Pathophysiology of Reproduction and Development

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Physiology Assessment Cover Sheet

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Date submitted: 26/05/2017

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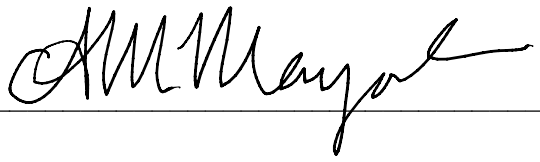
Signature: 

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Section 1: Pathology specimen

Specimen identification number: 11.12.3

Specimen identification: 14714A

How does this specimen relate to Development or Reproduction?

The specimen is a heart of a man known to have tetralogy of Fallot; a congenital heart defect.

To the best of your ability, describe the specimen. Take note of size, colour, structures, differences between tissues. You may draw the specimen but not photograph it. Marks are not dependent on artistic ability but on the ease of understanding the specimen.

This specimen is an abnormal heart from a forty-two year old man who had tetralogy of Fallot. The heart is displayed with its right on the left side of the observer and vice versa. It measures 12 cm across with a height of 13.5 cm and has been opened anteriorly. The endocardium can be seen on the interior surface of the heart, and the pericardium on the external surface. There was nothing abnormal about these on observation.

One of the major defects observed was the enlarged aorta. It was identified due to its known thickened walls compared to other vessels. It was located on superior right portion of the specimen (in terms of anatomical position), having been transposed with the pulmonary artery which was located on the left. Both had been cut open anteriorly exposing a second abnormality; a patent ductus arteriosus. This was an opening of significant size between the aorta, specifically, the aortic arch, and the pulmonary artery. Inferior to this, a small portion of the lung was still attached to the heart specimen.

Since the anterior surface had been cut away, the vena cava were unable to be identified on this specimen. The atria were identified and its interior walls were observed to be smooth, as normal. The right atrium was significantly larger than the left in size, though still smaller than what it should be normally. This situation was reversed in the ventricles with the left ventricle being much larger than the right, however both ventricles were of an abnormally large size in comparison to the heart as a whole, taking up approximately two thirds of its entire size. In addition, the chordae tendineae of the left ventricle were noticeably longer than those in the right ventricle, however its thickness was the same in each chamber. The chordae tendineae in each ventricle were attached to papillary muscles at the base of its respective chamber, and the surrounding walls contained the muscular ridges called trabeculae carneae. These had no obvious signs of abnormality. Furthermore, the walls of the right and left ventricles were of normal ratio compared to one another, with the left being thicker than the right. This was difficult to depict in Figure 1 due to the orientation of the heart. Located in the superior portion between the two ventricles was an obvious ventriculo-septal defect; a hole of approximately 1 cm joining the ventricles together.

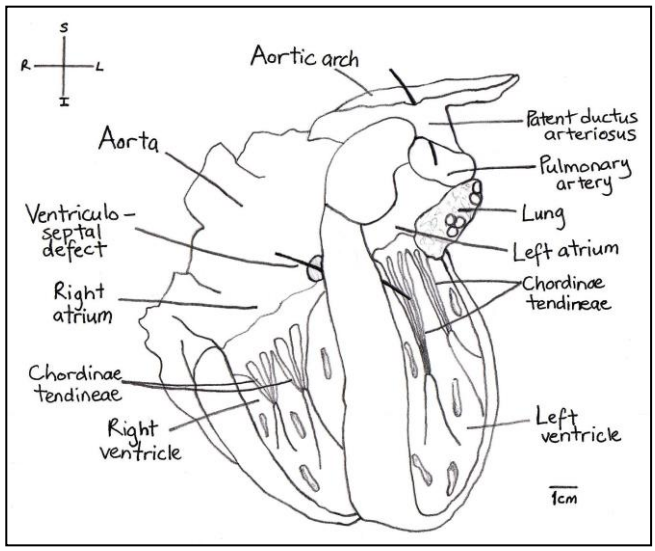

Figure 1. Drawing of an abnormal heart with tetralogy of Fallot, opened and displayed anteriorly. The specimen is located in the Ainsworth Interactive Collection of Medical Pathology in the Charles Perkins Centre at the University of Sydney (specimen identification no. 11.12.3; specimen identification: 14714A). Some major anatomical features are labelled. In particular, note the ventriculo-septal defect and patent ductus arteriosus.

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Section 2: Normal specimen
Specimen identification number: 11.000.2
Specimen identification: 15446A

To the best of your ability, describe the specimen. Take note of size, colour, structures, differences between tissues. You may draw the specimen but not photograph it. Marks are not dependent on artistic ability but on the ease of understanding the specimen.

This specimen of a normal heart has no history attached to it. It is displayed so that the left and right chambers are on the left and right of the observer. The specimen measures 12 cm across with a height of 13.5 cm and has been opened posteriorly. Observed in the interior of the heart is the endocardium, and on the exterior surface is the pericardium as normal.

Regarding one of the great vessels, the opening of the superior vena cava can be seen superiorly on the heart specimen and opens into the right atrium as normal. It has thin walls consistent with those of veins. The right and left atria and ventricles are similar in many regards as normal. Both atria have smooth walls and in the left atria a closed fossa ovalis can be seen. Each atrium opens into the ventricle on their respective side; called the atrioventricular orifice. Each atrium is approximately two thirds the volume of the its ventricle as normal. In both ventricles, a part of the tricuspid valve can be seen, the rest having been cut away when opening the heart. Chordae tendineae of normal thickness are attached to papillary muscles at the base of each respective chamber and on the inner walls are the muscular ridges called trabeculae carneae. The walls of the left ventricle are thicker than those of the right as normal.

The opening of the aorta was identified to be on the superior aspect of the heart, as expected. Its walls were thicker compared to other vessels, and within it semilunar valves were identified. Its origin was traced back to the left ventricle as normal. In close proximity to the aorta was the opening of the pulmonary trunk whose walls were thicker than some of the other vessels, contained semilunar valves, and was connected to the left atrium, as normal. Described in anatomical position, the placement of the pulmonary trunk was on the left lateral side of the heart with the aorta placed more medially, as normal. Following this, the superior vena cava was identified to the right of the aorta and could be seen to open into the right atrium as expected. The inferior vena cava could not be identified and was therefore likely cut open or removed when opening the heart. Similarly, the pulmonary veins were difficult to identify, however, the two superior openings out of the total four veins were thought to be identified as labelled in Figure 2. They both open into the left atrium as normal.

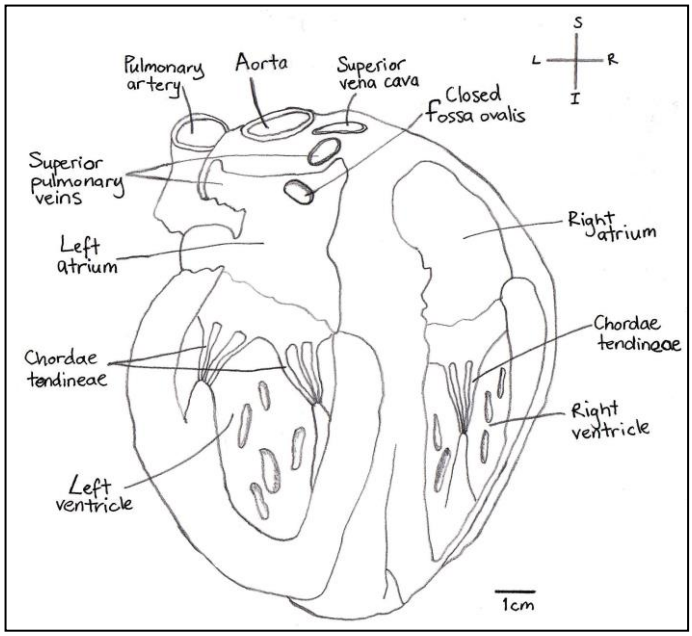

Figure 2. Drawing of a normal heart, opened and displayed posteriorly. The specimen is located in the Ainsworth Interactive Collection of Medical Pathology in the Charles Perkins Centre at the University of Sydney (specimen identification no. 11.000.2; specimen identification: 15446A). Some major anatomical features are labelled.

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Section 3: Molecular pathway aberrant in this condition.
Investigate the scientific literature to describe a molecular pathway that has been reported to be abnormal in the specimen you have described in Section 1. Any papers mentioned must be cited appropriately and can be done so on a separate page.

The *JAG1* gene encodes a Notch ligand called Jagged1 (JAG1) which is one of five ligands on the cell surface that is involved in the Notch signaling pathway (Eldadah et al. 2001 & Loomes et al. 1999). Notch signaling is a conserved pathway that is active during the development of many organs, including that of the heart (Grochowski et al. 2015). The JAG1-NOTCH (ligand-receptor) interaction is upstream of a cascade of events that eventually leads to transcription of target genes. Homozygous *JAG1* deletions were shown to be lethal during embryonic development (Xue et al. 1999), and mutations of the *JAG1* gene have been associated with tetralogy of Fallot in adults (Eldadah et al. 2001 & Bauer et al. 2010).

The JAG1 protein consists of a small intracellular domain, a transmembrane domain, and a larger extracellular component (Grochowski et al. 2015). Within the extracellular component are four motifs required for the protein to function. This includes a signal peptide, a DSL domain, several epidermal growth factor-like (EFG-like) repeats, and a cysteine-rich region. The signal peptide moves the protein to the cell surface where DSL is needed in binding JAG1 to NOTCH receptors and EFG repeats increase the affinity of their binding. In addition, the cysteine residues form disulfide bridges which help stabilize the protein.

JAG1 has been found to be associated with Alagille syndrome, a genetic disorder characterized by abnormalities in organs including those of the heart such as tetralogy of Fallot (Grochowski et al. 2015). It is caused by haploinsufficiency for JAG1; an autosomal dominant condition (Eldadah et al., 2001). It should be noted that although there are many types of mutation, none have been found to be more severe than others, suggesting that other factors play a role in the varying expression of the disease.

One mutation in particular, a missense mutation in the JAG1 gene, has been directly correlated with tetralogy of Fallot. It involves a point mutation (G274D) in the *JAG1* gene (Eldadah et al. 2001 & Grochowski et al. 2015). The mutation occurs on chromosome 20 and causes a change of G to A at the 274th position of nucleotide 821 (Figure 3A) which results in a substitution of aspartic acid (D) for glycine (G) (Figure 3C). Since this mutation affects the glycine in position 274 that is highly conserved in the EFG-like domains of JAG1, it affects the binding affinity of the JAG1 ligand to the NOTCH receptors. This has negative consequences on the expression of the protein at the cell surface.

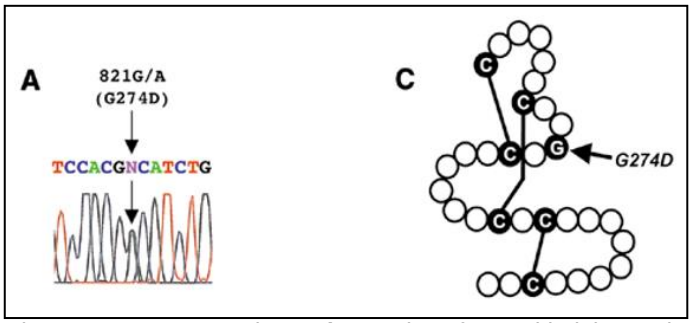

Figure 3. *JAG1* mutation G→A. Taken from Eldadah et al. (2001). (**A**) PCR revealed a change in an amino acid, specifically G to A at position 274 of nucleotide 821. (**C**) Schematic of an EFG-like domain showing the cysteine (C) disulphide bridges and the G274D substitution.

Although it is known that the substitution of the glycine in this domain causes abnormalities in protein folding, the actual function of the gene before and after substitution continue to be a subject of further research (Grochowski et al. 2015).

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