Heredity of patent ductus arteriosus in dogs

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Abstract

Background: Patent ductus arteriosus (PDA) is the most common cardiac congenital malformation in dogs. Screenings of the affected dogs highlight recurrent breeds, strongly suggesting genetic disorders to be the cause of said defect. The pathophysiological process is well known and the treatment keeps being developed with high-end devices, however the question of transmission is still unclear. Therefore genetic detecting tests are not even discussed yet.

Objectives: The first purpose of this synthesis is to reveal the genetic component of PDA by finding dogs' bloodlines (breeds and families) in which the defect is considerably present. Furthermore, an accurate description of the ductal closure mechanism at the molecular and genetic levels will lead to genes which can then be investigated for potential mutations. A highlight of those involved genes represents the second objective.

Methods: The literature has been mostly reviewed in *Pubmed* database and the OMIA website (Online Mendelian Inheritance in Animals). Data have been gathered and interpreted to attempt to identify the genetic origin of PDA.

Results: Females and purebred dogs, especially German Shepherd and small breeds such as Pomeranian, Miniature Poodle, Bichon Frise and Chihuhua are the most affected by PDA. It is also found in some families and in case of inbreeding across generations. The pathology occurs when the balance between relaxation and contraction of the VSMCs (Vascular Smooth Muscle Cells) is jeopardized.

Key words: patent ductus arteriosus, genetic/inheritance, dog, breed

L'hérédité de la persistance du canal artériel chez le chien

Résumé

Contexte : La persistance du canal artériel (PCA) est la malformation congénitale cardiaque la plus courante chez le chien. Le criblage des chiens atteints montre que certaines races sont plus affectées, suggérant une forte suspicion de troubles génétiques. Le processus pathophysiologique est bien connu et le traitement continue d'être développé au moyen d'outils de pointe. Cependant, la question de la transmission n'est toujours pas élucidée, des tests génétiques de dépistage n'étant par conséquent pas encore sujet de discussion.

Objectifs : Le premier objectif de cette synthèse est de révéler la composante génétique de la PCA en trouvant des lignées de chiens (races et familles) dans lesquels la malformation est considérablement présente. En outre, une description précise du mécanisme de fermeture du canal aux niveaux moléculaire et génétique conduira à des gènes pour lesquels de potentielles mutations peuvent etre à l'origine du PCA. La mise en évidence de ces mutations constitue le deuxième obective.

Méthodes : La littérature a principalement été examinée dans la base de données *Pubmed* et sur le site en ligne de l'OMIA (Online Mendelian Inheritance in Animals). Les données ont été réunies et analysées afin de tenter de trouver l'origine génétique de la PCA.

Résultats : Les femelles et les chiens de pures races, en particulier le Berger Allemand et les petites races comme le Poméranien, le Caniche Miniature, le Bichon Frisé et le Chihuhuales soient les plus affectés par la PCA. Celle-ci est également retrouvée dans certaines familles et en cas de consanguinité entre les générations. D'autre part, un équilibre compromis entre la relaxation et la contraction des CMLV (Cellules Musculaires Lisses Vasculaires) joue également un rôle dans la pathologie. La pathologie se produit quand l'équilibre entre la relaxation et la contraction des CMLV (Cellules Musculaires Lisses Vasculaires) est compromis.

Mots clés : Persistance du canal artériel, génétique/hérédité, chien, race

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Abbreviations

DA : Ductus Arteriosus

PDA : Patent Ductus Arteriosus

VSMCs : Vascular Smooth Muscle Cells

1. Introduction

The ductus arteriosus (DA), or ductus Botalli, takes its origin in the left sixth embryonic aortic arch. It is a normal structure in the foetus that connects the pulmonary artery to the proximal descending aorta to bypass the pulmonary circulation and restore blood in the systemic circulation. Indeed the lungs are useless in utero and oxygenation of blood is performed by placenta (Matsui et al., 2008). Under normal circumstances, the closure mechanism starts within minutes or hours after birth, which is not the case in Patent Ductus Arteriosus (PDA) (Silvain, 2014). In that case, PDA's direction is often from left to right, meaning from systemic to pulmonary circulation, but some are reversed (right to left meaning from pulmonary to systemic circulation) or bidirectional (Goodrich et al., 2007).

Clinical signs are cough, exercise intolerance and dyspnea. They are not always manifests, especially in puppies (Stanley et al., 2003) and in cases of small PDA. However, a large ductus is distinctively identified by auscultation revealing a wide pulse pressure, a strong arterial pulse and a machinery-like murmur (maximum intensity at the end of systole) (Goodrich et al., 2007). Ideally, PDA has to be treated, since bacterial endocarditis and pulmonary vascular occlusion may occur due to a difference of pressure between the pulmonary artery and the aorta, leading to a high ductal flow (Campbell et al., 2006). The two main methods to occlude a PDA are surgical ligation and transcatheter coil occlusion (Stanley et al., 2003) .

PDA is the most common cardiac congenital malformation in dogs, representing 25 to 30% of the congenital cardiac defects (Broaddus and Tillson, 2010). It is more commonly diagnosed in purebred dogs than in mixed breeds (Stanley et al., 2003). Amongst predisposed dogs, some breeds seem to be affected, as well as females in general (Smith et al., 2016).

Knowing those predispositions, the objective of this synthesis is to analyse current scientific

literature to identify them more clearly and to make the link with the heredity nature of this pathology. A gene investigation will be directed toward the ductus closure events and the associated pathologies.

2. Materials and methods

The general information about PDA expected to be knew in clinic were found in the articles' introduction and confirmed in a cardiology book (Smith et al., 2016) and in a PhD thesis (Silvain, 2014). *Pubmed* database was the most useful tool to screen the epidemiology, to understand the molecular mechanism of the ductal closure and to find potential associated disorders. This extensive search will highlight the genes encountered in the normal DA closure and the ones in the delayed closure. Websites listing inheritances disorders were also used to make the link with the involved genes, including *OMIA - Online Mendelian Inheritance in Animals* and CIDD (Canine Inherited Disorders Database) *(Patent Ductus Arteriosus (PDA) | University of Prince Edward Island)*.

Studies were relevant if they filled a couple of conditions. Only the most recent ones were kept, with a threshold established at year 2000. The dogs they studied (frequently puppies) had to be at term and not premature because PDA is more common in premature due to hypoxia, not because of a default DA structure (see below), and so has very little to do with heredity (Buchanan and Patterson, 2003). Moreover, dogs had to be picked randomly to avoid any selection bias.

In *Pubmed* database, a specific research was launched at first with the following key words : “patent ductus arteriosus”, “dog” and “genetic”. This research led to 23 articles on 04/10/2019. Amongst them, two were off-topic, one did not focused on dogs specifically and ten were outdated (before 2000), thus leaving 10 articles to precisely study. No more relevant articles were found when replacing “genetic” by “heredity” on 02/11/2019. Unfortunately it was not sufficient to answer this topic so a second research was launched on 28/03/2020. The crucial information missing were picked out from the resulting 967 articles, notably gender and breed predispositions.

Regarding breeds screening, the random component is important. First of all, a research on German Shepherd with PDA, for example, will not provide the actual breeds prevalence. Secondly, a treatment research for instance, will pick dogs according to their weight (transarterial coils will suit for large dogs and surgical ligation will be set aside for smaller ones). The breeds' results were

so broad that only breeds represented by a minimum of 3 dogs per study have been picked. Breeds and sex predispositions figures were not taken from isolated cases, except for litters because it will provide a major information about the inheritance.

Finally, all pieces of information needed for the topic have been picked, classified, analysed, compared and discussed. Figures such as numbers and percentages of female or breeds have been calculated in a spreadsheet.

3. Results : Epidemiology

As a start, the predisposed dogs' data will provide an insight about the heredity pattern and, as it will be discussed at the end, the prevention of PDA.

3.1 Gender predisposition

The majority of affected dogs are female, except for Stabyhoun in which the distribution is equal (den Toom et al., 2016). The amounts of females with PDA were retrieved from the literature and the results are reported in Table I below.

Table I: Gender predisposition

Articles	Number of dogs with PDA	Females with PDA (%)
Belanger et al., 2017	360	71.7
Bomassi et al., 2011	4	75
Boutet et al., 2017	35	65.7
Campbell et al., 2006	125	77.6
den Toom et al., 2016	46	50
Doocy et al., 2018	25	76
Glaus et al., 2003	16	75
Goodrich et al., 2007	204	75
Gordon et al., 2010	41	73.2
Hamabe et al., 2015	17	58.8
Henrich et al., 2011	21	66.7
Hildebrandt et al, 2010	28	64.3
Hogan et al., 2004	10	60
Oliveira et al., 2011	237	65
Piantedosi et al., 2019	120	74.2
Porciello et al., 2014	20	60
Saunders et al., 2014	520	73.1
Selmic et al., 2013	35	82.9
Spalla et al., 2016	34	82
Stanley et al., 2003	35	68.7
Van Israel et al., 2002	98	78.6
Van Israël et al., 2003	21	81
Wesselowski et al., 2019	28	57

In term of gender, dogs affected by PDA are for 71.7%, females, according to the gender screening reported in Table I. Reasons for such a result have not yet been clearly identified (den Toom et al., 2016). It could come from the estrogen receptor-α. Indeed, it has been shown that in human male infants, individuals heterozygous for one specific SNP (Single Nucleotiede Polymorphism) in ESR1 gene are less likely to develop PDA (Lewis et al., 2018).

3.2 Breeds predispositions

According to Smith et al. in 2016, predisposed breeds are Bichon Frise, Chihuahua, Cocker Spaniel, Collie, English Springer Spaniel, German Shepherd, Keeshond, Labrador Retriever, Maltese, Newfoundland, Poodle, Pomeranian, Shetland Sheepdog and Yorkshire Terrier, and seems to be inherited in Miniature Poodle (Smith et al., 2016) or Poodle (Parker et al., 2006). Not all studies agreed regarding which breed is the most often affected: for instance, Wesselowski et al. in 2019 published that German Shepherd was the breed most commonly suffering from PDA. That seems to be the reason why some studies gather only German Shepherd, although it might be because the pathology involves a larger open ductal in those dogs, which makes the treatment more challenging (Wesselowski et al., 2019).

Dogs are the second species counting the more inherited disorders after humans. Inputs on the breeding practice and selection pressure are consistent with the loss of gene diversity. In other terms, the quest for some specific traits characteristic to the nowadays breeds are accompanied of unintended mutations expressed by genetic disorders. The more ancient a mutation is in the dog domestication history, the higher the proportion of affected subset population will be (Bellumori et al., 2013). It thus would seem that while pure breeds tend towards a loss of heterosis, mixed-breed dogs will lean toward an increased heterosis, leading to the loss of damaging mutations and, consequently, healthier dogs. But once again, all studies do not agree, Bellumori et al. for instance in 2013 could not detect a significant difference between purebred and mixed-breed dogs with PDA (mean P value 0.480 and odds ratio 0.85 in an interval 0.60-1.22).

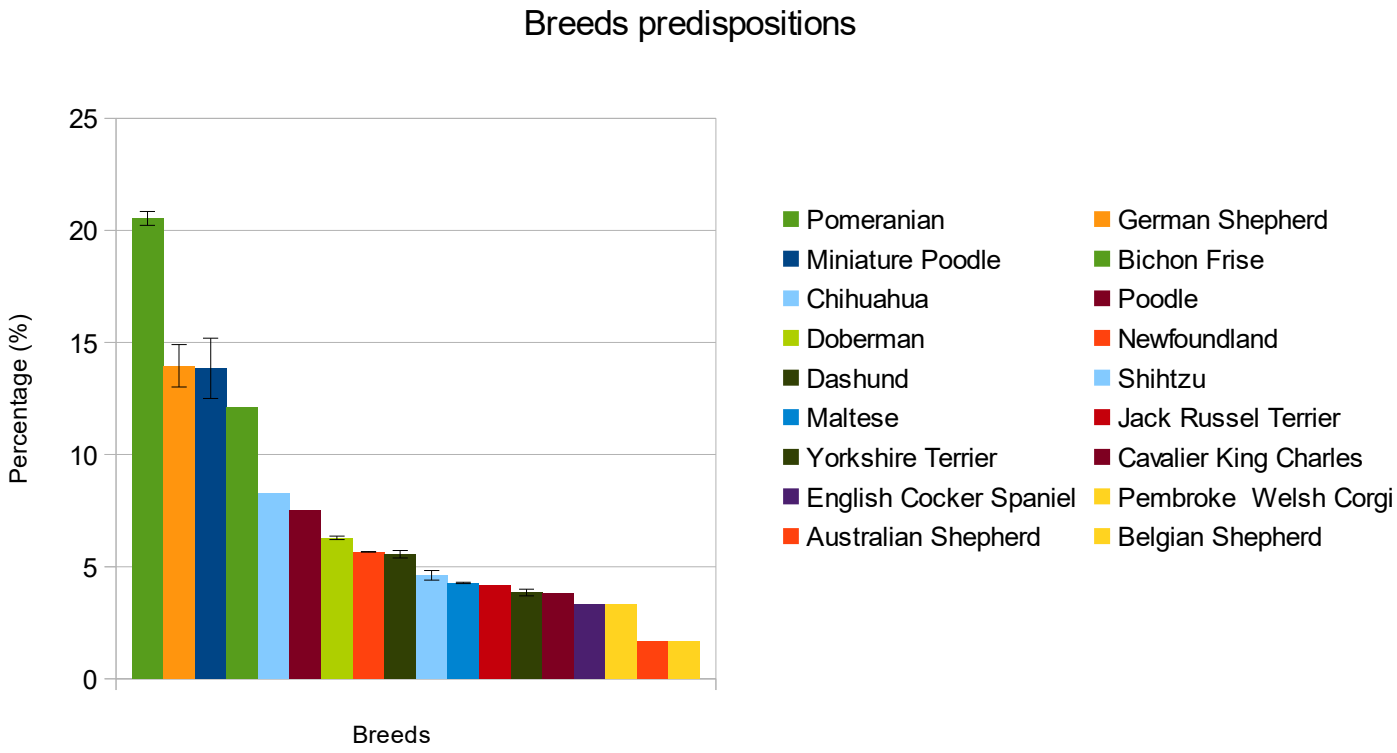
The prevalence of breeds with PDA found in the literature has been reported in Table II below.

Table II: Breeds predispositions

Articles	Total number of dogs	Number of pure breeds	Breeds (number of dogs per breed - most represented breeds only)																
			Australian Shepherd	Belgian Shepherd	Bichon Frise	Cavalier King Charles	Chihuahua	Dashund	Doberman	English Cocker Spaniel	German Shepherd	Jack Russel Terrier	Maltese	Miniature Poodle	Newfoundland	Pembroke Welsh Corgi	Pomeranian	Poodle	Shihtzu	Yorkshire Terrier
Bellumori et al., 2013	420	329																		
Boutet et al., 2017	35	28						3			4									
Doocy et al, 2018	25	19																		
Hamabe et al., 2015	17	17												4			6			
Oliveira et al., 2011	237		4	4		9		6	12		58		12		13					
Piantedosi et al, 2019	120	94							9	4	17	5	4	5	7	4				
Porciello et al., 2014	20	11																		
Saunders et al., 2014	520	465			63		43				30		23				30	39	24	20

Pure breeds represent 79.6% of dogs with PDA. The percentage of each breeds is summarized in Figure 1 below. The main reason purebred dogs are more affected may be that what makes them suitable for domestication could be linked to alleles more prone to cardiac disorders. (Bellumori et al., 2013).

Figure1 : Breeds prevalence in PDA cases



The figure shows the percentage of dogs with PDA for each breed. The percentage and the error-type (variance chosen) have been calculated from Table 1.

3.3 An inherited disorder among families

Another argument in favour of the inheritance is that offspring from parents with PDA are more likely to be born with the same malformation. In humans, PDA occurs in 5% of cases when a sibling suffers from PDA. (Bökenkamp et al., 2010).

When healthy dogs reproduce with dogs who were born with PDA, three outcomes are possible among the offspring: they can either be healthy, suffer from PDA, or show an intermediate condition. The probability for offspring from a healthy parent and an affected one to have PDA is 20%, against 80% when both parents have PDA (Broaddus and Tillson, 2010). However, even in litters from two healthy parents, the PDA can affect several puppies. In the report case of Bomassi et al. in 2011, a female Chihuahua gave birth to 6 puppies total from 2 different litters (from 2 different males). 2 puppies in each litter had PDA whereas their mother did not (fathers' medical

history unknown).

The chance for the offspring to have a PDA condition depends on a threshold regarding the grading phenotypic expression which is correlated with the amount of parents' defective genome (Broaddus and Tillson, 2010).

3.4 Inbreeding

According to Bökenkamp et al. in 2010, PDA is more likely to be observed in Iranian population than in United States population. Their study showed a higher prevalence of (non-syndromic) PDA (15% in Iran compared to 2-7% in the United States) with more consanguinity among the Iranian patients (63%) compared to the Iranian national average (25%).

PDA heredity observed from breeds and families is accentuated by inbreeding which increases recessive disorders, meaning less common breeds with less number of dogs are not spared due to a high rate of inbreeding (Bellumori et al., 2013). This is the case for Stabyhoun with an inbreeding coefficient rising to 31.4% and a PDA prevalence 7.5 to 13 times higher than in the overall dog population. This inbreeding coefficient is higher than the other dog breeds and even higher than the inbreeding in a single generation (25%) between sibling or a parent and an offspring. This can be explained by the low number of original members of this breed (14 actual and 6.5 effective, compared to several hundreds for some other breeds). The consequence can be seen on heritability which is 0.51 in Stabyhoun general population and 0.41 in Stabyhoun with PDA, both significantly close to each other and different from 0, PDA thus having a high hereditary component in this particular breed (den Toom et al., 2016).

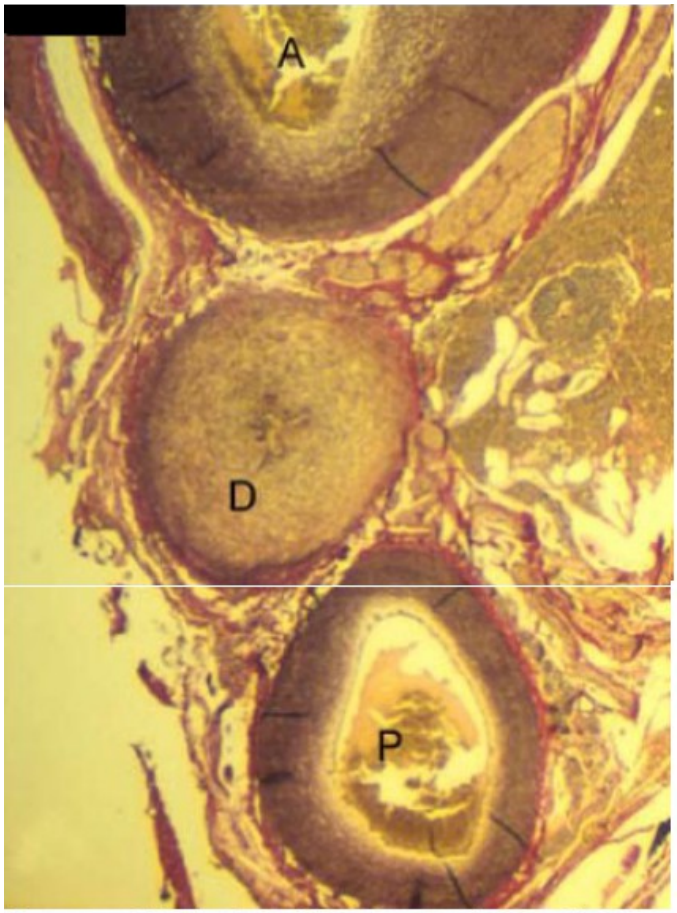
4. Results : Involved genes

4.1. Histopathological abnormalities

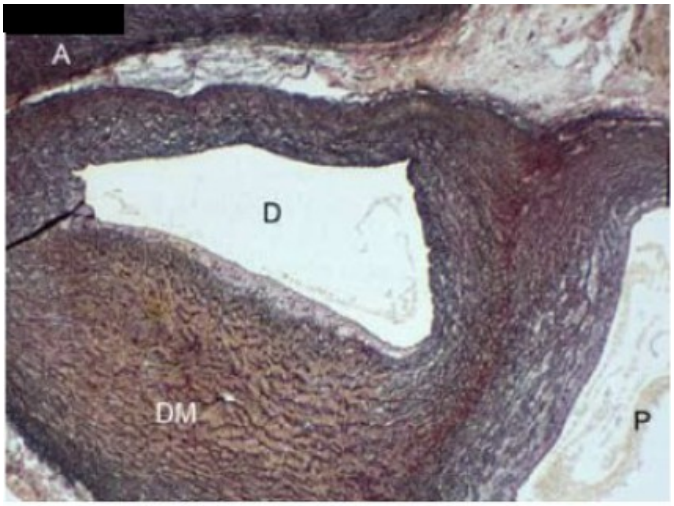
On the histological level, some recurrent abnormalities are observed on samples from PDA cases compared to patients with a normal ductus. The muscular tissue is dominant in healthy dogs with 98% of smooth muscle, the rest being mostly made by elastic fibers and collagen. On the

contrary, the elastic tissue dominates in PDA, the muscular mass being hypoplasic and asymmetric (Buchanan and Patterson, 2003). This configuration comes from an extension of aortic-like elastic tissue (Broaddus and Tillson, 2010). The entirety of the wall of PDA thus presents an asymmetric organisation between type I collagen, GAGs (GlycosAminoGlycans) and smooth muscle fibers (den Toom et al., 2016). The difference of layout is illustrated by transverse histologic sections in Figure 2. The abundant elastic fibers in the intima and in the subendothelial lamina would limit the access to VSMCs (Vascular Smooth Muscle Cells) from the media to the intima and prevent their proliferation. The ductal contraction is then limited, as well as the closure (Bökenkamp et al., 2010).

Figure 2: Transverse histologic sections of a normal ductus (left) and a PDA (right) (Buchanan and Patterson, 2003)



Transverse histologic section of a normally constricted ductus (*D*) in a 3-day-old mixed-breed dog. The ductus muscle is circumferentially uniform. The aorta (*A*) and pulmonary artery (*P*) have thicker elastic fibers.



Transverse histologic section of a PDA (*D*) and adjacent aorta (*A*) and pulmonary artery (*P*) in an 11-day-old dog with a grade 5 PDA. The ductus muscle (*DM*) is asymmetrically constricted. The portion adjacent to the aorta is not constricted and has a thicker elastic segment.

4.2. Physiological closure at molecular level

Brown Norway rats have been particularly studied because of their high prevalence for PDA (86%) (Bökenkamp et al., 2010). Because abnormalities in the wall structure are the major cause of PDA, the attention is focused on the genes regulating the VSMCs (Buchanan and Patterson, 2003). Those muscular cells are supposed to contract and close the ductus: if a gene is mutated by the time closure happens, it could have a consequence on the contraction. A complete closure mechanism at the cellular and molecular levels has been explained by Bökenkamp et al. in 2010 and is represented in Figure 3. It will serve as a basis to understand the impact of the different mutations on the mechanism. This mechanism has been mainly understood thanks to knockout mice experiments. Those mice who were subjected to a deletion of a DA closure regulating gene showed a PDA or at least a delay in the closure.

Figure 3: Molecular mechanism of physiological closure of the DA (Bökenkamp et al., 2010)

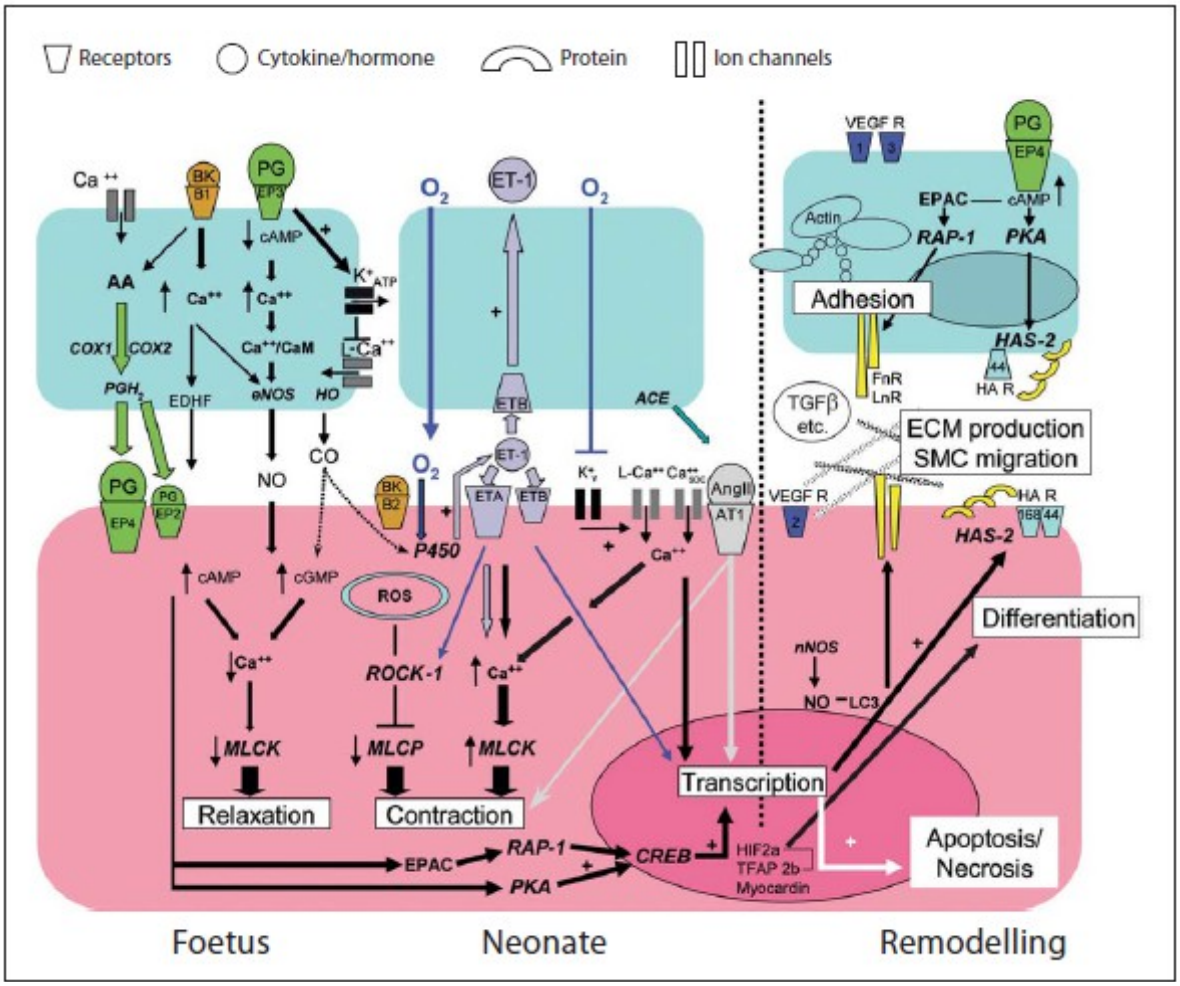


Diagram of the experimental data on intracellular and intercellular signaling related to ductus closure and remodeling that is presented in this review. ECs are depicted in light blue. VSMCs are indicated by the large pink rectangle. For the sake of clarity, not all downstream signaling steps are included. On the left side, the dominant signaling pathways in the fetus are shown. The middle section illustrates the changes related to the increase of oxygen saturation at birth. The section to the right of the vertical dotted line focuses on anatomical remodeling. Remodeling proceeds through a sequence of events including the differentiation of VSMCs and ECs, extracellular matrix production, SMC migration, and finally apoptosis and necrosis. *Abbreviations:* AA = Arachidonic acid; ACE = angiotensin-converting enzyme; Ang II = angiotensin II with AT1 receptor; BK = bradykinin with receptors B1 and B2; Ca^{++} = calcium ion and channels: Ca^{++}_{soc} = store-operated; L-Ca^{++} = voltage-dependent; CaM = calmodulin; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; CO = carbon monoxide; COX = cycloxygenase isoforms 1 and 2; CREB = cAMP response element-binding protein; ECM = extracellular matrix; EDHF = endothelium hyperpolarizing factor; EPAC = exchange proteins activated by cAMP; ET-1 = endothelin-1 with ET-A and ET-B receptors; HAS-2 = hyaluronan synthase-2; FnR = fibronectin receptor; HA hyaluronic acid receptors; CD44 and CD168 = receptors for hyaluronic acid-mediated motility; HIF-2a = hypoxia-inducible factor-2α; HO = hemoxygenase; K^+ = potassium ion and channels: K_{ATP} = ATP-sensitive channel; K_v = voltage-gated channel; LC3 = microtubule-associated protein; LnR = laminin receptor; MLCK = myosin light-chain kinase; MLCP = myosin light chain phosphatase; NO = nitric oxide; NOS = nitric oxide synthase isoforms (endothelial) eNOS and (neuronal) nNOS; PGH_2 = prostaglandin H_2; PG = prostaglandins, predominantly PGE_2 acting via prostaglandin receptors (EP 2, 3, 4); PKA = protein kinase A; RAP1 = small RAS-like GTPase acting downstream of EPAC; ROCK-1 = rho-associated, coiled-coil-containing protein kinase 1; ROS = reactive oxygen species; TFAP2B = transcription-factor-activating protein-2β; VEGF = vascular endothelial growth factor.

The ductus is maintained open during foetal life. It involves the pairing of bradykinin and prostaglandin on their respective receptor B1 and EP3 in the endothelial cells membrane. It leads to cascade events in the endothelial cells releasing prostaglandin H2, nitric oxide and carbon monoxide. All three of them enter in the VSMCs, prostaglandin by EP4 and EP2 receptor. EP4 activation requires cyclocygenase-1/2 expression. The cascade reaction eventually decreases the amount of Ca^{2+} and myosin light chain kinase in the VSMCs. The result is a loosening of the vascular wall (Bökenkamp et al., 2010).

At birth, the ductal closure begins with a physiological mechanism. When dioxygen crosses the endothelial cells, endothelin-1 and angiotansin II are able to fix themselves to their respective receptors ETA/ETB and AngII in the VSMC's membrane. In the cascade events leading to closure, bradykinine on B2 receptor as well as cytochrome P450 in the VSMCs are involved. Unlike the foetal cascade, this one catalyses myosin light chain kinase over phosphatase through a rho-kinase activation and a rise of Ca^{2+}. Calcium is partly rising due to an inhibition of the potassium voltage sensitive channel induced by dioxygen, which creates a depolarisation allowing the passageway of calcium throw their channel. The result is a contraction of the muscular cells and a closure of the ductus (Bökenkamp et al., 2010).

The role of prostaglandin is also essential in the closure (not described in Figure 2). Prostaglandin dehydrogenase and the loss of production by the placenta cause a drop prostaglandin E2 in blood to avoid the previous closure cascade. Prostaglandin I2 synthase has been highlighted by immunohistochemistry in endothelium of aorta and pulmonary artery as a key to maintain them widely open during foetal life. In order to close, the DA needs this expression preferentially localised in VSMCs. However, in case of PDA, the prostaglandin I2 synthase expression is mainly located in endothelium (Bökenkamp et al., 2010).

A remodelling is then established involving prostaglandin on EP4 again, vascular endothelial growth factor on their receptors VEGFR1/2/3 in the membranes of both endothelial cells and VSMCs, and TGFβ (Transforming Growth Factor beta). Three factors stimulate the following remodelling, which are HIF-2α (Hypoxia Inductible Factor 2 alpha), TFAP-2β (Transcription Factor Activating Protein 2 beta from the neural crest cells) and myocardin. They lead to an adhesion between endothelial cells, an extracellular matrix production and a differentiation and migration of the VSMCs. Furthermore, the intimal cushion formation needs EPAC (Exchange Protein Activated by cAMP) and protein kinase A pathway to produce hyaluronic

acid. All this events contribute to the physiological DA closure immediately after birth (Bökenkamp et al., 2010).

Over time, an anatomic closure happens within the first 48 hours to 1 month following the birth (Bökenkamp et al., 2010). The structure left behind is the *ligamentum arteriosum* (Broaddus and Tillson, 2010).

4.3. Inheritance mode through concurrent diseases

Many components are part of the balance between relaxation and contraction, and any mutation on the gene interfering with this balance could disrupt the DA closure (Bökenkamp et al., 2010). Multiple genes interact in this situation which is the reason why PDA is so called a polygenic disease. It cannot be explained by a single gene mutation with a Mendelian mode of inheritance (Parker et al., 2006). The fact there are multiple types of DA, varying by their shape, their length and their width is also in favour of polygenetic disease (Bökenkamp et al., 2010). Although, it has been observed a proportionality effect between the quantity of defect genome or the severity of PDA in affected parents and the severity of the PDA in the new born, which demonstrate PDA is a polygenic threshold trait or quasi continuous trait (Broaddus and Tillson., 2010).

The facts that PDA occurs in animals that cannot interbreed means, according to Bökenkamp et al. in 2010, it is related to a part of DNA that is common to all mammals. A complete dog genome sequence has been released but the research is for now focused on human PDA heredity (Parker et al., 2006) in which it has been found that 8-11% of humans with PDA have a chromosomal abnormality (Bökenkamp et al., 2010).

The OMIA website has not be able to highlight a mendelian trait for PDA despite the consideration as a genetic disorder. The website recorded three pathologies as a lead in humans in which PDA is involved. They are Char syndrome, Fontaine Progeroid syndrome and Intestinal Pseudoobstruction with natal teeth syndrome (*OMIA - Online Mendelian Inheritance in Animals*). Other human syndromes including PDA as one of the defects in which the heredity was more or less understood have been screened in the literature and recorded in Table III below.

Table III : Syndromes involving PDA in humans

Syndromes	Species	Genes	Location
Cantu (Lewis et al., 2018 ; Pierpont et al., 2018)	Human	ABCC9 KCNJE	12p12.1
Carpenter (Pierpont et al., 2018)	Human	RAB23	6p11.2
Char (*OMIA - Online Mendelian Inheritance in Animals*) (Pierpont et al., 2018)	Dog, cat, horse, cattle, sheep	TFAP2β	6p12.3
Charge (Pierpont et al., 2018)	Human	CHD7	8q12
Coffin-Siris (Pierpont et al., 2018)	Human	ARID1B SMARCB1 ARID1A SMARCB1 SMARCA4 SMARCE1	6q25 22q11 1p36.1 22q11.23 19p13.2 17q21.2
Cornelia deLange (Pierpont et al., 2018)	Human	NIPBL SMC1L1 SMC3	5p13 Xp11.22 10q25
DiGeorge (Lewis et al., 2018)	Human	TBX1	
Down (Pierpont et al., 2018)	Human		
Fontain progeroid (*OMIA - Online Mendelian Inheritance in Animals*)	Dog, cat, horse, cattle, sheep	SLC25A24	1p13.3
Goldenhar (Pierpont et al., 2018)	Human		
Holt–Oram (Lewis et al., 2018)	Human	TBX5	
Jacobsen (Pierpon et al., 2018)	Human, mice	Ets1	11q terminal
Loeys–Dietz (Lewis et al., 2018)	Human	TGFBR1/2	
Mowat–Wilson (Lewis et al., 2018 ; Pierpont et al., 2018)	Human	SMADPIP1 ZEB2	 2q22.3
Nance-Horan (Pierpont et al., 2018)	Human	NHS	Xp22.13
Noonan (Pierpont et al., 2018)	Human	PTPN11 SOS1 RAF1 KRAS NRAS	12q24.13 2p22.1 3p25.2 12p12.1 1p13.2

		RIT1 SHOC2 SOS2 BRAF	1q22 10q25.2 14q21.3 7q34
PDA (Overwater et al., 2018)	Human	ACTA2	
Periventricular heterotopia (Lewis et al., 2018)	Human	FLNA	
Simpson-Golabi-Behmel (Pierpont et al., 2018)	Human	GPC3	Xq26.2
Smith-Lemli-Opitz (Pierpont et al., 2018)	Human	DHCR7	11q12-13
Sotos (Pierpont et al., 2018)	Human	NSD1	5q35.3
Rubinstein–Taybi (Lewis et al., 2018 ; Pierpont et al., 2018)	Human	CREBBP CBP EP300	 16p13.3 22q13.2
Vacterl (Pierpont et al., 2018)	Human		
Townes-Brocks (Pierpont et al., 2018)	Human	SALL1	16p12.1

Each of those syndromes are accompanied by other congenital heart disease. Only Char and Fontain progeroid syndromes have respectively one and zero concurrent heart disorder. They are thus more relevant to find a more specific gene related to PDA. The transmission is autosomal and most of the time dominant (*OMIA - Online Mendelian Inheritance in Animals* ; Pierpont et al., 2018).

Other genes associated with PDA in humans are MYH11 (smooth muscle), TRFA1 (Transcriptional Factor Protein) and AGTR1 (Angiotensin II Type 1 Receptor). TFAP2β (Transcription Factor Activating Protein 2β) seems to be frequently involved in PDA as well, with single nucleotide polymorphism or heterozygous missense mutation in the DNA basic or transactivation domain (Lewis et al., 2018 ; *OMIA - Online Mendelian Inheritance in Animals*).

5. Discussion

Many studies report PDA as the first cardiac malformation, although Oliveira et al. in 2011 claim it is the third in the United States and the fourth in Europe. The incidence could have been

overestimated when dogs are referred for surgery to only a few centers (Oliveira et al., 2011). On the contrary, the impact may be higher because of a lack of report from breeders associations and because necropsy is not always performed due to the short life expectancy (den Toom et al., 2016).

Breed recorder results differ from one study to an other. P value and odds ratio not always being calculated, results might not always be significant, for instance in Table II, where statistical analysis from studies have not been taken into account, due to the lack of such analysis. It is still not sure if purebred are more affected and if it the case, which breed is the more affected by PDA, so the miniature Poodle and Pomeranian might not be as predisposed as we may have thought. Furthermore, Oliveira et al. in 2011, the most thorough article found interpreting the number of dogs per breeds, has shown PDA does not significantly affects Poodles, Pomeranians, and Yorkshire Terriers.

The inbreeding coefficient was calculated for Stabyhouns since 1942, whereas calculations for other breeds were only made between 1970-1990, sometimes dogs just being considered as non-related to an affected dog. Inbreeding is a major issue to which each breed is confronted. Among the most influential ancestors in this same breed, only one contributed more in the PDA cases compared to the reference population (den Toom et al., 2016). If the common ancestor could be identified, breeding with descendants of said ancestor could be avoided in order to prevent PDA in offspring. Furthermore, homozygosity is increased in purebred dogs so they are more likely to develop a recessive disorder which stays silent in heterozygous (Bellumori et al., 2013). PDA seems to escape this rule since most mutations for this specific disorder are dominant.

Involved genes belong to a part of DNA common to all mammals, as Parker et al. in 2006 stated. Moreover, PDA has been identified as a polygenetic disorder, meaning several genes are involved. Causal mutation events could occur independently from each other and have the same effect, without the need of an ancestral mutation.

The research of inheritance for PDA can either focus on specific genes such as prostaglandin pathway (Bökenkamp et al., 2010) or be general with GWA (Genome Wide Association) studying most known genes. The first type being specific, it would not cover for what researchers do not suspect, however it will prove economically more reasonable. In contrast, the second one can find involved genes that were not suspected, provided that the disease is not rare nor family-specific (Hajj and Dagle, 2012).

PDA being recognised as an hereditary disorder, the only way to prevent it is to exclude dogs who were born with PDA from breeding, as well as their parents. *(Patent Ductus Arteriosus (PDA) | University of Prince Edward Island)*

Thankfully, more genetic tools are developed and their increased use will have the effect to reduce costs, allowing inheritance disorder research to significantly increase in coming years (Parker et al., 2006).

6. Conclusion

Predisposed dogs for PDA lead to a genetic inheritance. The gender predisposition is ascertained, even though the reason is unclear, and has been quantified in this research, females representing 71.7% of dogs with PDA. Regarding the breed predisposition, purebred represent 89.4% of the affected dogs. Pomeranian, German Shepherd, Miniature Poodle, Bichon Frise and Chihuahua seem to be the most affected breeds but their proportion still differs depending on the reference. Each of this breed represent approximately 8 to 21% of the affected dog population. PDA has been shown as a polygenetic disorder but canine research in that matter is not exhaustive yet. It was more studied in humans where PDA appears in an important number of syndromes. A variable number of genes could be involved because plenty of them are part of the balance between ductal contraction and relaxation. TF2P2β has drawn attention for the disorder but further research is required to be definite, especially since several genes are suspected to interact. The inheritance is marked by an inbreeding coefficient higher in purebred dogs. Dogs' kennels should be very careful towards inbreeding and breeders' selection in order to avoid PDA transmission. Unfortunately, extra care dos not prevent homozygosity rising over selections, responsible for a higher risk to develop an inherited disorder.

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