# The cardiovascular implications of a rare unbalanced translocation involving a duplication of distal 10q and deletion of distal 15q

Gary LaCroix, MD; Lois J Starr, MD PhD; Anji Yetman, MD
University of Nebraska Medical Center, Omaha, NE;
Children's Hospital & Medical Center, Omaha, NE

## Background

We report a case of a male infant with a rare unbalanced translocation [46,XY,der(15)t(10;15)(q25.3;q26.1)].The patient presented with congenital heart disease and subsequent tracheal bleeding from multiple aortopulmonary collaterals.

## Case Report

The patient had a prenatal diagnosis of coarctation (CoA) and suspected trisomy 18. His clinical exam demonstrated low birth weight, microcephaly, craniofacial dysmorphia, and musculoskeletal anomalies including rocker bottom feet. Multiple organ systems were involved. Postnatal cardiac imaging demonstrated a small but apex- forming left ventricle, bicuspid aortic valve (BAV), hypoplastic aortic arch with long segment CoA, atrial septal defect, and numerous coronary fistulae to the right ventricle. The patient underwent CoA repair and ASD closure via a sternotomy. Multiple aortopulmonary collaterals were identified initially at 16 months of age and serially embolized as the patient developed symptoms, including tracheal bleeding and desaturation.

Fluorescence in situ hybridization (FISH) was normal for 13, 18, 21, and 22q11.2 probes. A karyotype revealed a derivative chromosome 15. Microarray delineated the rearrangement further to involve a 17.2 megabase (Mb) duplication of 10q25.3-q26.3 and a 10.1 Mb deletion at 15q26.1-q26.3.

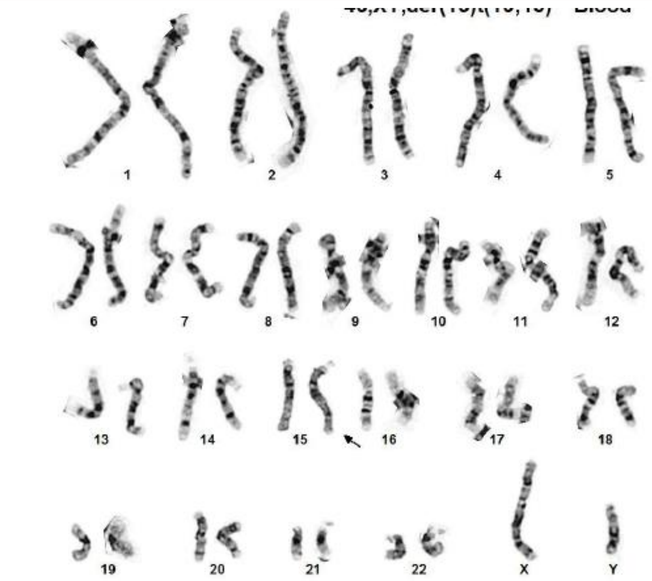


Figure 1: Blood karyotype demonstrating the unbalanced translocation. Part of the distal arm of chromosome 15 is deleted and replaced by additional genetic material from chromosome 10 (arrow).

## *NR2F2* (*COUP-TFII*) Gene

- Mouse models demonstrate involvement in atrial identity, coronary artery development, and in vein and lymphatic identity.[1, 2, 3]
  - In mice, veins gain arterial characteristics with ablation of the *NR2F2* gene.[4]
- Reported in patients with congenital heart disease including atrioventricular septal defects, double outlet right ventricle, tetralogy of Fallot, hypoplastic left heart syndrome, BAV, and CoA.[5, 6]
- *NR2F2* mutation disrupts synergistic transcriptional activation with GATA-4 transcription factor, which is associated with BAV.[7]
- Role in coronary fistulae or aortopulmonary collaterals not established in humans.

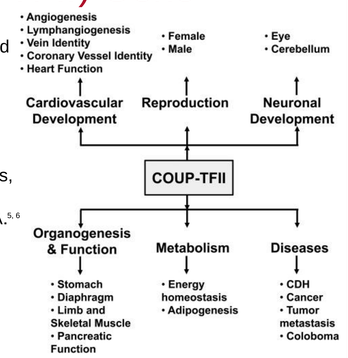


Figure 2: Involvement of COUP-TFII in physiological and pathological processes during mouse development [8]

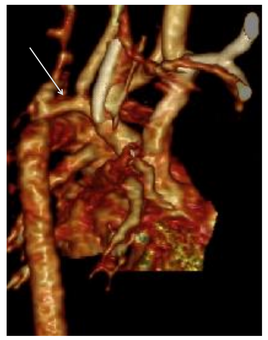

Figure 3: CT reconstruction prior to cardiac repair demonstrating hypoplasia of the transverse aortic arch (arrow). The arch is severely narrowed at the isthmus.

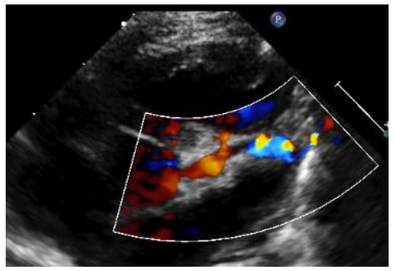

Figure 4: Transthoracic echocardiogram, parasternal short axis color doppler. The left main coronary artery and left anterior descending are dilated. Multiple fistulous connections to the right ventricle were present.

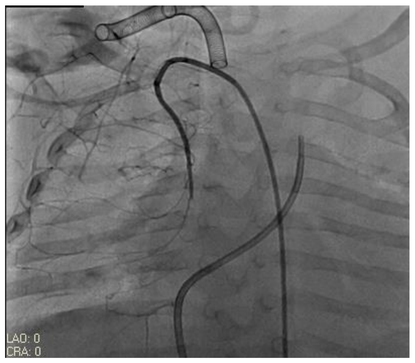


Figure 5: Power injection in the right internal mammary artery demonstrating multiple aortopulmonary collaterals. The pulmonary vascular resistance was elevated but normalized with FiO2/ iNO challenge.

## Other Genes and Features

- Chromosome 15
  - *IGF1R* deletion implicated in IUGR and growth restriction.[9]
  - *CHD2* deletion associated with developmental delay and seizures.[10]
- Chromosome 10
  - 3 copies of *NFkB2* gene implicated in ureteropelvic junction obstruction[11].
  - Skeletal abnormalities and developmental delays seen in duplications[12].
- One similar case report of a patient with 46,XY,der(15) t(10;15)(q25.2;q26.2) and a 5 Mb deletion of the terminal portion of 15q. The *NR2F2* gene was preserved. No cardiac defects were described.[13]

Figure 6: Our patient with ongoing developmental delays. Therapies have contributed in reaching milestones.

## Conclusion

Unbalanced translocations resulting in chromosome 10q terminal duplications and 15q distal deletions are profoundly rare. This patient harbors numerous genes with incorrect dosage due to the translocation. Of interest, *NR2F2* that encodes a transcription factor essential for normal cardiovascular development and angiogenesis was deleted. Loss-of-function of this gene has been associated with BAV, atrioventricular septal defects, double outlet right ventricle, and CoA with ventricular septal defect in single case reports and may have played a role in our patient's initial and ongoing cardiac disease.

Understanding of specific genes affected can guide appropriate treatment and anticipatory guidance. Familial cases of cardiac lesions may be attributed to an *NR2F2* deletion. Further research is needed to understand the variable expression of cardiac defects with an *NR2F2* mutation.

## References

1. Wu SP, Cheng CM, Lanz RB, et al. Atrial identity is determined by a COUP-TFII regulatory network. Dev Cell. 2013;25(4):417-426.
2. Su T, Stanley G, Sinha R, et al. Single-cell analysis of early progenitor cells that build coronary arteries. Nature. 2018;559(7714):356-362.
3. Aranguren XL, Beerens M, Coppiello G, et al. COUP-TFII orchestrates venous and lymphatic endothelial identity by homo- or hetero-dimerisation with PROX1. J Cell Sci. 2013;126(Pt 5):1164-1175.
4. You LR, Lin FJ, Lee CT, DeMayo FJ, Tsai MJ, Tsai SY. Suppression of Notch signalling by the COUP-TFII transcription factor regulates vein identity. Nature. 2005;435(7038):98-104.
5. Al Turki S, Manickaraj AK, Mercer CL, et al. Rare variants in NR2F2 cause congenital heart defects in humans. Am J Hum Genet. 2014;94(4):574-585.
6. Qiao XH, Wang Q, Wang J, et al. A novel NR2F2 loss-of-function mutation predisposes to congenital heart defect. Eur J Med Genet. 2018;61(4):197-203.
7. Wang J, Abhinav P, Xu YJ, et al. NR2F2 loss of function mutation is responsible for congenital bicuspid aortic valve. Int J Mol Med. 2019;43(4):1839-1846.
8. Lin FJ, Qin J, Tang K, Tsai SY, Tsai MJ. Coup d'Etat: an orphan takes control. Endocr Rev. 2011;32(3):404-421.
9. Abuzzahab, M. J., et al. IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. New Eng. J. Med. 349: 2211-2222, 2003.
10. Carvill G, Helbig I, Mefford H. CHD2-Related Neurodevelopmental Disorders. 2015 Dec 10. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
11. Chen CP, Chen YJ, Tsai FJ, Chern SR, Wang W. NFkB2 gene duplication is associated with fetal pyelectasis in partial trisomy 10q (10q24.1qter). Prenat Diagn 2008;28:364–5.
12. Jean-Pierre Fryns and Maj Hultén. Duplications of 10q. Unique. 2009.
13. Sun SC, Luo FW, Song HW, He JB, Peng YS. Distal trisomy of 10q with distal monosomy of 15q due to a paternal translocation. J Int Med Res. 2009;37(4):1230-1237.

## Acknowledgments

We would like to acknowledge our patient's parents. We are grateful for their permission to share this with our colleagues and for their amazing advocacy for their son.