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The Cardiopharyngeal Field in the Light of Evolutionary Medicine- Implications for Human Syndromes

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Review Article

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Abstract

Human syndromes are often complex and not easily explained by a single gene mutation. Syndromes have a mix of symptoms that result from a failure in complex developmental networks. An in-depth analysis of the development of the head and heart tissues has recently shown that the musculature, which constitute these distinct systems arise from a common pool of mesoderm progenitor cells within the cardiopharyngeal field (CPF). This CPF was shown to be present early in the evolutionary development of vertebrate embryos. Furthermore, analysis of the development of tunicates, chicken and mice lead to a better understanding of the evolution and development of head and heart muscles. This in turn has the potential to increase our understanding of syndromes in which mainly cranial and cardiac structures (in particular muscles) are involved. The application of the basic science of evolutionary biology to improve our understanding of health and disease is the basis of evolutionary medicine. This approach has already proven to be helpful in understanding the evolution of various medical phenomena, as for example the evolution of autoimmune diseases. At this moment, DiGeorge Syndrome is the only condition under investigation regarding the contributions of the CPF. However, with increased knowledge it should be possible to identify other human syndromes that relate to defects in this complex developmental network. Here, we review the current knowledge regarding the evolution of the cardiopharyngeal field and show how this knowledge contributes to the understanding of cardiopharyngeal syndromes in humans.

Keywords: Cardiopharyngeal field; Myocardium; Pharyngeal mesoderm; First heart field; Second heart field; Branchiomeric musculature

Introduction

Most human syndromes include a multitude of abnormalities, which are not easily explained by a single gene mutation. A syndrome is defined as "a group of signs and symptoms that occur together and characterize a particular abnormality" [1]. An observable mix of symptoms results usually from a failure in complex developmental networks. To understand the occurrence of abnormalities in human development the field of evolutionary medicine can make important contributions.

Evolutionary Medicine

Evolutionary Medicine is an interdisciplinary field that combines knowledge gained from evolutionary biology, developmental biology, medicine, public health and other health professions [2]. The knowledge of evolution of developmental networks, anatomical structures, and physiology, among others, improves the understanding of research and practice in medicine and epidemiology [3]. There are currently several examples on how evolutionary medicine has been proven to be helpful in understanding the evolution of antibiotic resistance [4], cancer [5,6], autoimmune diseases [7], and other health related issues [for more examples see: 2,3,8]. In this review, we highlight the research on the cardiopharyngeal field and how the knowledge of the evolution and development of this field might contribute to our understanding on why many human syndromes often include craniofacial and cardiac anomalies.

Cardiopharyngeal Field

Muscles develop from mesodermal cells with a myogenic fate, which is determined early in embryonic development during mesodermal differentiation. Different mesodermal population give rise to different muscle groups dependent on signals from surrounding tissues and intrinsic activation of specific gene cascades. The myogenesis of head muscles differs fundamentally from trunk muscles [e.g., 9,10-15]. Based on clonal studies in mice, several mesodermal populations were identified that give rise to specific muscle groups of the head, neck, and heart, which will be the focus of this review (Figure 1) [16-18].

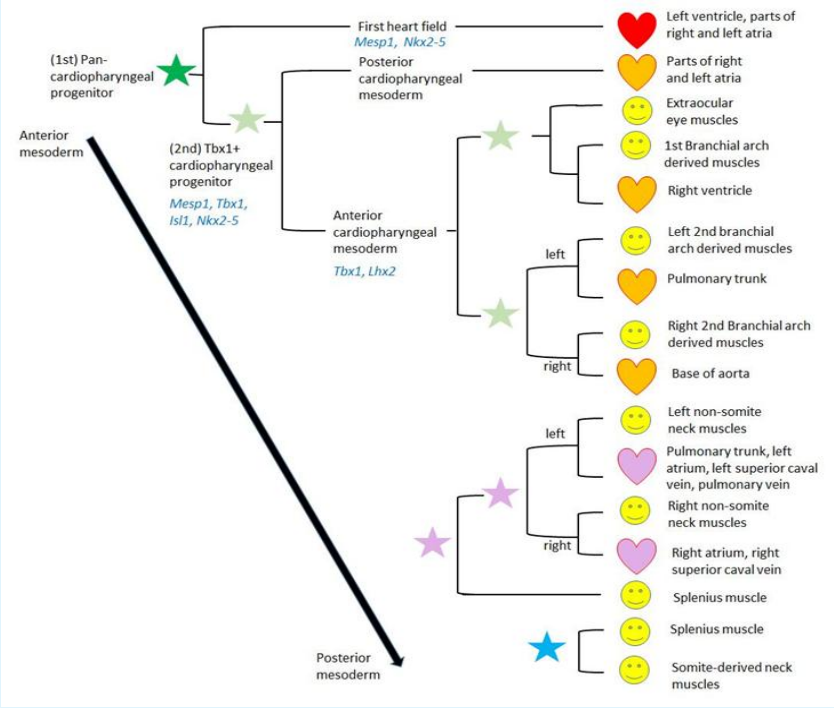

Figure 1: Proposed cell lineage tree in mice based on Lescroart et al. [16,18] and Diogo et al. [17].
Heads relate to cephalic (branchiomeric + somite derived head muscles) and hearts relate to myocardium derived from first heart field (red) and pharyngeal mesoderm (orange for 1st and 2nd pharyngeal arch mesoderm, purple more posterior pharyngeal arch mesoderm). Stars indicate common mesodermal progenitor cells. Dark green star is the pan-cardiopharyngeal progenitor of the cardiopharyngeal field, which gives rise to first heart field and pharyngeal mesoderm (light green star; Diogo et al. [17]). The latter includes the second heart field derived myocardium (orange hearts) and the branchiomeric mesoderm, which gives rise to muscles of the 1st and 2nd branchial arch (muscles of mastication, muscles of facial expression). Other mesodermal lineages also contribute to both cephalic neck and heart musculature, which correlate to posterior pharyngeal arch mesoderm (purple, probably 3rd-6th pharyngeal arch) and somite-derived mesodermal linages (blue star). The correlation of the latter two population to the cardiopharyngeal field has still to be elucidated. However, it is clear that they arise more posterior than the cardiopharyngeal mesodermal progenitors. Genes indicated in blue are essential markers for the specific mesodermal populations, however, the number of genes involved in CPF differentiation is by far great than shown here.

During the past several years it has become clear that the head and heart muscle development underlie complex processes, which are more closely linked to each other than previously thought [e.g., 15,16,18,19,20-25]. Those insights were summarized and led to the concept of the cardiopharyngeal field (CPF) [17]. The CPF is an area that contains the anterior lateral mesoderm of the first heart field and the adjacent pharyngeal mesoderm that differentiates into the second heart field -derived regions of the heart and branchiomeric muscles [Figure 1; 17,26]. The vertebrate heart starts its development as a tube formed by a population of precursor cells called first heart field (FHF). The adjacent second heart field (SHF), located in the pharyngeal mesoderm, gives rise to cells that are gradually added to the forming heart [27]. Portions of the heart tube originating from the FHF progenitor cells later form the left ventricle and parts of the atria. The cells from the SHF differentiate to heart muscle tissue (myocardium) of the right ventricle, the main portion of the atria and the outflow tract [19,20,28]. The anterior populations of progenitor cells of the SHF contribute to the arterial pole of the heart and the posterior populations to the venous pole [29].

The pharyngeal mesoderm gives rise to either skeletal muscles, i.e. branchiomeric muscles, or cardiac muscle (SHF-derived regions) dependent on the signals upon adjacent tissues such as neural crest cells (NCCs), pharyngeal endoderm or surface ectoderm [e.g., 21,25,30-32]. In turn, the cranial mesoderm is influencing NCC migration [33]. NCCs are crucial for the proper regulation of the CPF development: they control the arrangement of SHF-derived cells to the arterial pole of the heart, outline branchiomeric muscle patterns through neural crest derived mesenchyme, and give rise to the associated tendons and fascia [e.g., 31,34-36]. There are many syndromes that show a combination of cardiac and craniofacial malformations that can be related to NCCs [37,38].

The cardiac and branchiomeric muscle development from the common pool of mesodermal progenitor cells is coordinated by regulatory factors [reviewed by 17]. Within the CPF is an overlapping expression of genes that specify head muscles [e.g. *Tbx1*, *MyoR* (*Msc*), *Pitx2* and *Tcf21* (*Capsulin*)] and cardiogenic regulatory factors [e.g., *Nkx2-5*, *Isl1* (*Islet1*)] (Figure 1) [21,25,39,40]. *Tbx1* plays a crucial role in extending the heart's arterial pole by stimulating proliferation and delaying differentiation of SHF cells [41 and citations within]. It is also important for the activation of branchiomeric myogenesis and may directly regulate MyoD [42,43]. Furthermore, *Tbx1* acts upstream of *Lhx2*, a gene encoding a LIM- homeodomain protein, within a complex regulatory network that specifies cardiopharyngeal progenitors. Another gene encoding a LIM-homeodomain protein is *Isl1*, which is expressed in the mesoderm of pharyngeal arches and SHF. *Ils1* seems to delay the differentiation of branchiomeric muscles; however, progenitor cells that express *Isl1* contribute to heart and branchiomeric muscles, but not to extrinsic eye muscles or hypobranchial muscles [25,40]. This shows the important role of *Isl1* as marker for a discrete subset of CPF cells that are distinct progenitors of cardiovascular and skeletal muscle [40]. Nkx2-5 is a cardiac transcription factor that regulates the proliferation in the SHF and it modulates, together with *Isl1*, SHF progenitor-specific gene expression [44,45].

Clonal analyses in mice showed that SHF-derived regions of the heart are developmentally more closely related to branchiomeric muscles than to the FHF-derived regions of the heart [17,18,26,46]. This is supported by the observation that cardiac lineages contributing to the FHF and SHF diverge before the expression of *Mesp1* during early gastrulation [47,48]. Based on those and other studies, the head muscles in humans can now be described as at least seven groups (Figure 2) [49]: 1. mandibular arch muscles and cells related to the right ventricle; 2. left hyoid arch muscles and cells related to myocardium at the base of the pulmonary trunk; 3. right hyoid arch muscles and cells related to myocardium at the base of the aorta; 4. left muscles of the 3rd to 6th pharyngeal arch, including laryngeal and pharyngeal muscles, the neck muscles trapezius and sternocleidomastoideus, and cells related to the base of the pulmonary trunk and part of left atrium; 5. right muscles of the 3rd to 6th pharyngeal arch, including laryngeal and pharyngeal muscles, the neck muscles trapezius and sternocleidomastoideus, and cells related to the superior vena cava and part of right atrium; 6. extraocular muscles; and 7. Hypobranchial muscles, including tongue and infrahyoid muscles that derive from somites and migrate into the head and neck [16-18,50-52].

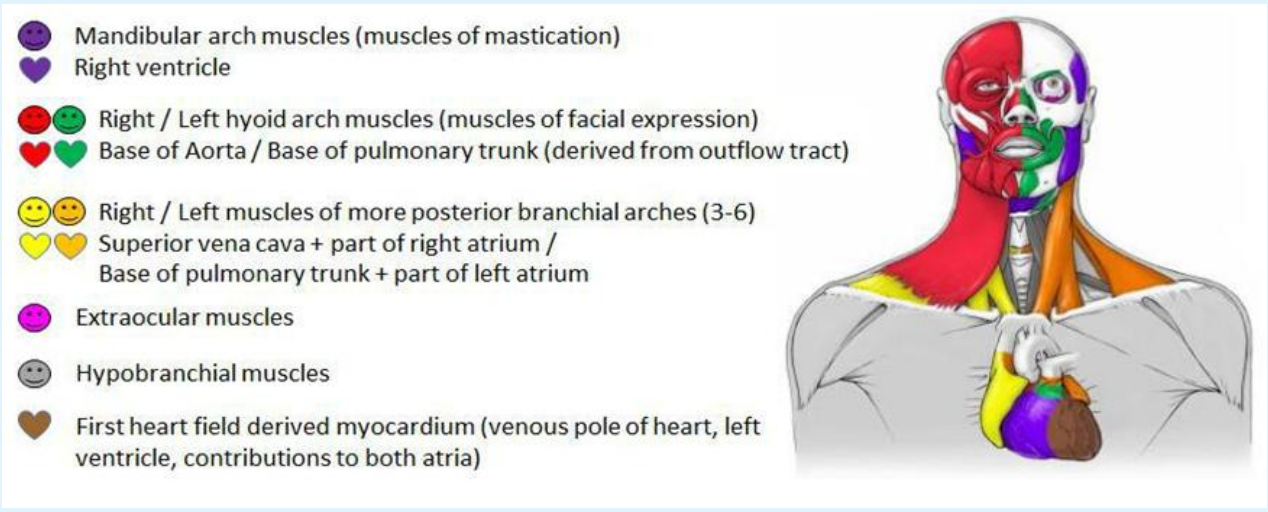

Figure 2: Developmental correlation of specific head muscle groups and specific myocardial regions. Same colors indicate a closer developmental relationship based on clonal descendants from a common progenitor. For example, purple muscles of mastication (mandibular arch or first pharyngeal arch) are closer correlated to the myocardium of the right ventricle than to other head muscles. The muscles of facial expression on the left side of the face are partially removed (green). Modified and with permission from Diogo, et al. [49].

The FHF and SHF both have a common mesodermal progenitor [46], but the evolutionary origin of this common field was just recently discovered [17]. The closer correlation of cell lineages that give rise to branchiomeric muscles and myocardium were shown to also exist in the urochordate ascidian *Ciona* [53], and in the amniotes chicken and mice [20,26,39,40,48]. Urochordates are the closest sister-group of vertebrates [54]. Studies have shown that the gene regulatory network underlying the differentiation of pharyngeal muscles and myocardium in ascidians is similar to the one in vertebrates. The ascidian heart derives in early embryogenesis from two *Mesp* expressing cells (B7.5 cells), which give rise to four embryonic trunk ventral cells (TVCs) [55]. Those TVCs express genes homologous to the vertebrate genes *Nkx2-5*, *Hand* [55,56], *Gata4, 5* and *6* [57] and migrate towards the pharyngeal endoderm [58-60]. This is followed by an asymmetrical division that produces heart precursors and secondary ventral cells. The latter cells divide again and give rise to second heart precursors and atrial siphon muscles; the latter correspond to branchiomeric muscles in vertebrates [23,53,61]. Thus, TVCs are cardiopharyngeal progenitors that produce cardiac and pharyngeal muscles, following a clonal pattern reminiscent of that seen in mice [61,62].

Thus, the CPF likely evolved in the last common ancestor of Olfactores (Olfactores = Vertebrata + Urochordata) [17]; which emerged ca. 514 million years ago [63], but some of the mechanisms were likely present even earlier [17]. The knowledge regarding the evolution of the CPF and the gene regulatory network underlying the muscular differentiation had profound implications for the reconstruction of the origin and early evolution of the vertebrate muscular system [64]. Furthermore, understanding the molecular basis of craniofacial and heart development is an important research area, because malformation of both systems are among the most frequent congenital defects in humans [65].

Cardiopharyngeal Syndromes

Many human syndromes include both craniofacial and cardiac abnormalities. Syndromes that are likely caused by defects in the gene regulatory network underlying the mesodermal differentiation of the CPF are called cardiopharyngeal syndromes. Importantly, those syndromes will also show other malformations not related to the CPF as genes are usually not only expressed at one location during development. To our knowledge, only the DiGeorge Syndrome is currently under investigation regarding the contributions of the CPF. The DiGeorge Syndrome is a developmental defect caused by a microdeletion of chromosome 22q11.2. It is also known as velocardiofacial syndrome, CATCH22 [66], or 22q11 Deletion Syndrome (22q11DS) and has an estimated prevalence of 1 in 3,000-6,000 births, what makes it to one of the most common microdeletion syndromes [67]. The microdeletion of the chromosome 22q11.2 causes the

compromise of the *Tbx1* gene [68], which is important for the specification of the pharyngeal mesoderm [43] that gives rise to the SHF-derived myocardium and branchiomeric muscles (Figure 1). For the DiGeorge Syndrome over 180 associated anomalies have been described [69]. Those anomalies include often cardiac anomalies, palatal anomalies, developmental delay, and immune deficiency; not as common are feeding problems, renal anomalies, and psychiatric disorders, among others. However, none of these features are obligatory or present in all patients [69]. Due to the diversity of symptoms, the clinical diagnosis is usually confirmed by a routine test available in most cytogenetic laboratories [70].

To find other potential cardiopharyngeal syndromes, we performed an extensive search of syndromes that show a combination of cranial and cardiac muscle defects and analyzed if they are likely caused by developmental defects related to the differentiation from the CPF. We began our search by using a keyword search in Google Scholar. Initially we searched for the following keywords and combination of them: human; genetics; head muscles; heart muscle; heart; branchiomeric muscles; diseases; anomalies; syndrome; variations; face malformation; cardiovascular defects; craniofacial anomalies; face defect; heart defect; craniofacial muscle patterning; facial muscle deformation; craniofacial defect. One typical search combination was for example: "head + heart + malformation + human" or "head + heart + syndrome".

This search revealed thousands of results, and we identified many potentially interesting syndromes. From this list, we searched for specific syndromes and decided to take a closer look at syndromes with the most google scholar hits (Table 1). We refined the search by using the syndromes' common name(s) and restricted the search to the past ten years. In those ten years, we were looking for review article summarizing the knowledge so far and searched then for articles that are newer than the latest review. Finally, we restricted the search to the time since the publication of the CPF in 2015 [17] to determine of any syndromes were already under investigation regarding disturbances of the CPF differentiation.

Syndrome	Google scholar	since 2007	since 2015
Williams Syndrome	2,800,000	1,260,000	38,400
Down Syndrome	2,850,000	1,340,000	74,300
CHARGE Syndrome	1,750,000	416,000	20,100
Costello Syndrome	86,100	23,800	13,400
Noonan Syndrome	52,800	17,800	9,030
DiGeorge Syndrome	30,000	16,000	4,360
22q11 Syndrome	34,700	16,800	6,700
DiGeorge + 22q11.2 Syndrome	8,880	6,170	1,490
DiGeorge + cardiopharyngeal	46	44	30
Fryns Syndrome	23,700	11,800	2,300
Leopard Syndrome	19,000	12,400	2,720
Ocular coloboma Syndrome	17,500	8,950	2,250
Pierre-Robin Syndrome	15,900	8,320	2,070
Alagille Syndrome	15,400	7,490	1,990
Wolf Hirschhorn Syndrome	9,120	5,750	1,330
Sotos Syndrome	8,330	4,550	1,150
Holt-Oram Syndrome	8,310	4,590	978
Microsomia Syndrome	8,260	4,490	1,110
Ellis-van Creveld Syndrome	6,060	3,380	680
2q13 Syndrome	5,860	3,800	828

16q12 Syndrome	4,250	3,020	644
Axenfeld-Rieger Syndrome	3,260	2,210	527
Andersen-Tawil Syndrome	1,820	1,540	394
1q36 Syndrome	402	290	66
Ritscher-Schinzel Syndrome	371	266	62
Frank-Ter Haar Syndrome	222	207	45

Table 1: Human syndromes with craniofacial and cardiac abnormalities, which might be caused by defects in developmental processes related to the cardiopharyngeal field (CPF) mesoderm differentiation. DiGeorge syndrome is already under investigation regarding the connection of cranial and cardiac development (double underlined). The google search was latest updated July 16th, 2017. After searching for the syndromes with the most hits, we restricted our search for publications in the past 10 years to find most recent review articles and finally restricted the search to the time since the publication of the CPF in 2015 [17].

Most of the syndromes identified in Table 1 could not be related to the interruption of developmental mechanisms linked to the development cardiopharyngeal mesoderm. Furthermore, none of the investigated syndromes, including DiGeorge Syndrome, could be shown to show a left-right correlation of cranial muscle malformation and specific heart malformation as would be expected by the developmental disturbance of the CPF mesoderm. A review of all syndromes listed in Table 1 would by far exceed the purpose of this review; however, we highlight in Table 2 a few syndromes, additionally to the above mentioned DiGeorge Syndrome, that might be of interest for future research regarding cardiopharyngeal syndromes.

Syndrome	Pathology	Mutation and relation to CPF development
Axenfeld – Rieger Syndrome	Dysplastic arcade mitral valve; mildly hypoplastic left ventricular outflow tract and aortic arch; ophthalmologic anterior segment abnormalities, extraocular anomalies incl. dental anomalies [71]	autosomal dominant; involvement of PITX2, FOXC1 (=Mf1) [71-73]; Pitx2 homeobox gene regulates development of eye muscles, branchiomeric muscles, tongue and laryngeal muscles, and outflow tract [74, 75]; FoxC1 plays an important role for the outflow tract and eye muscle development [76,77]
Holt-Oram syndrome	upper limb defects ranging from phocomelia to minor thumb anomalies; cardiac defects in 50–95% of cases, most often an ostium secundum type atrial septal defect and conduction anomalies; [78]	Mutation in TBX5 [78, 79], Tbx5 is essential in cardiomyocyte differentiation in concert with Nkx2-5 [79]
CHARGE Syndrome	complex mix of congenital anomalies, including craniofacial structures, tracheal development, peripheral nervous system and some organ systems, including the heart [80-83]	autosomal dominant; heterozygous loss of function mutation in CHD7 (see citations on the left); CHD7 regulates genes, which are important in neural crest guidance and is important in the anterior mesoderm during cardiovascular development [84,85]
Ocular coloboma Syndrome	cardiac and eye abnormalities including presence of ocular colobomata [86]	Oculo-auriculo-vertebral syndrome (OAVS) has similar clinical presentations as CHARGE Syndrome led to the assumption that here CHD7 might be also [87]; see above for CHD7

Table 2: Human syndromes that are potentially cardiopharyngeal syndromes based on the current knowledge of their gene mutations.

Concluding remarks

Numerous genes are involved in the proper development of the head and the heart. The signaling from surrounding tissue, in particular the neural crest, has also a huge impact on the differentiation of cardiopharyngeal mesoderm. Here, we presented only a fraction of genes relevant for the differentiation of musculature derived from the CPF. Most of the knowledge we have about the gene regulatory networks during development result from studies in developmental biology, genetics, and evolutionary biology. The combination of those fields with medicine, public health, and other health professions leads to evolutionary medicine and to a better understanding of complex human syndromes.

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