CLINICAL CASE REPORTS

Prenatal Diagnosis of Townes-Brocks Syndrome with Multicystic Renal Dysplasia: A Multisystem Genomic Perspective

Miguel Martins[1], Beatriz Sousa Ferreira[1], Rosário Almeida Lopes[1], Ana Isabel Correia[1], Rosário Pinto Leite[2], Márcia Martins[2], Rosete Nogueira[3,4,5], Osvaldo Moutinho[1]

ABSTRACT

Background: Townes-Brocks syndrome (TBS) is a rare autosomal-dominant disorder characterized by the anal-auricular-digital triad and frequent renal anomalies.

Case Presentation: A male fetus was first examined at 18w3d, showing unilateral multicystic renal dysplasia and preaxial polydactyly. Standard karyotype (46,XY) and chromosomal

microarray (Agilent 4 × 180 K) were normal. Rapid trio-exome sequencing detected a *de novo* truncating *SALL1* variant (c.1147_1151del), confirming the diagnosis of TBS. After multidisciplinary counselling, medical termination of pregnancy was performed at 23w6d.

Fetal autopsy confirmed sonographic findings and additionally disclosed intestinal malrotation.

Discussion: This case illustrates the diagnostic value of prenatal exome analysis in fetuses with atypical renal and limb anomalies and underscores that recognizing the classic anal-auricular-digital pattern remains pivotal.

Conclusion: When multicystic renal dysplasia coexists with imperforate anus and preaxial limb defects, targeted *SALL1* gene analysis should be prioritized. Integrating imaging, genomics and autopsy enables precise phenotyping and informed recurrence-risk assessment.

Keywords: case report; fetal anomalies; genomics; multicystic renal dysplasia; prenatal diagnosis and autopsy correlation; sall1; townes-brocks syndrome

1. Gynecology and Obstetrics Department, Unidade Local de Saúde de Trás-os-Montes e Alto Douro. 5000-508 Vila Real, Portugal. intgomiguel.martins@gmail.com; bia.sousaferreira@gmail.com; rosarioalmeidalopes@gmail.com; anacorreia87@gmail.com; osvaldomoutinho@gmail.com
2. Genetics Department, Unidade Local de Saúde de Trás-os-Montes e Alto Douro. 5000-508 Vila Real, Portugal. mlleite@chtmad.min-saude.pt; marciam@chtmad.min-saude.pt
3. Escola de Medicina da Universidade do Minho. 4710-057 Braga, Portugal. rosetenogueira@gmail.com
4. Instituto de investigação de ciências da vida e saúde (ICVS); ICVS/3B´s PT Laboratório Associado, 4710-057 Braga - Guimarães, Portugal. rosetenogueira@gmail.com
5. Placental and Embryo-Fetal Pathology Unit, LAP, Unilabs. 4250-170 Porto, Portugal. rosetenogueira@gmail.com

INTRODUCTION

Townes-Brocks syndrome or anus-hand-ear syndrome (TBS; OMIM#107480) stems from pathogenic variants in the *SALL1* gene and classically presents with imperforate anus, dysplastic ears and preaxial radial ray defects.[1] Although renal involvement occurs in up to 50% of cases, prenatal recognition is challenging, particularly when renal anomalies dominate the phenotype.[2] Advances in rapid trio-based exome sequencing (ES) have markedly improved elucidation of syndromic fetal malformations. Here, we report a fetus with unilateral multicystic renal dysplasia in whom ES yielded a definitive diagnosis of TBS, allowing informed counselling in line with the ethical principles of the Declaration of Helsinki.

CASE DESCRIPTION

A 29-year-old primigravida was referred at 18w3d after routine ultrasonography revealed a markedly enlarged, multicystic left kidney with absent contralateral abnormalities. Amniotic fluid volume was normal and there were no dysmorphic facial features. Detailed fetal ultrasound detected duplication of the left thumb without radial hypoplasia. Unfortunately, ultrasound images from local hospitals were unavailable for review.

Invasive testing via amniocentesis demonstrated a normal male karyotype (46,XY). Chromosomal microarray (Agilent 4 × 180 K) was unremarkable. Given the association of renal dysplasia and preaxial anomalies, rapid trio-ES was undertaken (turnaround ≈ 10 days). Analysis identified a heterozygous frameshift variant in the *SALL1*gene [NM_002968.4:c.1147_1151del p.(Lys383Argfs*62)] absent from gnomAD and predicted to escape nonsense-mediated decay, consistent with dominant-negative pathogenesis.[3,4] Parental ES confirmed the variant was *de novo*. American College of Medical Genetics and Genomics (ACMG) criteria classified it as pathogenic (PVS1, PS2, PM2).[5]

A multidisciplinary meeting involving obstetrics, clinical genetics, neonatology and pediatric nephrology discussed the reserved renal prognosis and variable neurodevelopmental outcomes. Following comprehensive counselling, the parents opted for medical termination of pregnancy at 23w6d.

Autopsy Findings

External examination (**Figures A and B**) revealed a coarse facies, low-set, posteriorly rotated ears with a preauricular pit, and left thumb duplication. No radial hypoplasia was present. The feet showed asymmetric camptodactyly and clinodactyly.

Internal examination (**Figures C, D and E**) revealed complete absence of the anal canal, consistent with a high anorectal malformation. The gastrointestinal tract showed intestinal malrotation, with abnormal positioning of the stomach and ileocecal appendix. The urinary tract demonstrated unilateral multicystic renal dysplasia on the left kidney, with normal bladder, prostate, and urethra.

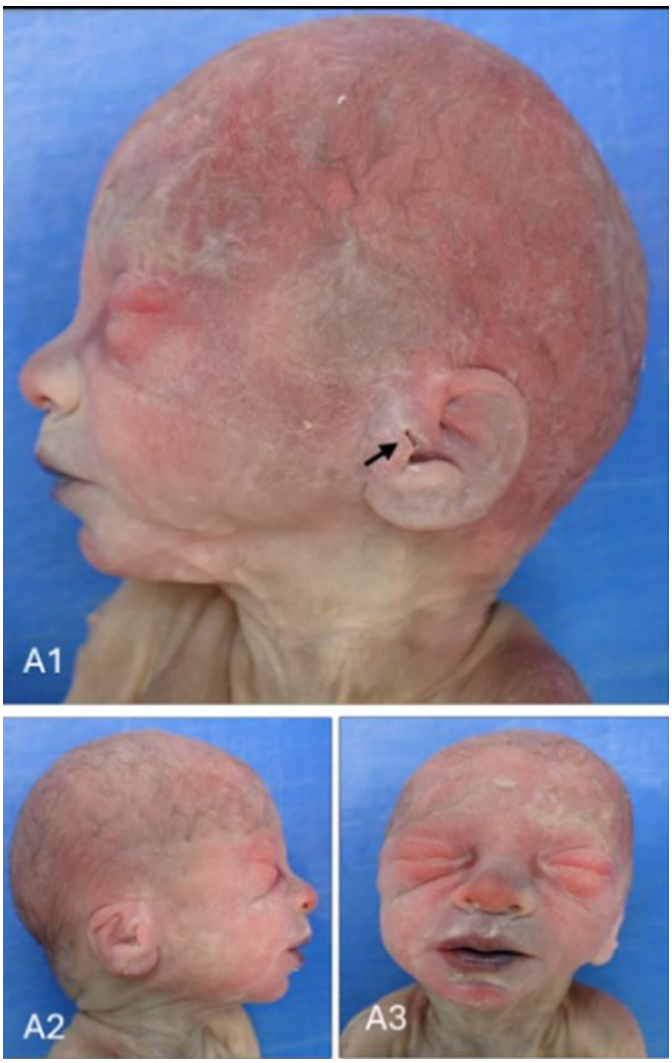

Figure A - External findings – (A1, 2), Dysplastic, low-set ears with a preauricular pit (arrow); (A3), coarse facial features.

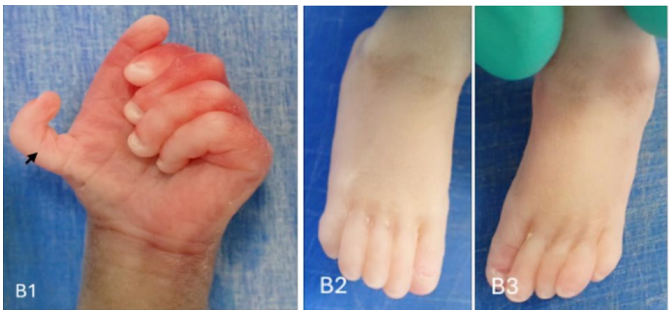

Figure B - External Findings – (B1) Malformation of the left thumb (small arrow) without radial hypoplasia; (B2, B3) Asymmetric camptodactyly and clinodactyly of the feet.

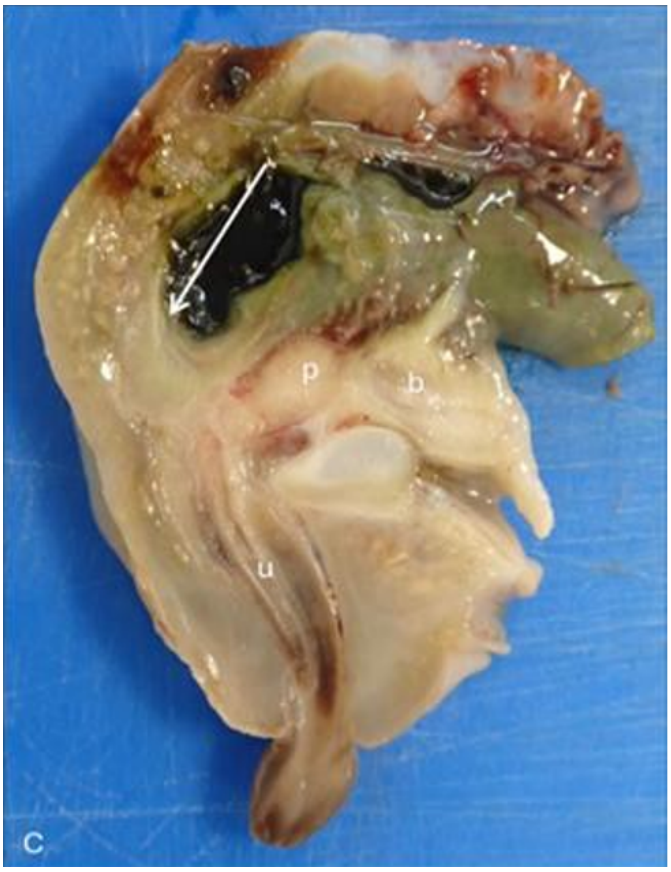

Figure C - Internal findings – anorectal malformation (arrow) with anal atresia; bladder (b), prostate (p), and urethra (u) are identified.

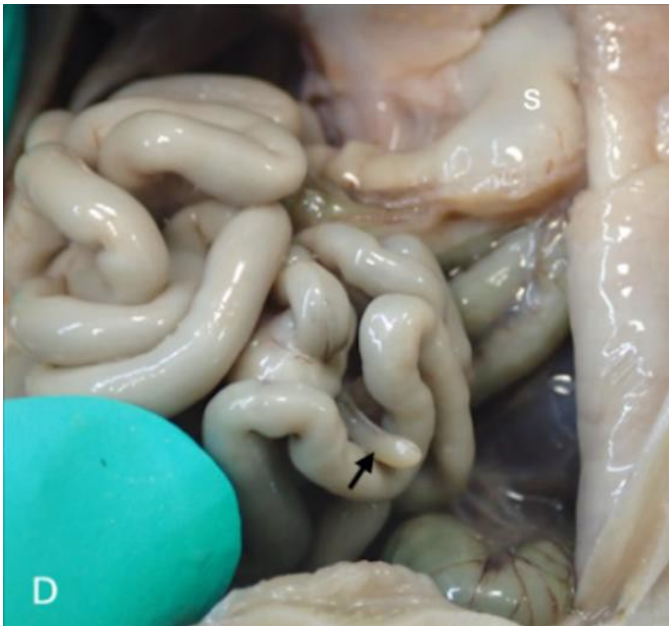

Figure D - Internal findings – Intestinal malrotation; stomach (s) and ileocecal appendix (arrow).

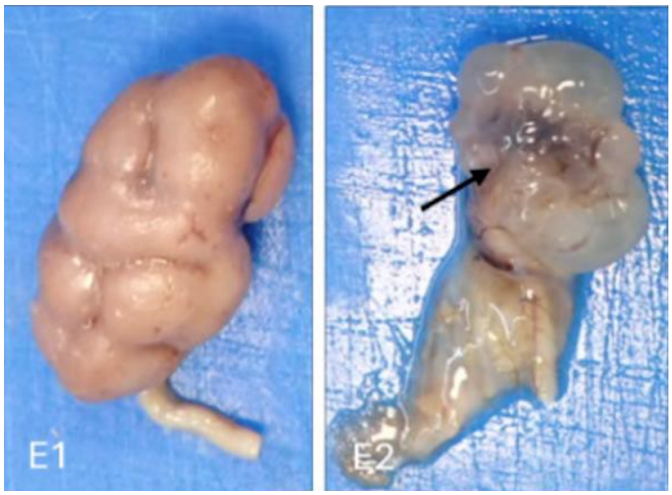

Figure E - Internal findings – (E1,2) Dysplastic kidneys with unilateral multicystic phenotype (arrow).

DISCUSSION

TBS is attributed predominantly to frameshift or nonsense variants clustering within exon 2 of the *SALL1* gene, resulting in truncated proteins that exert a dominant-negative effect during embryogenesis.[1,4] The identified variant expands the mutational spectrum and reaffirms exon 2 as a hotspot. Prenatal differentiation between TBS and VACTERL association or autosomal-recessive polycystic kidney disease (ARPKD) can be elusive when renal or limb anomalies appear isolated. Rapid trio-ES now achieves diagnostic yields of 20–40% in structurally abnormal fetuses, providing actionable information within a clinically relevant timeframe.[3] Our case exemplifies its benefit by clarifying prognosis well before fetal viability and facilitating parental decision-making. Importantly, a negative microarray does not obviate monogenic disorders; hence ES should be considered early when combinations of renal and limb anomalies are detected.

Renal outcomes in TBS vary from asymptomatic mild dysplasia to end-stage kidney disease (ESKD) in childhood. Although unilateral multicystic renal dysplasia may carry a favorable neonatal prognosis, long-term data remain limited, and renal failure has been reported even with apparently unilateral lesions. Imperforate anus and ear anomalies may be subtle prenatally, underscoring the need for meticulous limb and ear assessment whenever renal cystic disease is noted.

The ethical dimension of prenatal genomic testing mandates clear discussion of uncertain prognoses and psychosocial impact. Our counselling adhered to the Declaration of Helsinki, ensuring voluntary parental choice and respect for autonomy.

LIMITATIONS

Absence of longitudinal postnatal data precludes assessment of the full phenotypic spectrum. Functional validation of the novel *SALL1* variant was not feasible within the clinical timeline.

CONCLUSION

Multicystic renal dysplasia accompanied by preaxial thumb duplications should prompt targeted *SALL1* gene analysis. Rapid trio-exome sequencing offers a timely, cost-effective route to definitive diagnosis, enabling personalized counselling and accurate recurrence-risk estimation. Integration of imaging, genomics and autopsy remains the cornerstone of diagnosis in contemporary fetal medicine.

ETHICAL COMPLIANCE

This case report was prepared in accordance with the ethical principles of the Declaration of Helsinki. Formal approval from an ethics committee was not required for a single anonymized case report. Written informed consent for genomic analysis and publication was obtained from both parents.

AUTHORSHIP

Miguel Martins – Conceptualization; Data curation; Investigation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing

Beatriz Sousa Ferreira - Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing

Rosário Almeida Lopes - Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing

Ana Isabel Correia - Investigation; Project administration; Writing – original draft; Writing –
review & editing

Rosário Pinto Leite- Investigation; Resources; Validation; Writing – original draft

Márcia Martins - Investigation; Resources; Validation; Writing – original draft

Rosete Nogueira - Conceptualization; Methodology; Supervision; Validation; Visualization; Writing – original draft

Osvaldo Moutinho – Conceptualization; Supervision; Project administration; Visualization; Writing – original draft

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CORRESPONDENCE TO

Miguel Martins
Gynecology and Obstetrics Department
Unidade Local de Saúde de Trás-os-Montes e Alto Douro
Av. da Noruega, Lordelo
5000-508 Vila Real
Email: intgomiguel.martins@gmail.com

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