

**A missense mutation in the actin cardiac gene ACTC1 results in a varieties of congenital heart malformations and midline defects**

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**Family description:** a Lebanese family had 15 members with congenital heart defect (CHD): 8 isolated ASD, 2 ASD and PS, 2 ASD and AS or AR, 1 ASD and Ebstein anomaly, 1 VSD and the founder died from cardiac failure although he had neither coronary disease nor left ventricle obstruction. In addition, WPW (2), sinus bradycardia (1), and atrial fibrillation (1) were observed. Beside cardiac anomalies, 5 had a midline defect: pectus excavatum (4), kyphoscoliosis (1), hypertelorism (3), cleft lip and diastema between superior incisors (1). All other family members had neither cardiac nor midline anomaly.

**Positional mapping:** the genotype of 365 poly(AC) were obtained from 20 family members. Parametric (disease allele frequency 0.001, penetrance 0.95, phenocopy rate 0.06) and non-parametric analyses were performed. There was a major peak reaching 1.99 in the parametric analysis and a single peak in the non parametric analysis (15.13) in the same chromosome 15 region. The haplotypes showed that all affecteds but one had the same allele for marker (D15S1007). A recombination on the centromeric side between D15S1007 and D15S165 and on the telomeric side between D15S1007 and D15S1012 in affecteds gave the limit of the mutation interval which encompassed 7,750,000 nucleotides.

**Mutation identification:** in this interval of 143 genes is located the ACTC1 gene which encodes cardiac actin. A heterozygous missense variant was observed in the ACTC1 gene which changed a methionine to a threonine at position 84 (c.251T>C). The Met84 residue is highly conserved in mammals, physico-chemical properties of both residues are different and all prediction software anticipated a disease causing change. This mutation was found in all affected family members but one who is presumably a phenocopy.

**Cell biology:** the cDNA of the Actc1 gene was cloned and the mutation was introduced by side-directed mutagenesis to transfect a cell line derived from atrial mouse cardiomyocytes (HL-1). We plan to observe whether the mutant protein is incorporated in actin filaments and whether the kinetics of this contracting cell line is altered due to the mutant protein.

**Conclusion:** a novel ACTC1 dominant mutation was identified which gave CHD, arrhythmic anomalies and midline defects.