


# Anatomically corrected malposition of the great arteries (S,L,D) with mutation of Nodal gene

Carolina Putotto<sup>1</sup> , Elio Caruso<sup>2</sup>, Bruno Marino<sup>1</sup>, Maria Cristina Digilio<sup>3</sup>, Antonio Novelli<sup>4</sup> and Salvatore Agati<sup>2</sup>

## Brief Report

**Cite this article:** Putotto C, Caruso E, Marino B, Digilio MC, Novelli A, and Agati S (2023) Anatomically corrected malposition of the great arteries (S,L,D) with mutation of Nodal gene. *Cardiology in the Young* **33**: 160–162. doi: [10.1017/S1047951122001585](https://doi.org/10.1017/S1047951122001585)

Received: 12 October 2021

Revised: 25 February 2022

Accepted: 3 May 2022

First published online: 20 May 2022

### Keywords:

Anatomically corrected malposition of the great arteries; laterality defects; discordant atrioventricular connections; ventricular l-loop; Nodal gene

### Author for correspondence:

Dr C. Putotto, MD, Department of Pediatrics, Obstetrics and Gynecology, Division of Pediatric Cardiology, “Sapienza” University of Rome (Italy) Policlinico Umberto I, Viale Regina Elena 324, Rome, 00161, Italy.  
Tel: +39 3398644911.  
E-mail: [carolina.putotto@uniroma1.it](mailto:carolina.putotto@uniroma1.it)

<sup>1</sup>Department of Pediatrics, Obstetrics and Gynecology, Division of Pediatric Cardiology, Sapienza University of Rome, Rome, Italy; <sup>2</sup>Mediterranean Pediatric Cardiology Center “Bambino Gesù Children’s Hospital”, San Vincenzo Hospital, Taormina, Italy; <sup>3</sup>Medical Genetics, Rare Diseases Unit, Department of Pediatrics, Genetics and Rare Diseases Research Area, Bambino Gesù Children Hospital, IRCCS, Rome, Italy and <sup>4</sup>Laboratory of Medical Genetics, and Laboratory Multimodal Medicine Research Area, Bambino Gesù Children Hospital, Rome, Italy

### Abstract

Anatomically corrected malposition of the great arteries is a rare CHD, involving alignment and position of the great arteries. We report an infant with situs solitus, atrioventricular discordance, and ventriculoarterial concordance with the aorta arising anteriorly and to the right of the pulmonary artery. A mutation of Nodal gene, implicated in the pathogenesis of human left–right patterning defects, was found.

Anatomically corrected malposition of the great arteries is a rare and very interesting cardiac defect with peculiar alignment of the great arteries.<sup>1–10</sup> Initially named anatomically corrected “transposition” of the great arteries,<sup>5</sup> this malformation stimulated an interesting debate on morphology and nomenclature of CHD.<sup>1–9</sup> The ventriculoarterial connections are concordant, with the pulmonary artery usually posterior and aligned with the morphologically right ventricle, while the aorta arises from the morphologically left ventricle but usually located anteriorly and with a quite variable infundibular morphology.<sup>1–6</sup> Notably, in this cardiac malformation, the great arteries are parallel to each other rather than in a spiral relationship.

This CHD has been described in all types of viscerio-atrial arrangements, with and without atrioventricular concordance, with sub-aortic, sub-pulmonary, or bilateral infundibula and associated with many other cardiac malformations, such as tricuspid atresia and coronary artery abnormalities.<sup>1–9</sup> The difference between so-called isolated ventricular inversion and “corrected malposition of the great arteries” is that in ventricular inversion the great arteries maintain their normal spiral relationship.<sup>1–6</sup>

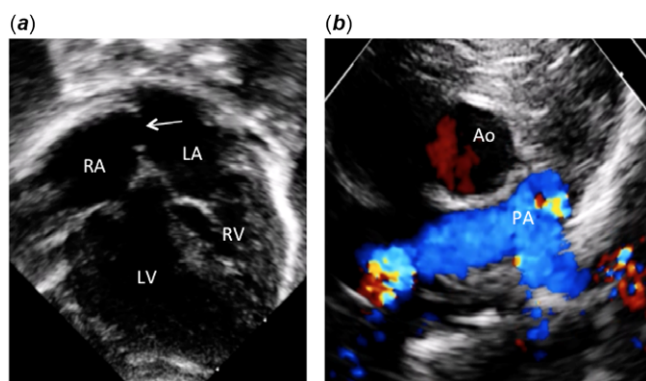
In patients with viscerio-atrial situs solitus, two anatomical forms of anatomically corrected malposition of the great arteries were reported. The more frequent type consists in atrioventricular concordance (d-ventricular loop) with the aorta arising anteriorly and to the left from the left-sided morphologically left ventricle [S,D,L] with physiological normal blood circulations.<sup>1,3–6</sup> The more rare type consists in atrioventricular discordance (l-ventricular loop) with the aorta arising anteriorly and to the right from the right-sided morphologically left ventricle [S,L,D].<sup>2,5–9</sup> In this latter form, the blood circulations are parallel to each other and the haemodynamic status is that of transposition of the great arteries.

We report a child with anatomically corrected malposition of the great arteries [S,L,D], successfully treated with Mustard operation, associated with a mutation of Nodal gene.

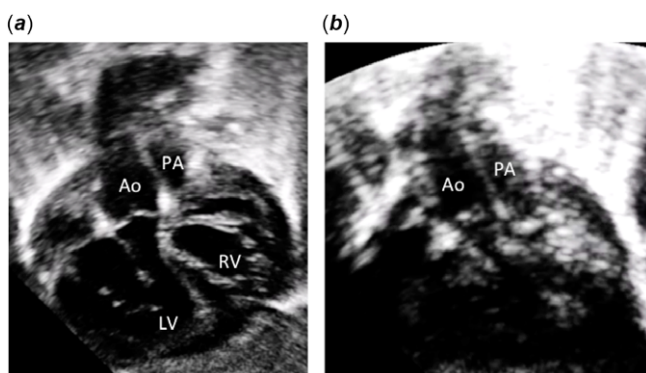
### Case report

A full-term female neonate with a prenatal diagnosis of “ventricular inversion” was admitted, at birth, to the neonatal ICU with profound cyanosis. Two-dimensional colour Doppler echocardiography showed levocardia, situs solitus of the atria, and discordant atrioventricular connections with l-loop of the ventricle (Fig 1a and c). The ventriculoarterial connections were concordant with the aorta arising anteriorly and right-sided from the right-sided morphologically left ventricle (Figs 1b, 2a and b). The pulmonary artery arose posteriorly and left-sided from the left-sided morphologically right ventricle (Fig 2a). The two great arteries are parallel to each other without spiralisation (Fig 2b). There was a small interatrial communication that required a Rashkind procedure at 3 days of age. The ventricular septum was intact (Figs 1a and 2a). The diagnosis of anatomically corrected malposition of the great arteries [S,L,D] was done, and the patient underwent a successful Mustard operation at 5 months of age. No extracardiac anomalies were detected clinically and by cerebral and abdominal ultrasound examinations.

© The Author(s), 2022. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.



**Figure 1.** Apical and parasternal two-dimensional echocardiographic pictures. (a) Apical four-chamber view showing atrioventricular discordance with l-ventricular loop. Note the inverted atrioventricular valve offsetting and the large atrial septal communication (arrow) after Rashkind procedure. (b) Parasternal short axis view showing the aorta located anteriorly and to the right of the pulmonary artery. Ao: aorta; PA: pulmonary artery; LV: left ventricle; RV: right ventricle; RA: right atrium; LA: left atrium.



**Figure 2.** Subcostal two-dimensional echocardiographic pictures. (a) Subcostal view showing ventriculo-arterial concordance. The aorta arises anteriorly from the right-sided morphologically left ventricle and the pulmonary artery arises posteriorly from the left-sided morphologically right ventricle. (b) Subcostal view showing the short sub-aortic and sub-pulmonary infundibulum and the parallel position of the great arteries. Ao: aorta; PA: pulmonary artery; LV: left ventricle; RV: right ventricle; RA: right atrium; LA: left atrium.

Based on the rarity and complexity of the cardiac anatomy, a genetic study was suggested. Next Generation Genetics testing was performed by the Twist Custom Panel kit (clinical exome – Twist Bioscience) and analysed on NovaSeq6000 (Illumina) platform. The heterozygous c.817G > A missense variant in *Nodal* gene was detected, leading to the aminoacidic change p. Ala273Thr (rs770958126).

The genetic variant was validated on re-extracted DNA and verified by bidirectional Sanger sequencing. Standard chromosomal analysis and SNParray were normal.

## Discussion

*Nodal* gene is a member of the TGF- $\beta$  superfamily of developmental regulators and is critical for early embryonic patterning in vertebrates. *Nodal* signalling has been shown to play an important role in anterior–posterior axis patterning and left–right axis determination.<sup>11</sup> Disruption of *Nodal* signalling in mammals has been linked

to cardiac malformations due to defects in left–right patterning of the embryo, such as heterotaxia with left–right asymmetry of the thoracoabdominal organs.<sup>12</sup> Loss-of-function mutations in several genes belonging to the *Nodal* signalling pathways, including *Nodal* itself, *Cripto*, *Cryptic*, *Lefty1*, *Lefty2*, and *FoxH1*, have been identified in patients with cardiac laterality defects.<sup>13</sup> Interestingly, mutations in *Nodal* gene in humans have been detected also in cases of isolated or syndromic transposition of the great arteries.<sup>12</sup> It is possible that the same genetic defect could lead to a variety of cardiac laterality malformations, ranging from heterotaxia to transposition of the great arteries with viscerio-atrial situs solitus.<sup>14</sup> In addition, epidemiological studies are showing familial aggregation of heterotaxia, d-transposition of the great arteries, and congenitally corrected transposition of the great arteries with situs solitus. In some of these families, multiple mutations in laterality genes, including *Nodal* and *ZIC3*, have been identified.<sup>15</sup>

The present case is the first in which a mutation of *Nodal* gene is reported in association with anatomically corrected malposition of the great arteries with discordant atrioventricular and concordant ventriculoarterial connections [S,D,L]. Although there is no definitive evidence that the mutation reported is causal of this cardiac defect, we suggest that this genetic variant of *Nodal* gene could be considered pathogenic in this peculiar case. Moreover, we do not know if this mutation could be the cause of the l-loop of the ventricle<sup>16</sup> or of the specific conotruncal anomaly or both. However, the involvement of *Nodal*, a very important gene for the development of the left–right asymmetry, is not surprising in this complex cardiac malformation that shows evident signs of ventricles and great arteries laterality defects.

**Acknowledgements.** None.

**Financial support.** This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

**Conflicts of interest.** None.

**Ethical standards.** None.

## References

1. Van Praagh R, Durnin RE, Jockin H, et al. Anatomically corrected malposition of the great arteries (S, D, L). *Circulation* 1975; 51: 20–31.
2. Pasquini L, Sanders SP, Parness I, et al. Echocardiographic and anatomic findings in atrioventricular discordance with ventriculoarterial concordance. *Am J Cardiol* 1988; 62: 1256–1262.
3. Kirklin JW, Pacifico AD, Barger LM Jr, Soto B. Cardiac repair in anatomically corrected malposition of the great arteries. *Circulation* 1973; 48: 153–159.
4. Sanders SP, Toba S. Unusual ventriculo-arterial alignments and connections. *World J Pediatr Congenit Heart Surg* 2020; 11: 355–357.
5. Van Praagh R, Van Praagh S. Anatomically corrected transposition of the great arteries. *Br Heart J* 1967; 29: 112–119.
6. Thiene G, Pellegrino PA, Maddalena F, Gallucci V. Malposizione anatomicamente corretta delle grandi arterie [Anatomically corrected malposition of the great arteries (author's transl)]. *G Ital Cardiol* 1975; 5: 332–341.
7. Cavalle-Garrido T, Bernasconi A, Perrin D, Anderson RH. Hearts with concordant ventriculoarterial connections but parallel arterial trunks. *Heart* 2007; 93: 100–106.
8. Zakheim R, Mattioli L, Vaseenon T, Edwards W. Anatomically corrected malposition of the great arteries (S,L,D). *Chest* 1976; 69: 101–104.
9. Arciprete P, Macartney FJ, de Leval M, Stark J. Mustard's operation for patients with ventriculoarterial concordance. Report of two cases and a cautionary tale. *Br Heart J* 1985; 53: 443–450.

10. Bernasconi A, Cavalle-Garrido T, Perrin DG, Anderson RH. What is anatomically corrected malposition? *Cardiol Young* 2007; 17: 26–34.
11. Brennan J, Norris DP, Robertson EJ. Nodal activity in the node governs left-right asymmetry. *Genes Dev* 2002; 16: 2339–2344.
12. Mohapatra B, Casey B, Li H, et al. Identification and functional characterization of NODAL rare variants in heterotaxy and isolated cardiovascular malformations. *Hum Mol Genet* 2009; 18: 861–871.
13. Roessler E, Pei W, Ouspenskaia MV, et al. Cumulative ligand activity of NODAL mutations and modifiers are linked to human heart defects and holoprosencephaly. *Mol Genet Metab* 2009; 98: 225–234.
14. Versacci P, Pugnali F, Digilio MC, et al. Some isolated cardiac malformations can be related to laterality defects. *J Cardiovasc Dev Dis* 2018; 5: 24.
15. De Luca A, Sarkozy A, Consoli F, et al. Familial transposition of great arteries caused by multiple mutations in laterality genes. *Heart* 2010; 96: 673–677.
16. Noël ES, Verhoeven M, Legendijk AK, et al. A Nodal-independent and tissue-intrinsic mechanism controls heart-looping chirality. *Nat Commun* 2013; 4: 2754.