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Two Patients with the Heterozygous R189H Mutation in ACTA2 and Complex Congenital Heart Defects expands the Cardiac Phenotype of Multisystemic Smooth Muscle Dysfunction Syndrome

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De novo heterozygous mutations changing R179 to histidine, leucine or cysteine in the *ACTA2* gene are associated with Multisystemic Smooth Muscle Dysfunction Syndrome (MSMDS). Characteristic hallmarks of this condition, caused only by these specific *ACTA2* mutations, are congenital mydriasis (mid-dilated, non-reactive pupils, figure 1), a large persistent ductus arteriosus (PDA), aortic aneurysms evolving during childhood, and cerebrovascular anomalies. We describe two patients, a 3-day-old newborn and a 26-year-old woman, with this unique mutation in association with a huge PDA and an aorto-pulmonary window. In addition, one showed a coarctation of the aortic arch and the other a complete interruption of the aortic arch type A; thereby expanding the spectrum of cardiac congenital heart defect of this syndrome. Each patient displayed a huge PDA and an extra-cardiovascular phenotype consistent with MSMDS. These observations exemplify that a functional alpha 2 smooth muscle actin is necessary for proper cardiovascular organ development, and demonstrate that a very exceptional congenital heart defect (aortopulmonary window) can be caused by a mutation in a gene encoding a contractile protein of vascular smooth muscle cells.

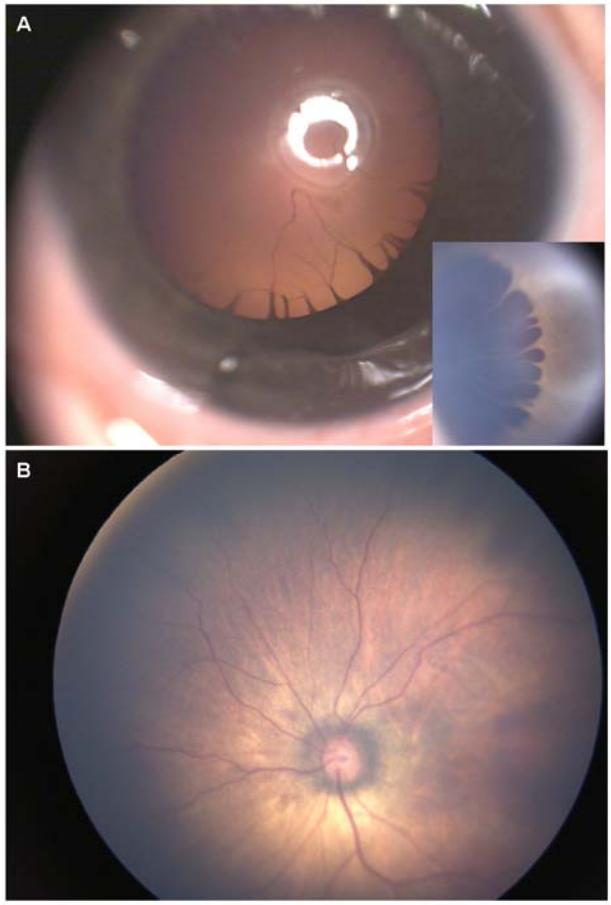

Figure 1: Digital images of the iris of patient 1 showing a persistent extensive pupillary membrane with multiple wisks. The iris stroma appears hypoplastic, the pupil being only partially dilated.