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Research Article

Gene-targeted deletion of *OPCML* and *Neurotrimin* in mice does not yield congenital heart defects

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Abstract

Jacobsen syndrome (11q-) is a rare chromosomal disorder caused by deletions in distal11q. Many of the most common and severe congenital heart defects that occur in the general population occur in 11q-. Previous studies have demonstrated that gene-targeted deletion in mice of ETS-1, a cardiac transcription factor in distal 11q, causes ventricular septal defects with 100% penetrance. It is unclear whether deletion of other genes in distal 11q contributes to the full spectrum of congenital heart defects that occur in 11q-. Three patients with congenital heart defects have been identified that carry a translocation or paracentric inversion with a breakpoint in distal 11q

disrupting one of two functionally related genes, *OPCML* and *Neurotrimin*. OPCML and Neurotrimin are two members of the IgLON subfamily of cell adhesion molecules. In this study, we report the generation and cardiac phenotype of single and double heterozygous gene-targeted *OPCML* and *Neurotrimin* knockout mice. No cardiac phenotype was detected, consistent with a single gene model as the cause of the congenital heart defects in 11q-. © 2014 Wiley Periodicals, Inc.

INTRODUCTION

Jacobsen syndrome (11q-, OMIM #147791), is caused by deletions in the distal region of the long arm of human chromosome 11. Half of all 11q- patients are born with congenital heart defects, including ventricular septal defects, left-sided defects, septal defects, and many of the most common heart defects that occur in the general population. Hypoplastic left heart syndrome, a uniformly fatal congenital heart defect, occurs in 5–10% of all 11q- patients, higher than for any other known chromosomal disorder or genetic syndrome [Grossfeld et al., **2004**]. Recently, through identification of a cardiac "critical" region in distal 11q, we proposed the *ETS-1* transcription factor as a candidate gene for at least a subset of the congenital heart defects that occur in 11q-. Gene-targeted deletion of *ETS-1* in mice caused ventricular septal defects, and the phenotype was dependent on the genetic background [Ye et al., **2010**]. It is unclear whether additional genes in distal 11q might contribute to the spectrum of congenital heart defects that occur in 11q-, or if they are caused exclusively by the deletion of *ETS-1* under the influence of additional genetic background/modifier, epigenetic, and/or environmental factors.

We identified a patient with multiple congenital defects including congenital heart disease, pulmonary valve stenosis and an atrial septal defect, who underwent repair and carries a balanced translocation in distal 11q. Mapping of the breakpoint demonstrated that the translocation disrupted a gene in distal 11q, OPCML. Interestingly, Iida et al. [**2000**] reported on a patient with heterotaxy including a complex constellation of congenital heart defects who carried a paracentric inversion in 11q. The distal breakpoint mapped to a gene in 11q located adjacent to *OPCML*, *Neurotrimin*. Most recently, Luukkonen et al. [**2012**] reported on a patient with intracranial and thoracic aortic aneurysms with a balanced translocation in which one of the chromosomal breakpoints was also in 11q, and disrupted the *Neurotrimin* gene. These authors proposed that the cardiac phenotype was due to disruption of the *Neurotrimin* gene.

OPCML and Neurotrimin are both members of the IgLON super family of cell adhesion molecules and share about 70% amino acid sequence homology. The IgLONs are an immunoglobulin subfamily of glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecules comprised of four members: OPCML/OBCAM, Neurotrimin/hNT/CEPU-1, Kilon/NEGR1/Neurotractin, and LAMP/LSAMP. All four

IgLON members are highly conserved across species. The IgLONs function as cell adhesion molecules and have been hypothesized to regulate neurite outgrowth, synaptogenesis [Struyk et al., 1995 ; Gil et al., 2002 ; Miyata et al., 2003a , 2003b ; Krizsan-Agbas et al., 2008 ; Sugimoto et al., 2010 ; Akeel et al., 2011] and may also function as tumor suppressor genes [Sellar et al., 2003 ; Ntougkos et al., 2005 ; Cui et al., 2008 ; McKie et al., 2012]. To date, the role of the IgLON family members in cardiac development and disease is unknown.

We hypothesized that deletion of *OPCML* and/or *Neurotrimin* might contribute to the spectrum of congenital heart defects that occur in11q-. Here we describe the generation and phenotypic characterization of gene-targeted *OPCML* and *Neurotrimin* knockout mice. Deletion of either gene individually, or in combination as a double heterozygote, did not cause congenital heart defects, supporting a model in which deletion of *ETS-1* along with other modifying factors is necessary and sufficient to cause the congenital heart defects that occur in 11q-.

METHODS

Mapping and Molecular Cloning of the Chromosome 11 and 17 Translocation Breakpoints

Fluorescence in situ hybridization (FISH): Human YAC and BAC clones were used as described previously [Tunnacliffe et al., 1999 ; Grossfeld et al., 2004]. Genomic Southern blots were performed using 10 μg of total genomic DNA for each digest, and run out onto a 0.8% agarose gel at 50 V overnight. Probes were generated by PCR from intervals within the ~50 kilobase (kb) region implicated by FISH mapping. Five million counts of P32 labeled probe were used for each hybridization, performed at 65°C for 2 hr. The blot was washed under high stringency conditions using 0.1× SSC and 0.1% SDS at 65°C. The blot was then exposed overnight at −80°C using two fluorescent amplification screens. Genome walking was performed as described by the manufacturer (Clontech, Mountain View, CA). Specifically, genomic DNA libraries were generated by digesting 10 μg of patient genomic DNA with each of the following four restriction enzymes: *Eco* RV, *Dra* I, *Pvu* II, and *Ssp* I. Gene-specific primers were designed using the sequences at the ends of the restriction site intervals identified by genomic Southern blotting. Two PCR reactions were performed, using the original primer and then a nested primer just 3′ to the first primer. PCR products were cloned into the TA cloning vector (Invitrogen, Carlsbad, CA), and direct DNA sequencing was performed.

Northern Blotting, Southern Blotting, and Western Blotting

A specific *OPCML* and *Neurotrimin* cDNA probe PCR product was subsequently radiolabeled using [32P]dATP by random priming (Invitrogen, San Diego, CA). Human heart RNA blots (Clontech) were hybridized with the radiolabeled probe and visualized by autoradiography, using the manufacturer's protocol for high stringency conditions. Southern- and Western-blotting were performed as described above [Li et al., 2005].

Generation of *OPCML* and *Neurotrimin* Knockout Mice

Floxed *OPCML* and *Neurotrimin* mice were generated by standard techniques using a targeting vector containing a neomycin selection cassette flanked by FRT sites at the Transgenic Core Facility of the University of California, San Diego [Li et al., **2005**].

Exon2 of *OPCML* or exon2 of *Neurotrimin* was inserted into two flanking LoxP sites. After electroporation of the linearized targeting vector into R1 embryonic stem (ES) cells, G418-resistant ES cells were screened for homologous recombination by Southern blot analysis. Heterozyogous recombinant ES clones were identified and microinjected into blastocysts from C57BL/6J mice to generate male chimeras. Male chimeras were bred with female Black Swiss mice to generate germline transmitted floxed heterozygous mice ($OPCML^{f\text{-}neo/+}$ or $Neurotrimin^{f\text{-}neo/+}$). To generate global *OPCML* or *Neurotrimin* knockout mice, $OPCML^{f\text{-}neo/+}$ and $Neurotrimin^{f\text{-}neo/+}$ mice were bred with *protamine-Cre* (*Pro–Cre*) mice [O'Gorman et al., **1997**]. Cre expression in *Pro–Cre* mice is restricted to male germ cells undergoing spermatogenesis. *Pro–Cre* / $OPCML^{f\text{-}neo/+}$ and *Pro–Cre* / $Neurotrimin^{f\text{-}neo/+}$ males were then crossed to female breeders to generate germline heterozygous null mutant offspring ($OPCML^{neo/+}$ and $Neurotrimin^{neo/+}$). Heterozygous mice were interbred to generate homozygous knockouts. *OPCML* and *Neurotrimin* double heterozygous $OPCML^{neo/+}$ / $Neurotrimin^{neo/+}$ mice were generated by crossing $OPCML^{neo/+}$ and $Neurotrimin^{neo/+}$ single heterozygote mice.

Genotype Analysis

Progeny from these crosses were genotyped by PCR analysis using total genomic DNA derived from mouse tail. The genotype primer sequences were as follows:

OPCML wild-type-specific:

- Forward, AAGCAATGAGCAGGCAAGAT;
- Reverse, GGCCAGGAGAAAATGAAACA.

OPCML mutant allele:

- Forward, Neo, AATGGGCTGACCGCTTCCTCGT;
- Reverse, TCCACCAGCTTCAAATGCTA.

Neurotrimin wild-type-specific

- Forward, AGAGGAGGAAAAGCCAAGGG;
- Reverse, GGGAGGCCTGAGTGGGTGG.

Neurotrimin mutant allele

- Forward, Neo, AATGGGCTGACCGCTTCCTCGT;
- Reverse, GTACAGAACAGCTTAGCACACCC.

PCR products were visualized by ethidium bromide staining.

Histological Analysis

Mouse tissue was dissected for histological analysis as described previously [Ye et al., **2009**]. Adult mice were euthanized and the heart was dissected for histological analysis. Tissue was fixed in 4% paraformaldehyde overnight at 4°C and embedded in paraffin. Serial sagittal sections were cut at 9 μm from paraffin blocks and stained with hematoxylin and eosin.

Echocardiography

Transthoracic echocardiograms to assess cardiac structure and function were performed as described previously [Bose et al., **2007**], using a Visual Sonics Vevo 660 imaging system (VisualSonics, Inc., Toronto, Canada). Fifteen parameters were measured, as listed in Supplemental Table II (see Supporting Information Online) and were assessed on six homozygous knockout mice at ages 3 and 8 months, along with six wild type and age-matched littermate controls.

RESULTS

1. Identification of *OPCML* as a candidate gene for congenital heart defects: Disruption of *OPCML* by a balanced translocation in a patient with congenital heart disease and other features of Jacobsen syndrome
    1. Clinical history: The patient is an Italian female born with multiple physical findings previously reported to occur in 11q- [Mattina et al., **2009**]. She was the third child of healthy and nonconsanguineous parents, born at 39 weeks gestation by cesarean due to a previous cesarean delivery. The mother had two previous miscarriages. Prenatal ultrasound detected mild increased of amniotic fluid. Growth parameters at birth were weight 2,740 g, length 48 cm. After birth, she had respiratory failure due to trachea/laryngomalacia and Pierre Robin sequence (micrognathia, cleft of the soft palate), and required a tracheostomy. She had feeding difficulty and required placement of a gastric tube. A cardiac ultrasound showed an atrial septal defect and pulmonary valve stenosis that progressed, requiring surgical treatment at age 9 years. Craniofacial features include frontal bossing, hypertelorism, telecanthus, epicanthal fold, low-set ears, and fifth finger clinodactyly. Because of frequent episodes of breathing difficulties until age 3, she needed surgical interventions to remove granulomas from the tracheostomy site. At 7 years old the tracheostomy was closed without further respiratory problems. The patient is now 16 years old (Fig. 1). She has curly hair, ulerythema ophryogenes, hypertelorism, epicanthal folds, and low-set ears with hypertrophic earlobes, mild scoliosis, flat feet, and moderate cognitive disability with absent language, autistic traits and auto aggressive behavior. Karyotype analysis performed shortly after birth showed a balanced translocation between chromosomes 11 and 17: 46,XX t(11,17); (q25,q21).
    2. Molecular mapping and cloning of the translocation breakpoints
    UCSD IRB-approved consent was obtained. Fluorescence in situ hybridization

(FISH) was performed on metaphase chromosomes derived from the patient, using overlapping human YAC clones and BAC clones spanning distal 11q. The breakpoint was localized to within a ~30–50 kb region. Genomic Southern blot analysis subsequently narrowed the breakpoint region to a ~4.5 kb interval (Fig. 2A, B).

The molecular cloning of the translocation breakpoints of the derivative 11 and 17 chromosomes was performed by the genome walking technique. DNA sequencing of the chromosome 11 breakpoint fragment confirmed a 401 bp hybrid fragment whose 5′ and 3′ ends contained, respectively, 333 base pairs of chromosome 11 sequence from within a 3.4 kb Hind-III/Pst-1 fragment, and 68 base pairs of chromosome 17 sequence that was localized to 17q21, the same sub-band identified by karyotype analysis to harbor the breakpoint (Fig. 2C). The chromosome 17 breakpoint fragment was also cloned by genome walking. A 176 base pair hybrid fragment containing 47 base pairs of chromosome 17 sequence and 129 base pairs of chromosome 11 sequence was determined. Analysis of the sequences derived from the derivative 11 and 17 chromosomes demonstrated that the translocation resulted in a 26 base pair deletion of chromosome 11 sequences and an 18 base pair deletion of chromosome 17 sequences flanking the breakpoint.

3. Analysis of genes in the region of the translocation breakpoints
   BAC clones containing or adjacent to the translocation breakpoints were assessed for the presence of genes and exons by using a NIX analysis, furnished by the U.K. Human Genome Mapping Project Resource Centre (UK HGMP-RC). The chromosome 11 translocation breakpoint was between exons 1 and 2 of a previously described gene, *OPCML* . This was confirmed independently by performing Southern blot analysis of BACs spanning the translocation breakpoint using exon 1 and 2 specific-probes (data not shown). Exon 1 was contained in BAC clone RP11-419F8, which was shown by FISH to be telomeric to the breakpoint, and exon 2 was contained in RP11-15J5, which was shown to be centromeric to the breakpoint, thereby confirming the location of the breakpoint to be between *OPCML* exons 1 and 2. The chromosome 17 breakpoint also interrupted a gene, *Ankyrin–Fibronectin* , *type III* .

4. Cardiac expression of OPCML and Neurotrimin
   To determine whether OPCML and Neurotrimin are expressed in the human fetal and adult heart, we performed northern blot analyses. As shown in Figure 3, there was weak but detectable expression of OPCML in the human fetal heart, and selective expression of OPCML in the ventricles in adult human heart. In contrast, there was stronger expression of Neurotrimin in the fetal heart compared to OPCML, and there was robust and selective expression in the right atrium with much weaker expression in the left atrium and ventricles in the adult heart. We performed in situ studies in mice which demonstrated weak expression of OPCML in E9.5, 10.5, and 14.5 hearts (data not shown), and previously reported studies demonstrated robust expression of Neurotrimin in E14.5 embryonic hearts, specifically in the outflow tracts, atria, and ventricles [Diez-Roux et al., **2011**].

2. Gene-targeted disruption of *OPCM* and *Neurotrimin* in the mouse
   We generated gene-targeted knockouts of *OPCML* and *Neurotrimin* using Cre–LoxP technologies separately, as shown in Figures 4A and 5A. Heterozygotes *OPCML* $^{neo/+}$ or *Neurotrimin* $^{neo/+}$ mice were crossed and the offspring were genotyped. Homozygous knockout mice consistent with a Mendelian segregation pattern were detected (see Supplemental Table I—in Supporting Information Online), indicating postnatal viability for both gene-targeted knockout mouse strains.
   Northern blot analysis of RNA from the brains of *OPCML* knockout mice confirmed that the *OPCML* transcript was not detectable in the homozygous knockout mice and is at a reduced level in the heterozygous mice compared to the wild type (Fig. 4D). Western blot analysis of protein from the brains of *Neurotrimin* mice confirmed that the Neurotrimin protein was not detectable in the homozygous knockout mice (Fig. 5D).
   We also generated *OPCML* $^{neo/+}$ / *Neurotrimin* $^{neo/+}$ double heterozygous knockout mice by crossing single heterozygous *OPCML* and *Neurotrimin* knockout strains. Genotyping was confirmed by PCR analysis (Figs. 4C and 5C), as described above.

3. Characterization of the cardiac phenotype of *OPCML* and *Neurotrimin* gene knockout mice
   All *OPCML* and *Neurotrimin* homozygous knockout mice survived past the neonatal period, and no knockout mice died prior to the time they were sacrificed. We performed histopathologic analysis by H&E staining of five *OPCML* and *Neurotrimin* knockout mouse hearts at age P3 (Fig. 6) and 8 months (data not shown), with 5 littermate controls for each stage. In addition, echocardiograms were performed on 6 knockout and 6 wild type littermate controls at ages 3 and 8 months for both knockout strains. This included assessment of 15 structural and functional parameters as described previously [Ye et al., **2009**], listed in Supplemental Table II (see Supporting Information Online). For both *OPCML* and *Neurotrimin* homozygous knockout mice, the cardiac structure and function were normal.
   Because the single gene knockouts did not have a cardiac phenotype and 11q- patients with congenital heart defects have a loss of one copy of both *Neurotrimin* and *OPCML* , we hypothesized that a double heterozygote deletion might cause congenital heart defects. Accordingly, double heterozygous knockout mice were generated and were detected in predicted Mendelian numbers. Histopathologic analysis was performed on five 3-month-old double heterozygous knockout mice that demonstrated normal cardiac structure (data not shown).

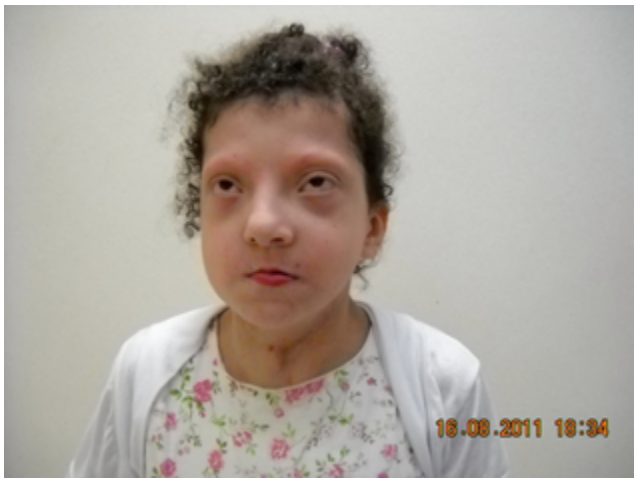

Figure 1.

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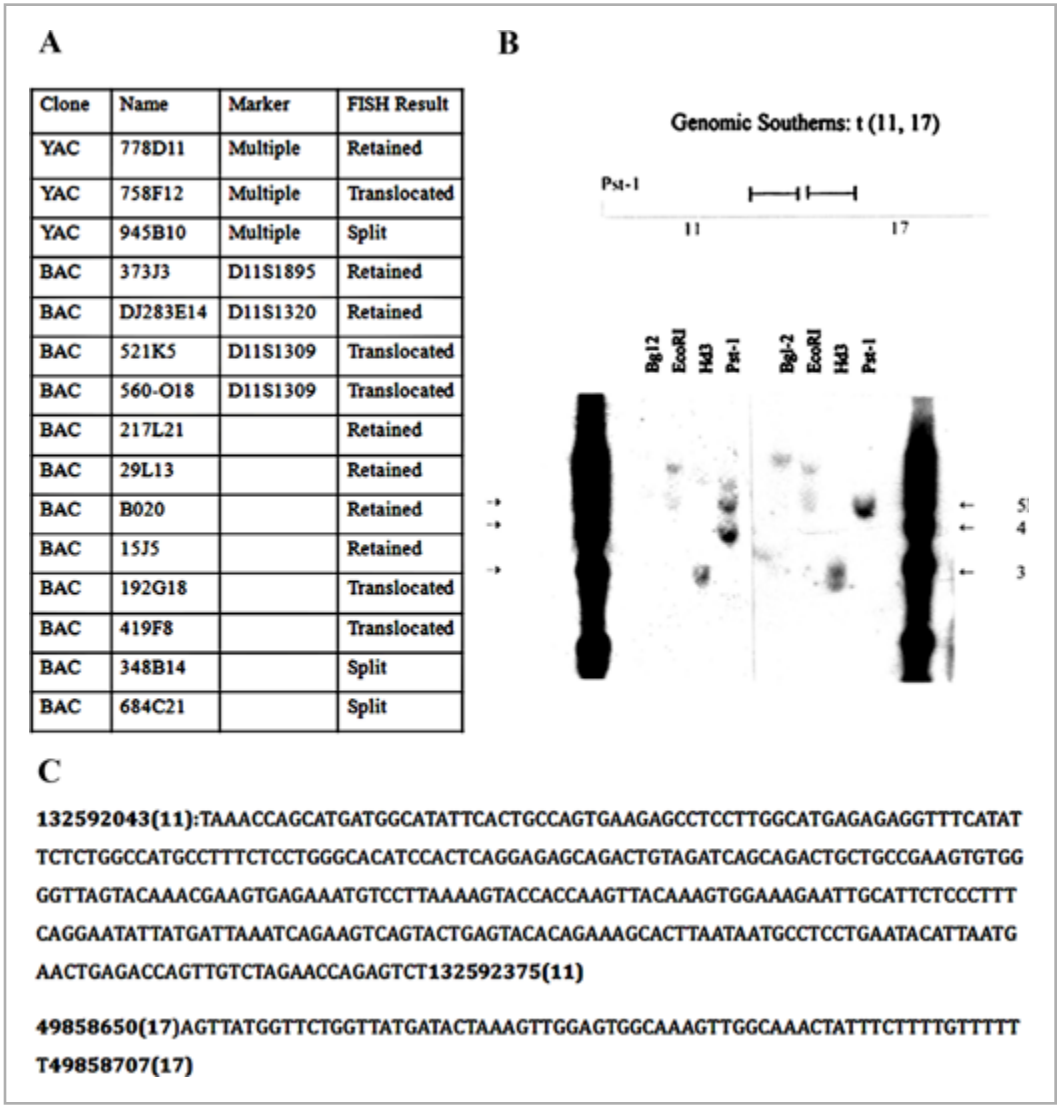
Photograph of proband with 46,XX t(11,17); (q25,q21), demonstrating dysmorphic features observed in 11q- including frontal bossing, hypertelorism, and epicanthal folds (See text for additional details).



A

Clone	Name	Marker	FISH Result
YAC	778D11	Multiple	Retained
YAC	758F12	Multiple	Translocated
YAC	945B10	Multiple	Split
BAC	373J3	D11S1895	Retained
BAC	DJ283E14	D11S1320	Retained
BAC	521K5	D11S1309	Translocated
BAC	560-O18	D11S1309	Translocated
BAC	217L21		Retained
BAC	29L13		Retained
BAC	B020		Retained
BAC	15J5		Retained
BAC	192G18		Translocated
BAC	419F8		Translocated
BAC	348B14		Split
BAC	684C21		Split

C

132592043(11):TAAACCAGCATGATGGCATATTCACTGCCAGTGAAGAGCCTCCTTGGCATGAGAGAGGTTTCATAT
TCTCTGGCCATGCCTTTCTCCTGGGCACATCCACTCAGGAGAGCAGACTGTAGATCAGCAGACTGCTGCCGAAGTGTGG
GGTTAGTACAAACGAAGTGAGAAATGTCCTTAAAAGTACCACCAAGTTACAAAGTGGAAAGAATTGCATTCTCCCTTT
CAGGAATATTATGATTAAATCAGAAGTCAGTACTGAGTACACAGAAAGCACTTAATAATGCCTCCTGAATACATTAATG
AACTGAGACCAGTTGTCTAGAACCAGAGTCT132592375(11)

49858650(17)AGTTATGGTTCTGGTTATGATACTAAAGTTGGAGTGGCAAAGTTGGCAAACTATTTCTTTTGTTTTT
T49858707(17)

Figure 2.

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A: Human genomic clones used for FISH. **B**: Genomic Southern blot analyses subsequently narrowed the breakpoint region. **C**: DNA sequences of the junction fragments of the chromosome 11 and 17 breakpoints: 401 bp breakpoint fragment containing 333 bp from chromosome 11, disrupting the OPCML gene, and 68 bp from chromosome 17, disrupting the ankryin repeat and fibronectin-III domain-containing gene.

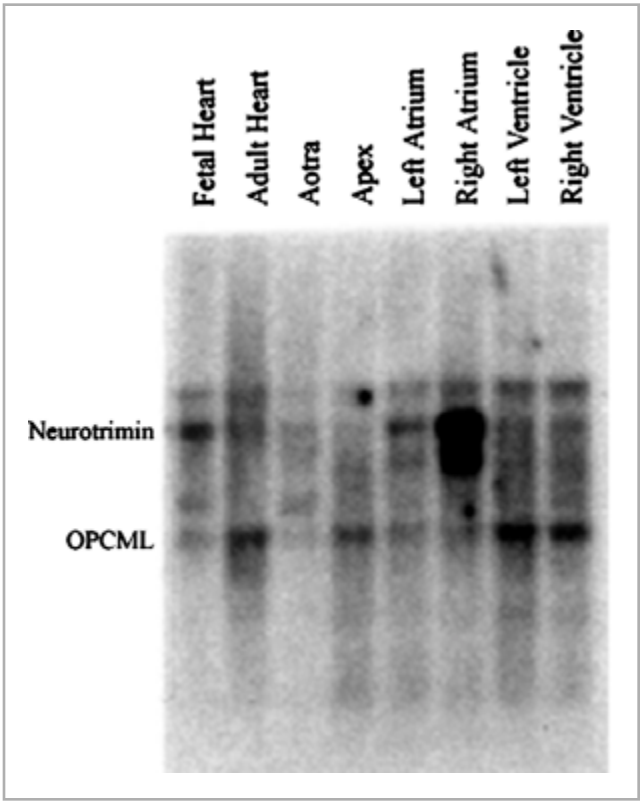

Figure 3.

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Human Northern blots analysis demonstrating expression of OPCML and Neurotrimin in fetal and adult heart (see text for details).

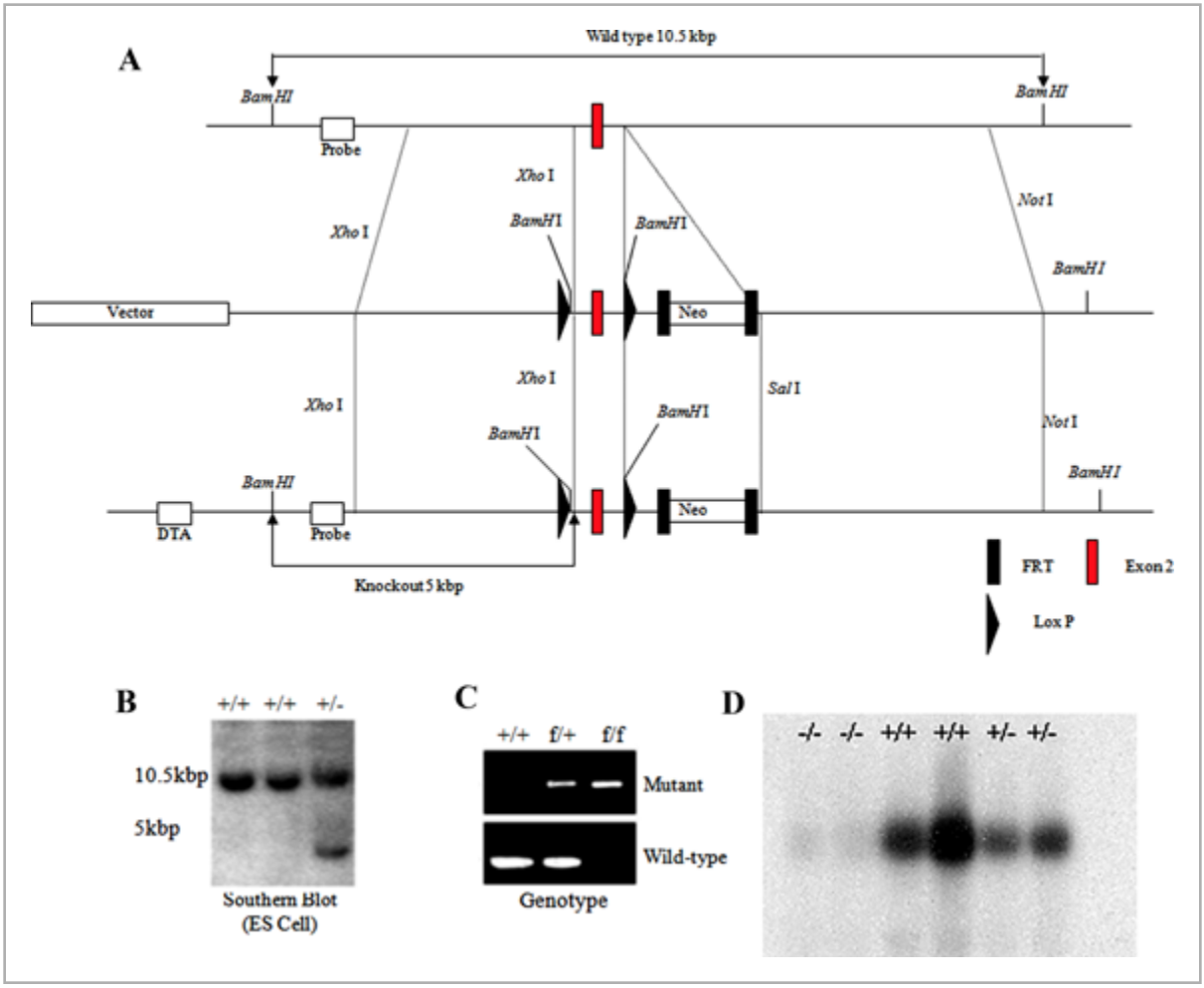

Figure 4.

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A: Strategy for gene-targeted knockout of OPCML, using Cre–Lox approach. **B**: Genomic Southern blot demonstrating wild type and floxed alleles. **C**: PCR demonstrating wild type and knockout alleles. **D**: Northern blot analysis demonstrating complete loss of OPCML transcript in the homozygous knockout allele. RNA was obtained from whole brain.

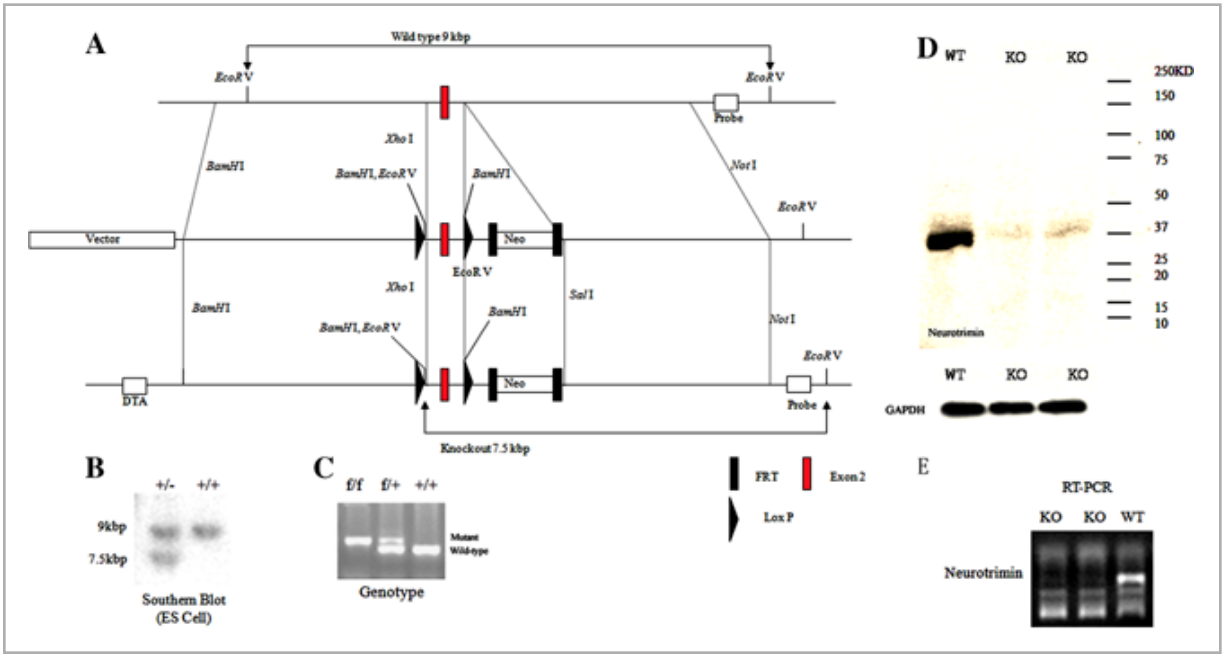

Figure 5.

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A: Strategy for gene-targeted knockout of Neurotrimin, using Cre–Lox approach. **B**: Genomic Southern blot demonstrating wild type and floxed alleles. **C**: PCR demonstrating wild type and knockout alleles. **D**: Western blot analysis and RT-PCR demonstrating loss of Neurotrimin protein and mRNA in the homozygous knockout mice, Neurotrimin antibody (R&D Systems, BAF1235). GAPDH antibody was used for normalization. Protein and RNA were obtained from whole mouse brain.

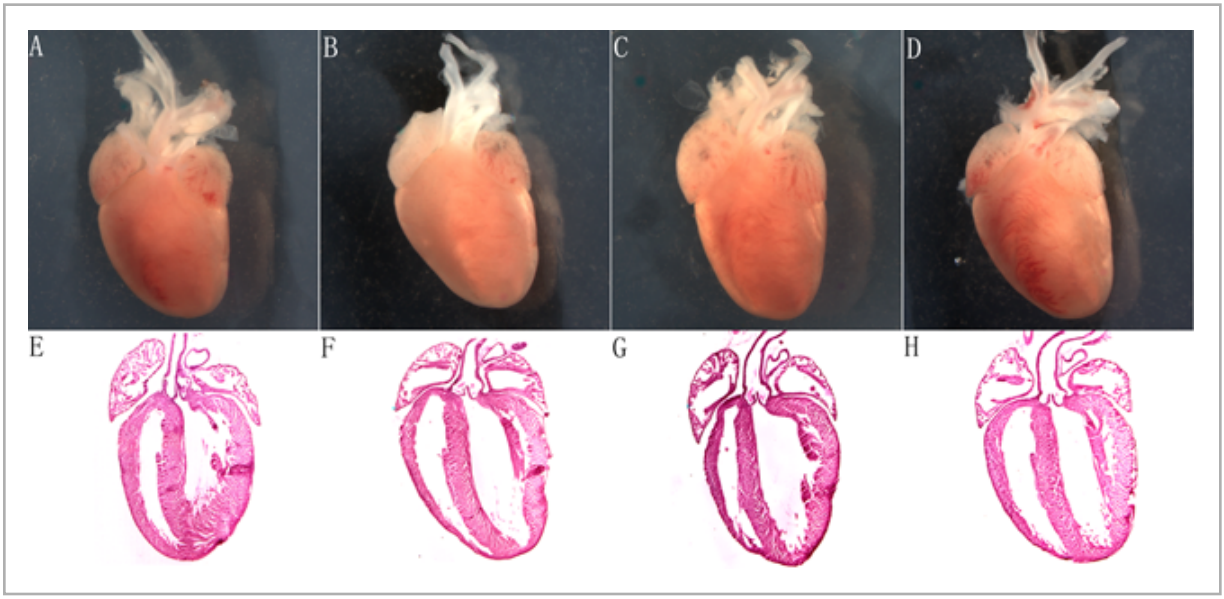

Figure 6.

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Histological analysis of postnatal day 3 OPCML and Neurotrimin knockout mice heart. **A**–**D**: Intact heart; **E**–**H**: paraffin section and H&E staining of the heart. A, E: OPCML wild type; B, F: OPCML knockout; C, G: Neurotrimin wild type; D, H: Neurotrimin knockout.

DISCUSSION

Congenital heart defects are the most common form of human birth defect, affecting almost 1% of all newborn infants. Jacobsen syndrome is caused by deletions in distal 11q. Many of the most common and severe congenital heart defects that occur in the general population occur in 11q- [Grossfeld et al., **2004**]. Consequently, understanding the genetic mechanisms of congenital heart defects in 11q- will likely have important implications for the general population.

Our previous studies identified the ETS-1 transcription factor as a candidate gene for causing congenital heart defects in 11q-. In a C57/B6 background, gene-targeted deletion of ETS-1 in mice caused ventricular septal defects, the most common congenital heart defect in 11q-, with 100% penetrance [Ye et al., **2010**]. It was unclear whether additional genes in distal 11q might contribute to the spectrum of congenital heart defects in 11q-, or if deletion of ETS-1, under the influence of other genetic, epigenetic and/or environmental modifiers, causes the full spectrum of congenital heart defects.

We now describe the cardiac phenotype of gene-targeted deletion of two functionally related genes in distal 11q, *OBCAM* and *Neurotrimin* . These two genes were identified as candidate genes based on the molecular characterization of the breakpoints of three different patients with translocation

breakpoints mapped to distal 11q and with congenital heart disease. OBCAM and Neurotrimin are members of the IgLON subfamily of cell adhesion molecules, and previous studies have implicated a role for cell adhesion molecules in cardiac development [Linask et al., **2005**].

Our results demonstrated that neither gene-targeted deletion of *OBCAM* nor *Neurotrimin* individually, or together as a double heterozygote, resulted in a cardiac phenotype. There are several possibilities to account for these results. First, due to the functional redundancy of these two genes, homozygous deletion of both genes in mice may be required to yield a cardiac phenotype. Second, the phenotype might depend on genetic background, and in these studies, only a single genetic host background was utilized. Third, at least one of the cardiac phenotypes described in the human patients carrying a disruption of Neurotrimin, vascular aneurysms, is a progressive disease and it is possible that these are only present in mice that are older than those we analyzed. Although we did not specifically assess for the presence of abdominal aortic aneurysms (no obvious thoracic aortic or cerebral aneurysms were detected), the fact that *Neurotrimin* knockout mice survived well into adulthood (age 18 months prior to being sacrificed) in the predicted Mendelian frequency makes it unlikely that any significant, life-threatening aneurysms were present. Fourth, the cardiac phenotypes in these three patients may be due, at least in part, to disruption of a gene and/or regulatory sequence at the reciprocal translocation or inversion breakpoint. In two of the patients described, a known gene was disrupted at the reciprocal translocation breakpoint (*UVRAG* and *Ankyrin–Fibronectin* , *type III* in 11q13.5 and 17q21, respectively), and currently nothing is known about the function of these genes in general, or specifically in heart development. In light of our current results, future studies on the function of these genes in normal organ development and their role in human disease is warranted. Similarly, the cardiac phenotype may be due to the generation of a fusion gene product as a result of the translocation/inversion that would not have been generated from a gene-targeted knockout.

Taken together, the results of these studies are consistent with a single gene model for causing the spectrum of congenital heart defects in 11q-, with additional modifier genes influencing the development and type of congenital heart defect. *ETS-1* is a cardiac transcription factor expressed in multiple cardiac lineages during early heart development, and there is a strong precedent for cardiac transcription factors causing diverse congenital heart defects [Rana et al., **2013**]. Consistent with this model, since the original preparation of this manuscript we have analyzed gene-targeted deletion of *ETS-1* in a mixed genetic background, and identified additional, more complex cardiac phenotypes including tetralogy of Fallot and a single ventricle (manuscript in preparation). Based on our mouse studies, the incomplete penetrance and variable cardiac phenotypes in 11q- patients might be due to multiple factors, including most likely additional genetic modifiers. Other contributory factors might include the degree of expression of the single retained copy of ETS-1 as well as potentially epigenetic and environmental factors, all of which will be the focus of future investigation (Fig. 7).

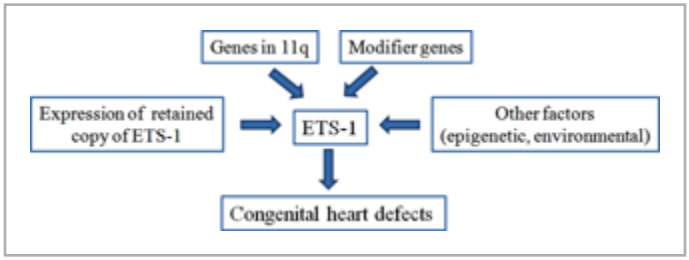

Figure 7.

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Schematic diagram demonstrating a single gene model, ETS-1, with additional multiple factors that could determine the presence and type of congenital heart defects in 11q- patients. Current evidence implicates that deletion of ETS-1 is necessary, with additional genetic modifier(s).

Supporting Information

REFERENCES