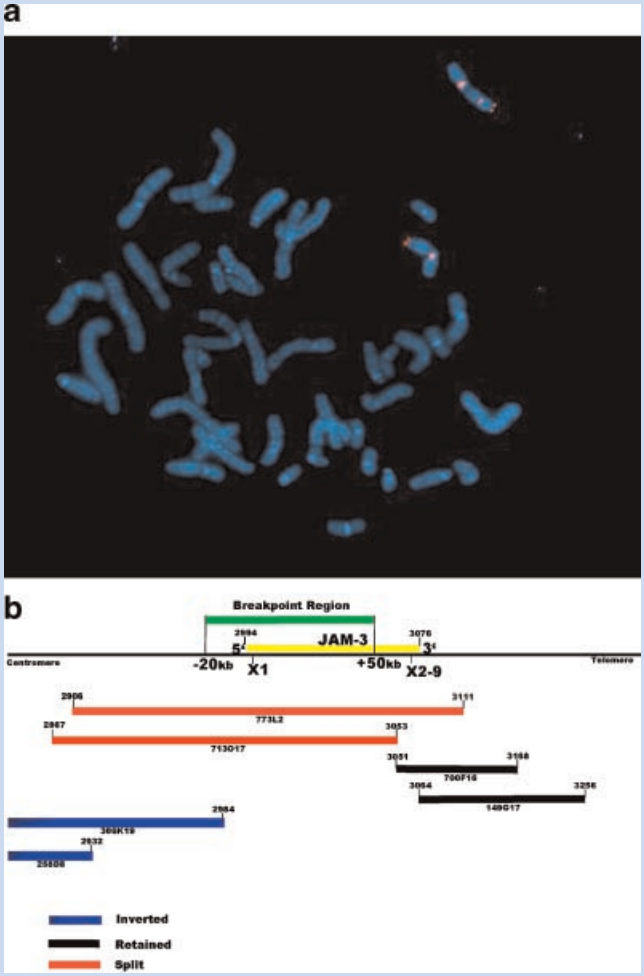

FIG. 1. Mapping of distal breakpoint of paracentric inversion in a patient with hypoplastic left heart and congenital thrombocytopenia. A: FISH demonstrating split signal in chromosome 11q using the subtelomeric probe RP11-773L2, indicating the breakpoint is within the region of the probe. A chromosome 11 centromeric probe was used to identify chromosome 11. Both probes are shown in red. The inverted chromosome is in the upper right corner (two signals in 11q), and the normal chromosome is in the right center of the panel (one signal). B: Schematic diagram indicating exact location of the distal breakpoint using overlapping human BAC probes.

Analysis of ED17.5–18.5 *JAM-C* Knockout Mice

Initially, five ED17.5–18.5 *JAM-C* null embryos and seven wild-type littermate controls underwent histopathologic analysis of their hearts. We hypothesized that if haplo-insufficiency of *JAM-3* caused HLH in the 11q- patients, then deletion of JAM-C in mice would cause either HLH or possibly a less serious cardiac flow defect such as isolated valve abnormalities or ventricular septal defects. The hearts from all five mutants had normal structure, specifically normal chamber sizes, an intact atrial and ventricular septum, and normal valves (Fig. 2, Table I).

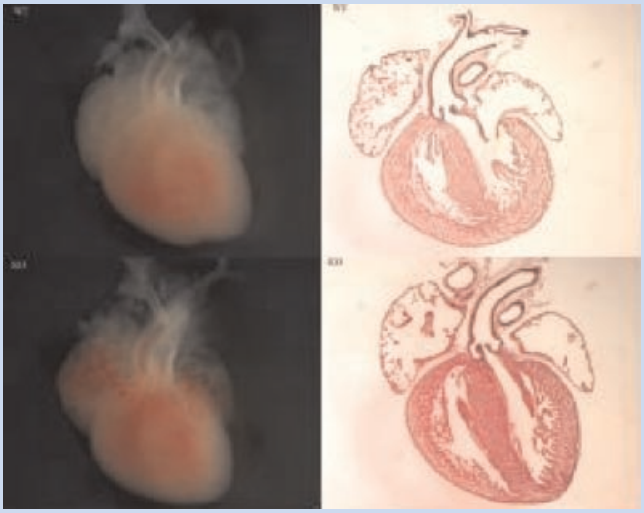

FIG. 2. Gross and histologic analysis of *JAM-C* null knockout mouse heart, and wild-type littermate control, indicating no structural heart defects in the mutant heart. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I. Echocardiographic Analysis of Surviving *JAM-C* Knockout Mice

Genotype	WT	KO	KO/WT, %
No.	4	4	
BW, g	26 ± 2.74	20.75 ± 2.90	80
HR, bpm	569 ± 33	515 ± 27	91
IVSd, mm	0.67 ± 0.04	0.61 ± 0.03	91
LVIDd, mm	3.31 ± 0.145	3.17 ± 0.15	96
LVPWd, mm	0.65 ± 0.035	0.61 ± 0.03	94
IVSs, mm	1.05 ± 0.08	1.1 ± 0.06	105
LVIDs, mm	1.75 ± 0.10	1.56 ± 0.12	89
LVPWs, mm	1.25 ± 0.09	1.1 ± 0.10	88
Ao-ET, msec	47 ± 3	47 ± 2	100
Ao-HR, bpm	569 ± 33	504 ± 25.5	89
FS, %	47.0 ± 3.1	50.6 ± 3.94	106
EDD/PWD	5.10 ± 0.065	5.24 ± 0.26	103
VCF, circ/sec	10.15 ± 1.23	11 ± 1.15	108
LVDd/BW	0.13 ± 0.009	0.161 ± 0.02	124
LVM(d), mg	67.6 ± 9.6	55.8 ± 5.95	83
LV/BW, index (%)	0.258 ± 0.015	0.275 ± 0.019	107

JAM-C KO mice age range, 8–24 weeks.
WT: wild-type; KO: knockout; BW: body weight; HR: heart rate; IVSd: interventricular septum, diastole; LVIDd: left internal diameter, diastole; LVPWd: left ventricular posterior wall dimension, diastole; IVSs: interventricular septum, systole; LVIDs: left ventricular internal diameter, systole; LVPWs: left ventricular posterior wall, systole; Ao-ET: aortic ejection time; Ao-HR, bpm: aorta heart rate, beats per minute; F: fractional shortening; EDD/PWD: end diastolic dimension (LV)/posterior wall diastole VCF, circ/sec: velocity of circumferential fiber shortening; LVDd/BW: left ventricular dimension, diastole/body weight; LVM(d) mg: left ventricular mass (diastole), milligrams; LV/BW: left ventricle/body weight.

TABLE II. Genotypes of 183 21-Day-Old Mice

WT	Het	KO	Total
64	112	7	183

Analysis of JAM-C Null Adult Mice

One hundred eighty-three newborn pups analyzed, and seven homozygous knockouts surviving past the neonatal period were identified (Table II). Three of these mice died spontaneously at ages 4, 5, and 6 months. Of the three mutant mice that died spontaneously, at least two of them appeared sick prior to death. At least one of these was jittery, with decreased activity prior to death. Two of the surviving mutants underwent cardiac analysis at age 2 months, including echocardiography, electrocardiograms, and histopathology. Prior to sacrifice, they had normal activity, were not jittery, but had growth retardation (Fig. 3, Tables III and IV). The two other surviving mutant mice underwent echocardiographic and histopathologic analysis at age 6 months. One of these mice was lethargic and jittery. This mouse also had growth retardation. The other mouse sacrificed at age 6 months appeared mildly ill (slightly decreased activity), jittery, but did not have growth retardation. All four of the surviving mutant postnatal mice had normal cardiac structure and function. Electrocardiograms were performed on two of the mutants and were normal. Cardiac analysis was not performed on the three mice that died.

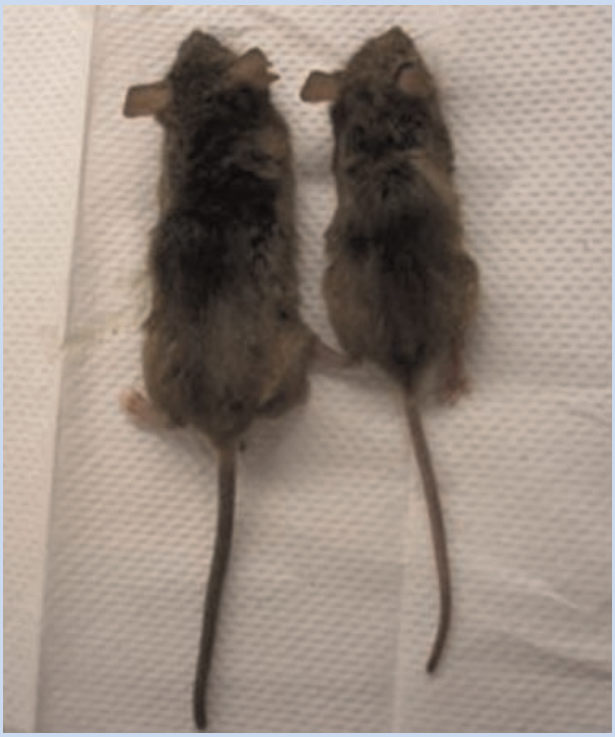

FIG. 3. *JAM-C* null and wild-type littermate control, demonstrating mild growth retardation in the mutant (see Table IV). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Analysis of Other Organ Systems

Extra-cardiac findings and cause of death. Five of seven *JAM-C* mutant mice had mild growth retardation, and weighed 17% less than wild-type littermate controls at age 2 months (Fig. 3, Table IV), although this difference was not statistically significant. In addition to the cardiac analysis, a complete histopathologic organ survey was performed on the two mice (one male, one female) that were sacrificed at age 6 months, along with two wild-type littermate controls. The male mutant lacked mature sperm cells in the epididymis and seminal vesicles, consistent with a defect in spermatogenesis as described previously [Gliki et al., 2004]. Both mutants had megaesophagus (Fig. 4), also previously reported [Imhof et al., 2007]. All other organ systems analyzed appeared normal in the knockout mice compared to wild-type littermate controls, including the lungs, liver, kidney, brain, thymus, spleen, small and large intestine, and stomach. In addition, platelet counts in the 2-month-old mice were normal (data not shown).

DISCUSSION

Cardiac Phenotype

Previous studies, combined with the current study, provide strong evidence implicating JAM-3 to cause the congenital heart defects in 11q-. Towards that end, we performed a cardiac phenotypic analysis on neonatal and adult *JAM-C* targeted knockout mice. In all cases, the hearts analyzed had normal intracardiac structure, function and rhythm. Although we did not analyze the distal descending aorta (i.e., to rule out coarctation of the aorta), there was no indirect evidence of a critical coarctation of the aorta, for example, ventricular dilation or hypertrophy, in these mice. Because we were not able to analyze the hearts of the three adult knockout mice that died, we cannot exclude the possibility that they died either from an arrhythmia, and/or from acquired heart disease. Nonetheless, our results indicate that loss of JAM-C in mice, in a mixed genetic background, does not cause the congenital heart defects that occur in human patients with 11q-.

Recently, Wenger et al. [2006] described a patient with many of the clinical features of 11q-. This patient had an interstitial deletion in distal 11q, within the region of the terminal deletions that had been reported previously in 11q-. Interestingly, this patient had a severe congenital heart defect, double outlet right ventricle. The distal end of the interstitial deletion in this patient was just centromeric to *JAM-3*. Consistent with this, we subsequently found by array comparative genomic hybridization mapping that the patient with the paracentric inversion also had an interstitial deletion centromeric to *JAM-3* (data not shown). Most recently, two siblings with interstitial deletions in distal 11q and congenital heart defects have been reported [Van Zutven et al., 2009]. One patient had an atrial and ventricular septal defect, hypoplasia of the aortic arch and a patent ductus arteriosus. The sibling had HLH. The deletion in both of these siblings was 8.2 Mb, with the distal

TABLE III. Extracardiac Findings in Surviving JAM-C Null Mice

Mouse #	Age	Sex	Growth retardation	Platelets	Jittery[a]	ME	Lungs	Sick[b]
1	2	M	Yes	nl	No	ND	ND	No
2	2	M	Yes	nl	No	ND	ND	No
3	4	M	Yes	ND	Yes	ND	ND	Yes
4	5	F	Yes	ND	Yes	ND	ND	Yes
5	6	M	No	ND	?	ND	ND	?
6	6	F	Yes	ND	Yes	Yes	nl	Yes
7	6	M	No	ND	No	Yes	nl	Yes

ME, megaesophagus.
[a]Mouse #4 was jittery before death, and #5 had not been evaluated for jitteriness within 2 weeks of the time it died, but did not show jitteriness prior to that time.
[b]Mouse #5 was last assessed 2 weeks prior to the time of death, and did not appear ill, mouse #6 appeared severely ill at the time of sacrifice, mouse #7 appeared mildly ill at the time of sacrifice.

breakpoint ~1 Mb centromeric to *JAM-3*. Consequently, based on our mouse and human data, it is unlikely that haplo-insufficiency of *JAM-3* causes left-sided congenital heart defects in 11q- patients.

Extra-Cardiac Findings and Cause of Death

Seven surviving adult homozygous *JAM-C* knockout mice were identified. Platelet counts were performed on two 2-month-old surviving adults. The counts were normal, indicating that JAM-C is not required for platelet production or survival. Based on previous studies, we cannot rule out the possibility that JAM-C is required for normal platelet function. In this regard, previous studies have implicated that haplo-insufficiency of FLI-1 causes at least some of the aspects of Paris–Trousseau syndrome, the platelet disorder that occurs in most 11q- patients [Hart et al., 2000; Spyropoulos et al., 2000].

Five of the seven mutant survivors had mild growth retardation, which occurs commonly in 11q- patients. Growth retardation preceded sickness or death by approximately 2 months or more,

TABLE IV. Weight of Wild-Type Versus Mutant JAM-C Mice at Age 2 Months

Genotype	Age (month)	Weight
WT JM11	2	29.0
WT JM13	2	30.0
WT JM104	2	22.8
WT JM114	2	18.5
WT JM137	2	28.7
WT JM163	2	23.1
Average		25.4
KO JM12	2	21.0
KO JM58	2	27.0
KO JM105	2	23.2
KO JM106	2	24.7
KO JM115	2	14.6
KO JM138	2	20.7
KO JM162	2	16.6
Average		21.1

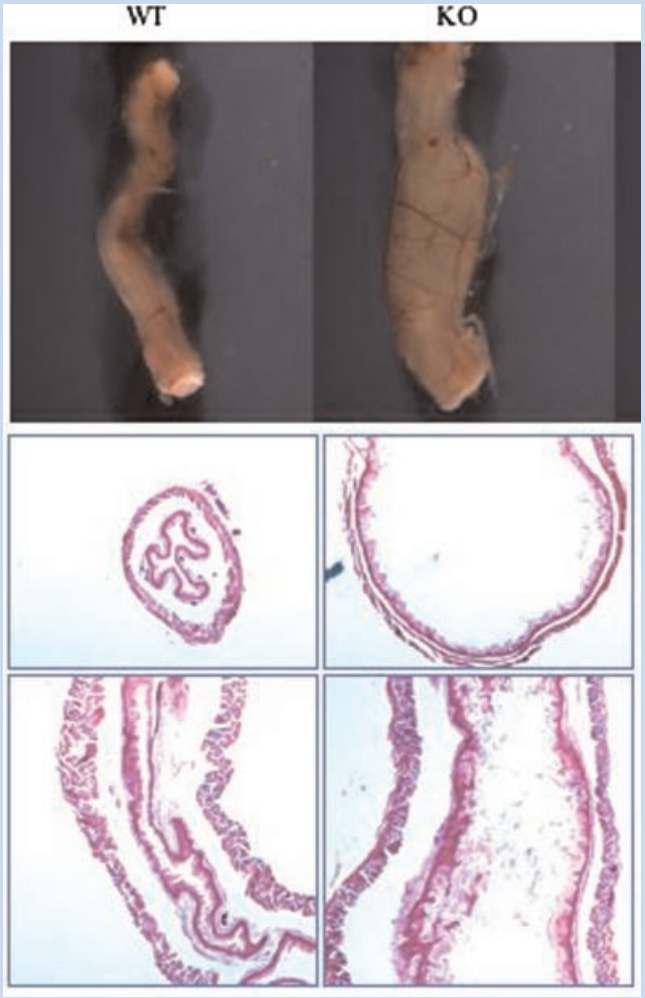

FIG. 4. Gross and histologic analysis of esophagus, demonstrating megaesophagus in the *JAM-C* mutant. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and at least one mutant mouse that appeared sick did not have growth retardation. Consequently, growth retardation is unlikely to be related to the cause of death in these mice. Of the three mutant mice that appeared sick or died, at least two of them were jittery, which was a relatively late development. In addition, analysis of the lungs from a sick 6-month-old mutant demonstrated normal lung histology without evidence of infection. There appears to be multiple causes of death in *JAM-C* knockout mice. The majority of homozygous knockout mice die shortly after birth from an unknown cause. These mice appear cyanotic and in respiratory distress (8). Our analysis of the hearts from ED17.5–18.5 embryos indicates that newborn mice do not die from structural heart defects. Among the minority of homozygous knockout mice that survive to adulthood, there are likely at least two potential causes of death. Imhof et al. [2007] demonstrated opportunistic infection in the lungs to be one likely cause of death. In our study, we identified a dying mouse that had normal lung histology, suggesting a different cause of death. Notably, we observed jitteriness to occur as a late development in most of the sick or dying knockout mice. Jitteriness can be due to numerous etiologies, including sepsis, metabolic derangements, or neurologic causes. Of potential relevance, Scheiermann et al. [2007] have demonstrated that *JAM-C* knockout mice have a motor neuron defect, which is suggestive of a neuromuscular cause of death. The multiple etiologies of death in these mice are likely indications of the complex and important functions of JAM-C.

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