

## The Roberts Syndrome: A case report of an infant with valvular aortic stenosis and mutation in ESCO2

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### Abstract

Roberts syndrome, which is inherited as an autosomal recessive group of disorders, is a rare syndrome characterized with symmetrical extremity defects, craniofacial abnormalities, and prenatal and postnatal growth retardation. Here, we present a case of Roberts Syndrome brought to the clinic with diarrhoea and multiple abnormalities, that had tetra phocomelia, growth and developmental retardation, abnormality of complete cleft lip-palate accompanied with Aortic stenosis and PDA, and in which cytogenetic analysis identified premature centromere separation. Mutation analysis of ESCO2 revealed a splice site mutation [c.1131+1G>A] in intron 6 in homozygous status in the patient and heterozygous status in the parents. Our case is the first Robert- Syndrome with valvular aortic stenosis in the literature, to the best of our knowledge.

**Keywords:** Roberts syndrome, Tetrachomelia, Cleft palate, Aortic stenosis, ESCO2.

### Introduction

Roberts Syndrome (RBS) is an autosomal recessive malformation characterized with symmetrical extremity defects, craniofacial abnormalities, prenatal and postnatal growth retardation and mental retardation. It was first defined by John Roberts in 1919 in a case of a baby boy with bilateral cleft lip and tetra-phocomelia.<sup>1,2</sup> The finding of cytogenetic 'premature centromere separation (PCS)' is present in the majority of Roberts cases.<sup>3</sup> It has been determined that the disease is caused by mutation in ESCO2 ( establishment of cohesion 1 homolog 2) gene which encodes a protein essential for regulating sister chromatid cohesion.

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ductus arteriosus have previously been reported.<sup>4</sup> The reasons for death of these patients are generally cardiac, renal anomalies and infections.

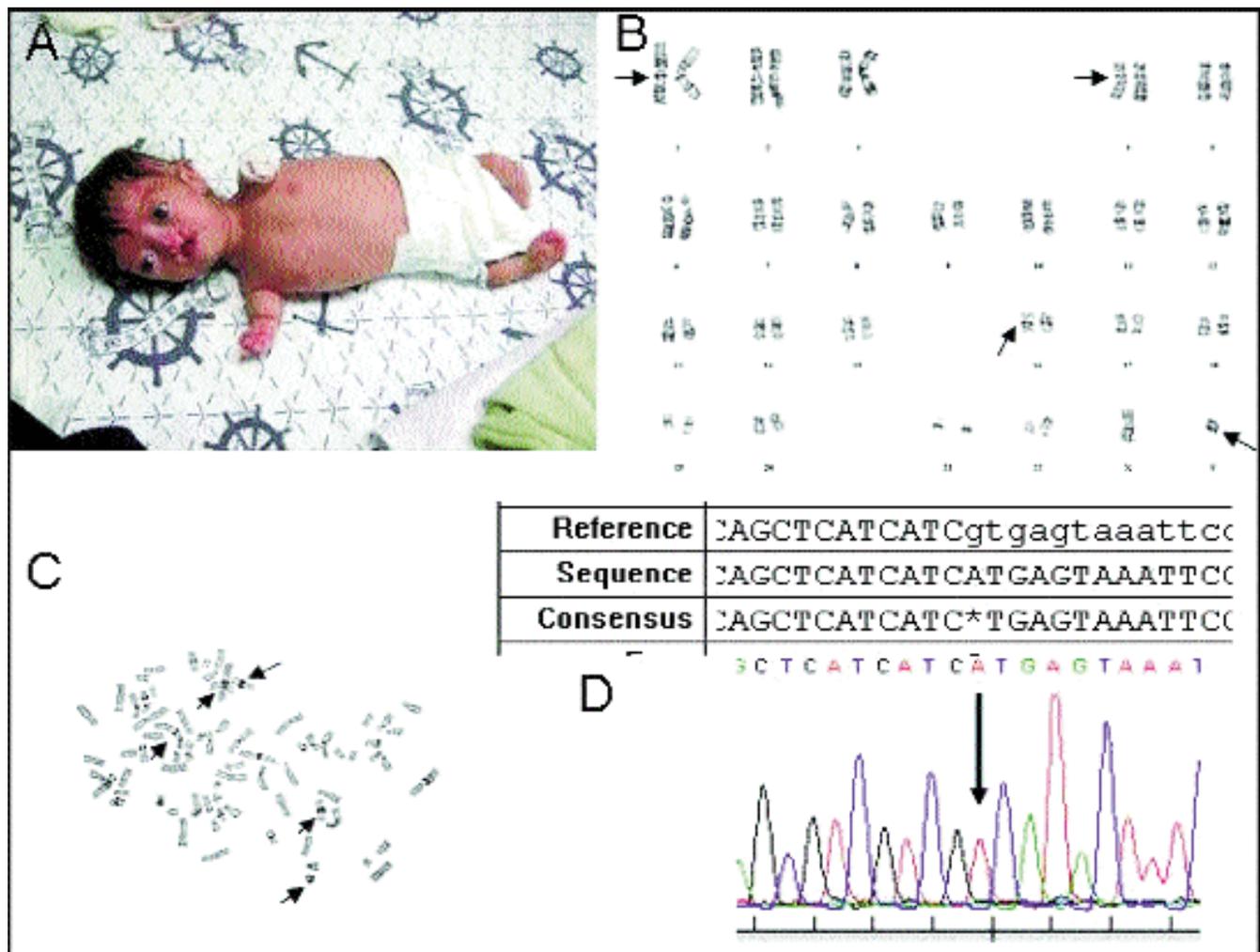
Valvular aortic stenosis was determined in our case, which had not been reported previously in literature. Since this was the first in this respect, we aimed to report the case.

### Case Report

A two month old boy presented to our clinic in December 2012, with watery diarrhoea and multiple anomalies. He was the second live infant, born with 1900 gram weight at term whose mother and the father were second-degree relatives [cousins]. The mother had no history of infection, teratogenic drug intake, diabetes mellitus, smoking, alcohol use or X-Ray exposure during pregnancy. The medical history, revealed, that although multiple congenital abnormalities had been determined on foetal ultrasonography, there was no history of congenital abnormality in the family.

On physical examination, his body weight was 2300 gram [ $< 3p$ ], height was 40 cm. [ $< 3p$ ], and head circumference was 31 cm [ $< 3p$ ]. On examination of the head and neck, there was a prominent frontal bone, open and flat forehead, microcephaly, sparse hair, hypertelorism, shallow orbits, exophthalmia, blue sclerae, megalo cornea, fuzzy corneas, malar hypoplasia, nasal hypoplasia, depressed nasal bridge, low and and rear-positioned ears, malformed helices, complete cleft lip, complete cleft palate and short neck. On cardiological examination, the cardiac pulse was 126/minute and it was rhythmic. There was a 3/6 systolic ejection murmur which was auscultated in all cardiac foci, but most prominent at the aortic focus. On genital examination, the testicles were in the scrotums, there was a large penis, and right inguinal hernia and hydrocoele. On examination of the skeletal system, there were tetrachomelia, 4 fingers in each hand [oligodactyly], hypoplastic thumbs, bilateral pes equinovarus and flexion contracture in all extremities. The other systemic examinations were normal (Figure-1a).

On upper extremity X-Ray, the radius and ulna were aplasic bilaterally, the humeruses were short bilaterally,



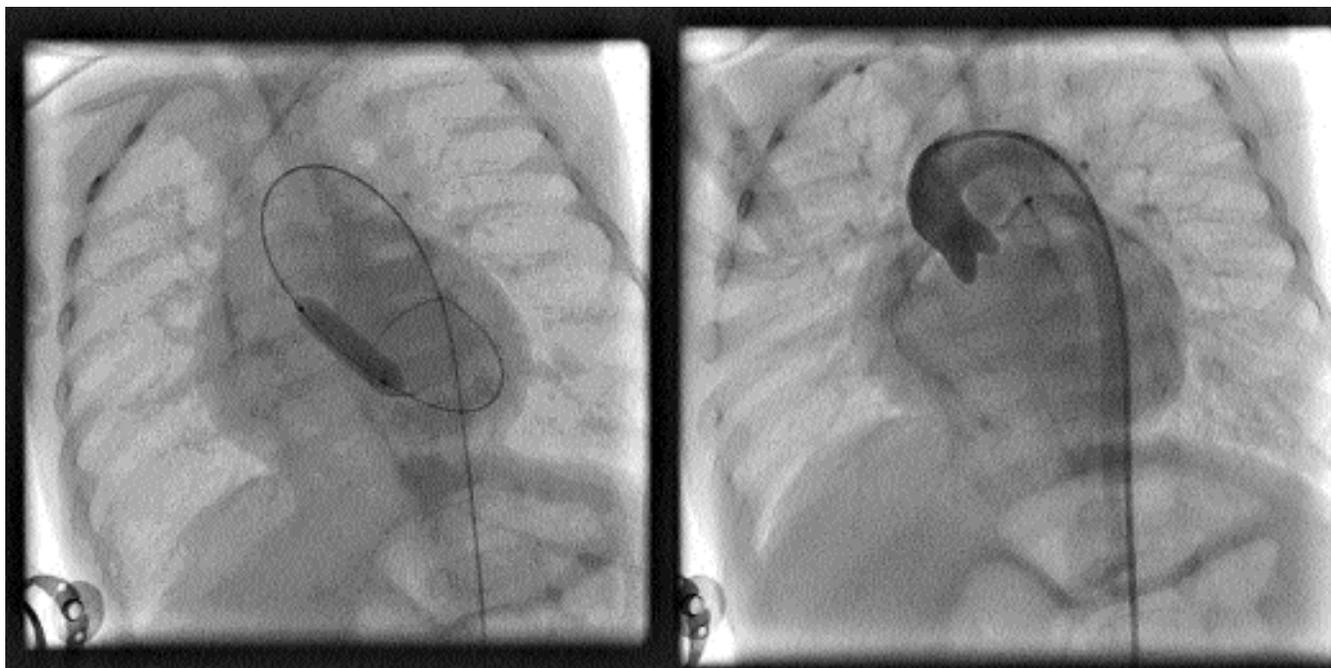
**Figure-1:** General appearance, cytogenetics [GTG and C banding], sequence chromatogram A: The patient with bilateral cleft lip - palate and tetraphocomelia. B: Karyotype with GTG banding. Note the heterochromatin repulsion at the centromeres and heterochromatic regions [arrows] B. C: Banding shows separation of the heterochromatic region [arrows]. D: Identification of a G to A transition at 5' splice site in intron 6 of ESCO2 gene. Representative sequence chromatogram of the affected homozygous.(patient's parents allowed the photograph).

and there were 3 metacarpal bones in the right hand and 3 metacarpal bones in the left hand. On lower extremity X-Ray, the femurs were short bilaterally, the tibia and the fibula were aplastic, there were 5 fingers in the left foot and 5 fingers and metatarsal bones in the right foot. There were no other skeletal abnormalities. The trans-fontanelle and the abdominal ultrasound were normal.

The chromosomal analysis revealed a karyotype of 46 XY and premature centromere separation in 95.8% of the evaluated metaphase plaques. Parental chromosome analysis were also performed and showed normal karyotype without premature centromere separation. With this result, the case was diagnosed as Roberts

syndrome. The analysis of the sequencing of ESCO2 gene revealed a homozygous G>A transitions at position 1131+1 in intron 6 [c.1131+1G>A] in the patient.

The findings on an Echocardiography included aortic valve stenosis [70 mmHg gradient], Patent Ductus Arteriosus [2.5 mm of thickness, with L-R shunt], Pulmonary Hypertension, 2nd degree tricuspid insufficiency, 1st degree pulmonary insufficiency, 1st degree mitral insufficiency, and mild stenosis in the left branch of the pulmonary artery. Due to 92 mmHg gradient at valvular level on cardiac catheterization, our patient underwent balloon valvuloplasty due to the critical aortic stenosis. Following balloon valvuloplasty, the gradient was decreased to 21



**Figure-2:** A) Aortic balloon valvuloplasty process. B) Stenotic aortic valve and normal arcus aorta (left anterior oblique view).

mmHg. The general condition of the patient and his oral intake resolved following valvuloplasty, but he was re-hospitalized at the 4th week following the procedure with the diagnosis of sepsis, with deterioration in the general condition and oral intake. In spite of 2 weeks of antibiotic therapy and supportive treatment, he died at the 4th month of his life due to sepsis.

## Discussion

Roberts Syndrome is a very rare congenital malformation. Its prevalence is unclear. Thus far, about 150 cases of different racial and ethnic backgrounds have been reported in the literature.<sup>4</sup> The major abnormalities required to make the diagnosis of Roberts Syndrome include: mental retardation, growth retardation with prenatal onset and continuing postnatally, midline craniofacial abnormalities, tetra-hypomelia that are more prominent in the upper extremities varying from phocomelia to simple shortness of the extremity and accompanying extremity abnormalities.<sup>2,4-6</sup> In 2005, the disease gene was determined by Vega et al.<sup>2</sup> All of the above findings were determined in our case.

The craniofacial and extremity abnormalities seen in this syndrome include cleft lip and palate, craniosynostosis, microcephalia, silver-coloured or sparse hair, micrognathia, ocular hypertelorism, exophthalmia, eyelid coloboma, corneal blurring, cataract, mid-facial capillary haemangioma, ear malformations, low-set ears, maxillary

protrusion, malar hypoplasia, hypoplastic mandible, nasal hypoplasia and short neck bilateral symmetrical tetraphocomelia or hypomelia, brachydactyly/oligodactyly.<sup>4-6</sup> In Roberts Syndrome, the upper extremities are affected more frequently than the lower extremities. In our case, these involvements were observed to be severe.

Cardiac anomalies are observed in about 50% of the cases. Atrial septal defect, ventricular septal defect, patent ductus arteriosus have previously been reported.<sup>7</sup> However, valvular aortic stenosis has not been mentioned in the literature. Aortic stenosis diagnosed in our case is the first in literature in this respect. The reasons for death of these patients are generally cardiac, renal anomalies and infections. In our case, our patient who had undergone a successful balloon valvuloplasty in the 3rd postnatal month, however died due to sepsis at the postnatal fourth month.

The diagnosis of RBS depends on cytogenetic tests. Characteristic chromosomal anomalies such as premature centromere separation [PCS, heterochromatin push] and/or ESCO2 mutations on the 8th chromosome are determined on cytogenetic evaluation and molecular studies.<sup>2,4,8</sup> Despite the observation of PCS as a characteristic chromosomal finding in most of the RBS cases, there are also some reported cases with normal chromosomes.<sup>9</sup> In the case review of Schule et al, although our case had the same mutation with their third case, no

cardiac pathology was observed. There is no correlation between the cytogenetic anomalies, genetic mutation and the phenotypic severity of this syndrome.<sup>8</sup> Van Den Berg did not detect PCS in 21 of the 100 cases of Roberts syndrome. For this reason, absence of PCS is not accepted as an exclusion criterion.<sup>2</sup>

## Conclusion

RPS is a syndrome with severe anomalies and a fatal course. The cardiac pathologies of VSD, PDA, subvalvular aortic stenosis and ASD have been reported in previous literature. The valvular aortic stenosis determined in our case is the first in the literature, and it indicates that valvular pathologies should be paid attention to in the cardiac evaluation of these patients.

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