Developmental Biology 444 (2018) S110–S143

Contents lists available at ScienceDirect

Developmental Biology

journal homepage: www.elsevier.com/locate/developmentalbiology

Neurocristopathies: New insights 150 years after the neural crest discovery

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ARTICLE INFO

Keywords:
Neural crest
Embryonic development
Cell migration
Neurogenesis
Peripheral nervous system
Schwann cells, neurocristopathies, diseases, syndromes

ABSTRACT

The neural crest (NC) is a transient, multipotent and migratory cell population that generates an astonishingly diverse array of cell types during vertebrate development. These cells, which originate from the ectoderm in a region lateral to the neural plate in the neural fold, give rise to neurons, glia, melanocytes, chondrocytes, smooth muscle cells, odontoblasts and neuroendocrine cells, among others. Neurocristopathies (NCP) are a class of pathologies occurring in vertebrates, especially in humans that result from the abnormal specification, migration, differentiation or death of neural crest cells during embryonic development. Various pigment, skin, thyroid and hearing disorders, craniofacial and heart abnormalities, malfunctions of the digestive tract and tumors can also be considered as neurocristopathies. In this review we revisit the current classification and propose a new way to classify NCP based on the embryonic origin of the affected tissues, on recent findings regarding the molecular mechanisms that drive NC formation, and on the increased complexity of current molecular embryology techniques.

1. Introduction

A key feature that separates vertebrates from other craniate organisms is the neural crest (NC). This cell population arises at the border between the neural and non-neural ectoderm during late gastrulation and early neurulation. After its induction, the newly formed NC cells (NCC) delaminate from their tissue of origin and migrate from the entire neuraxis of the vertebrate embryo to specific locations, where they will give rise to cells of the peripheral nervous system (PNS), melanocyte cells, cartilage and bone cells of the cranium and cells that comprise the enteric nervous system (ENS), among others (Bronner and LeDouarin, 2012). The formation of the NC is therefore a multistep process, requiring contact-mediated tissue interactions between neural ectoderm, non-neural ectoderm and the underlying mesoderm in concert with an intricate series of molecular signals. These signals include the bone morphogenetic protein (BMP), Wnts, fibroblast growth factors (FGFs) and retinoic acid (RA) (Lewis et al., 2004; Mayor and Aybar, 2001; Villanueva et al., 2002).

The combination of these signals requires a timely and spatially coordinated interplay to establish the competence to form the NC in avian, fish and amphibian embryos. Even though it has been shown that in mouse some signals are not required to form the NC, there is a clear conservation of most of the mechanisms that lead to the formation of this cell population (Barriga et al., 2015). The interaction of these signals establishes a newly formed ectodermal cell population at the neural plate border that initially drives the expression of a set of genes, the neural plate border specifiers, which are responsible for the establishment of NC identity and include the genes *pax3, pax7, zic3, msx1* and *tfap2a*, among others. Their expression is followed by more specific NC specifier genes such as *snai1/2, sox9/10* and *foxd3*. These proteins directly regulate effector genes that direct the delamination, migration and differentiation of the NC (Sauka-Spengler and Bronner-Fraser, 2008).

After being induced, NCCs undergo a process known as epithelial-to-mesenchymal transition (EMT) and migrate to different locations within the embryo to generate a wide diversity of cell derivatives (Fig. 1). In this transition, NCCs delaminate from the NT and the neuroepithelium to different regions of the embryo and undergo a transformation from epithelial-like cells to mesenchymal-like cells. This transition is promoted by an activation of BMP and a simultaneous upregulation of the Wnt pathway (Ahlstrom and Erickson, 2009).

Abbreviations: BMP, bone morphogenetic protein; DRG, dorsal root ganglia; EMT, epithelial-to-mesenchymal transition; ENS, enteric nervous system; Eph, ephrin receptor; FGF, fibroblast growth factor; Hh, Hedgehog cell signaling pathway; NC, neural crest; NCC, neural crest cells; NCP, Neurocristopathies; NCSCs, neural crest stem cells; Sem, semaphorin; Shh, Sonic hedgehog

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https://doi.org/10.1016/j.ydbio.2018.05.013
Received 29 November 2017; Received in revised form 16 May 2018; Accepted 17 May 2018
Available online 23 May 2018
0012-1606/

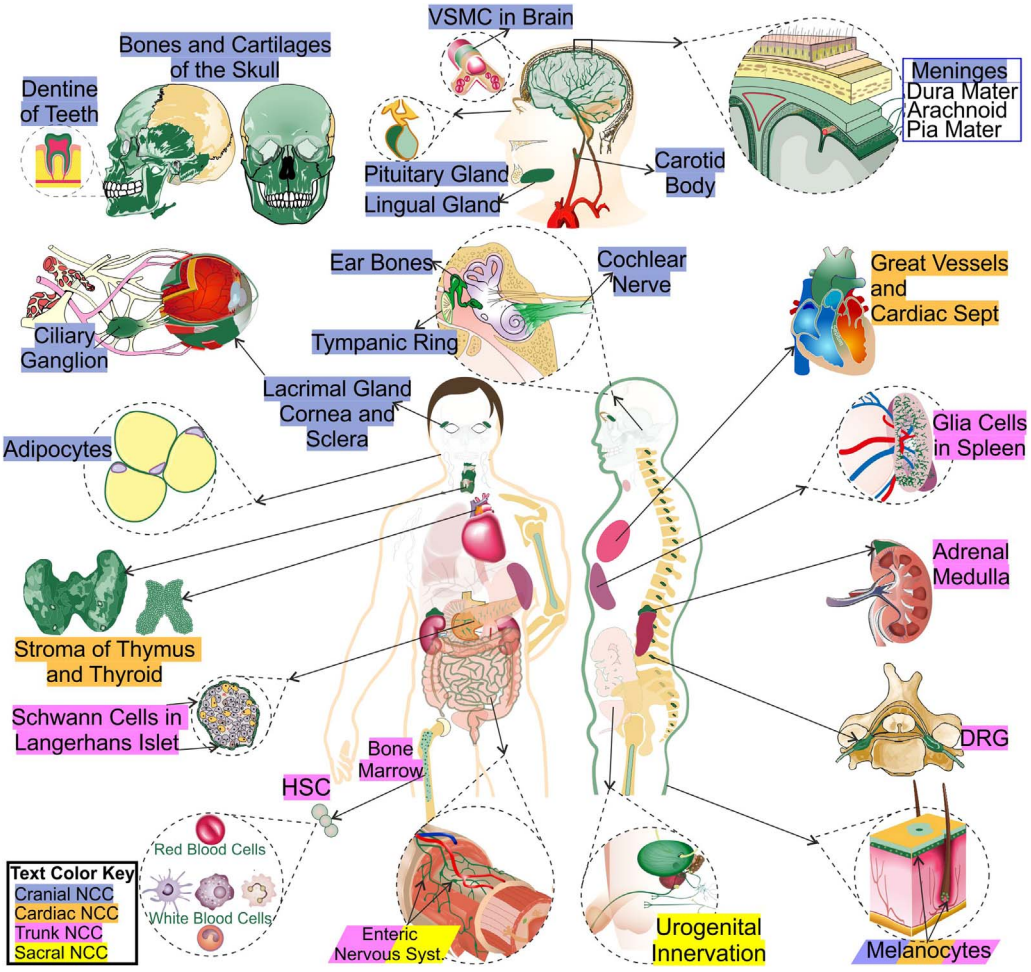

Fig. 1. Contribution of the NC in adult tissues and organs. Schematic representation showing cells and tissue that arise from the NC, represented in green. The different colors of the names stand for the NC section that contributes most to the development of each derivative.

2. Neural crest derivatives

The derivative tissues arising from the NC originate from four different segments of the anterior-posterior axis (cephalocaudal axis): cranial, cardiac, trunk and sacral NC. The **cranial** NC participates in the formation of the cartilage and bone of the head, nerve ganglia, adenohypophysis, vascular smooth muscle cells (Majesky, 2007; Wang et al., 2017), carotid body (Pearse et al., 1973), connective tissue, different eye tissues (corneal endothelium and stroma; trabecular meshwork, iris stroma, ciliary body stroma and anterior sclera (Trost et al., 2013; Williams and Bohnsack, 2015; Yoshida et al., 2006)), lacrimal gland (de la Cuadra-Blanco et al., 2003; Garg and Zhang, 2017), dental pulp (Janebodin et al., 2011; Waddington et al., 2009), pigment cells, hair follicles (Sieber-Blum et al., 2004), olfactory epithelium (Barraud et al., 2010), adipocytes (Billon et al., 2007; Sowa et al., 2014) and the cranial meninges of the brain (Decimo et al., 2012). The **cardiac** NC participates in the development of the heart (Lajiness et al., 2014; Verberne et al., 2000), the aorticopulmonary septum, the innervation of the lung (Aven and Ai, 2013; Freem et al., 2010), the enteric ganglia of the gut, the PNS, the melanocytes, the stroma of thyroid and thymus glands (Figueiredo et al., 2016; Wang et al., 2017; Zachariah and Cyster, 2010) and the cardiac ganglia. On the other hand, the **trunk** NC contributes to neurons and glia of the dorsal root ganglia (DRG) and the sympathetic ganglia, the Schwann cells that line the ventral roots (non-myelinating glia in bone marrow, (Coste et al., 2017; Isern et al., 2014; Komada et al., 2012)), Schwann cells in the Islets of Langerhans (Plank et al., 2011; Shimada et al., 2012), chromaffin cells (adrenal medulla, (Unsicker et al., 2005), pigment cells of the skin (melanocytes) and the neurons of the enteric nervous system (ENS). Finally, the **sacral** NC will generate the enteric ganglia and the sympathetic ganglia (Vega-Lopez et al., 2017), and lower urogenital tract innervation (Anderson et al., 2006; Wiese et al., 2017).

3. Neurocristopathies: Definition and suggestion for a new type of classification

An alteration in the occurrence and timing of the above cell signals or in the specific participant molecules may result in a disruption of NCC development and lead to a set of syndromes and diseases called Neurocristopathies (NCP), which comprises a broad spectrum of congenital malformations affecting an appreciable percentage of newborns (Watt and Trainor, 2014). Moreover, since NCCs migrate along the entire embryo, they are susceptible to subtle changes in the environment both during migration and upon arrival at their destination. This means that little modifications in the external cues that modulate NCC migration have a deep effect on the normal migration and differentiation of these cells, thus becoming a causative factor for the development of NCP.

Robert Bolande (1974) introduced both the concept of NCP and its designation (Bolande, 1997). Bolande divided neurocristopathies into four categories: tumors, tumor syndromes, malformations, and all other NCP. More recently a new classification was proposed that grouped NCP according to the stage of NC development that is affected during the onset of the disease. In addition, some NCP are not exclusive members of one category but there is an appreciable overlap between

the stages of development at which NCP arise (Etchevers et al., 2006; Watt and Trainor, 2014). Altogether, this method allows the classification of NCP into three main groups: NCP arising from defects in NC induction and specification (1), NC migration (2) and NC differentiation (3).

In this review we propose a new method for classifying NCP that allows the rapid and efficient organization and identification of this group of pathologies. The previous strategy for NCP classification takes into account only a subset of NCP. Thus, we decided to make a more accurate arrangement and to include a wider set of diseases into this classification based on new findings in this area. To that end, we first created a rigorous classification and identification strategy to choose all the NCP (diseases/syndromes) that had been linked to this category by previous experimental evidence. The next step was to establish the main criteria for classification of the NCP. In particular, we included many diseases that are not entirely a product of abnormal NC development. Instead, we considered some diseases that have, at least partly, an affected NC derived tissue.

As mentioned above, the previous strategy of classification was based on the developmental process that was affected during the onset of the disease. We decided to consider as the main criteria of classification the axial origin of the NC population that contributes to the derived tissue affected in a particular NCP. According to this classification, some diseases have a single axial origin, i.e., they arise from a defect in the development of only one NC population (e.g. cranial NCP, such as craniosynostosis). Additionally, some NCP arise from a defect in two or more NCC populations, which therefore makes them NCP of multi-axial origin. We consider that this new classification could provide an easier way to understand and diagnose a particular NCP. For example: it helps tracing the origin of the affected cell population in the NCP in a more direct way; it facilitates interpreting which developmental processes and genes could be causing a NCP; a proper classification method could minimize the guessing in reaching a final diagnosis; and it contributes to communicate the basic science knowledge with the medical experts. Proper diagnosis of NCP is complex, but we hope that the new classification criteria could serve as a sort of guide map.

This NCP classification is intended to help physicians understand the causal mechanism that drives the formation of a certain NCP. Moreover, we hope this new classification will help in the selection of the correct diagnostic tests as well as in the implementation of accurate medical treatments and therapies. We also think that this new approach will help identify, group, and properly name syndromes and conditions that are constantly being discovered via a single systematic and standardized classification.

In addition, in this review we will also consider several new diseases and syndromes which have not been previously included into the NCP classification. As a step further, we will try to incorporate them into the new classification method, based on recent advances in the knowledge of the underlying mechanisms that govern the onset of the disease. One of the methods we will use to include diseases into the NCP classification will be the consideration of newly found derivatives that have been recently associated with NC development. Another additional method is the consideration that NC development also depends on epigenetic signals (chemical changes to DNA and its associated proteins, histones, which can alter gene expression) that are not encoded in the genome. Specifically, the proper expression of a gene set is regulated and maintained through epigenetic mechanisms that are important for the establishment of cell populations (Bird, 2007). With this in mind, one can consider an NCP as arising not only from genetic mutations of NC-specific genes, but also from epigenetic mechanisms that modulate the transcriptional output of NC cells. In summary, the increasing volume of findings and information that have enriched the knowledge of developmental biology and NC research in recent years has enabled us to propose this novel classification as well as to expand the number of diseases in the NCP group.

In the next sections we will describe the most important NCP and propose new diseases that should be incorporated into the NCP category. We will also address the importance of model organisms in the study and understanding of NCP. The emergence of animal models for each NCP is important not only to investigate the pathogenesis of the disease, but also to identify potential therapies aimed at improving the symptoms. Finally, we will provide an overview of the potential therapies that open up a new promising avenue of research in the field of NCP diseases.

As a first approach we will classify NCP according to NC population (cranial, cardiac, trunk, or sacral) contribution during embryonic development. Drawing on recent molecular analyses from the model organism community we will later consider additional molecular facts to improve the present classification. (Fig. 2)

3.1. Neurocristopathies originated from Cranial NCC

3.1.1. 3MC syndrome

The 3MC syndrome encompasses four rare autosomal recessive disorders previously known as Carnevale, Mingarelli, Malpuech and Michels Syndromes. The main features of the 3MC syndrome are facial dysmorphism, including widely spaced eyes (hypertelorism), opening in the upper lip (cleft lip) with an opening in the roof of the mouth (cleft palate), highly-arched eyebrows, narrowing of the eye opening (blepharophimosis), droopy eyelids (blepharoptosis), abnormal fusion of bones in the skull (craniosynostosis), developmental delay and hearing loss. This phenotype is the result of complex embryological processes, including abnormal NC induction and specification. Mutations in the *COLEC11* and *MASP1/3* genes were found in patients with 3MC syndrome (Rooryck et al., 2011). Additionally, the *COLEC10* gene is expressed in craniofacial tissues during development, acts as a cell migratory chemoattractant, and is also mutated in the 3MC syndrome (Munye et al., 2017).

3.1.2. Auriculo Condylar syndrome (ACS)

Auriculo Condylar Syndrome (ACS) is a craniofacial birth disorder affecting NCC development within the first and second pharyngeal arches (Passos-Bueno et al., 2009). The term "auriculo" refers to the ear and "condylar" to the mandibular condyle, which is the upper portion of the mandible that forms part of the temporomandibular joint. The most common features of this disease are malformed outer ears, unilateral (asymmetric) or bilateral mandibular condyle hypoplasia, temporomandibular joint abnormalities, unusually small chin (micrognathia), an unusually small mouth (microstomia), full cheeks leading to a round face, and the typical auricular mEtcheversalformation with a cleft between the lobe and helix of the ear (“question mark ear”) (Clouthier et al., 2013; Kokitsu-Nakata et al., 2012).

Besides the core features, patients with ACS can also manifest a narrow mouth, hearing loss, palatal abnormalities, downward displacement or retraction of the tongue (glossoptosis), cleft palate, respiratory abnormalities and apneas (Kokitsu-Nakata et al., 2012; Masotti et al., 2007; Storm et al., 2005). Defects in these structures resemble those observed in animal mutant models in which endothelin 1 (*EDN1*) and endothelin receptor type A (*EDNRA*) signaling is disrupted (Clouthier et al., 2013). In particular, EDN1-EDNRA cell signaling plays a critical role in the specification of mandibular identity in post-migratory NCCs in different animal models (Bonano et al., 2008; Gordon et al., 2015; Sabrautzki et al., 2016). This information was recently used to identify the genetic basis for the majority of ACS cases. Both autosomal dominant and recessive inheritance of mutations in phospholipase C beta 4 (*PLCB4*) and *EDN1* have been reported along with autosomal dominant mutations in guanine nucleotide-binding protein (G protein), an inhibiting activity polypeptide 3 (*GNAI3*) (Kido et al., 2013; Leoni et al., 2016; Romanelli Tavares et al., 2015). The EDN/EDNR signaling pathway has also been linked to other NCP,

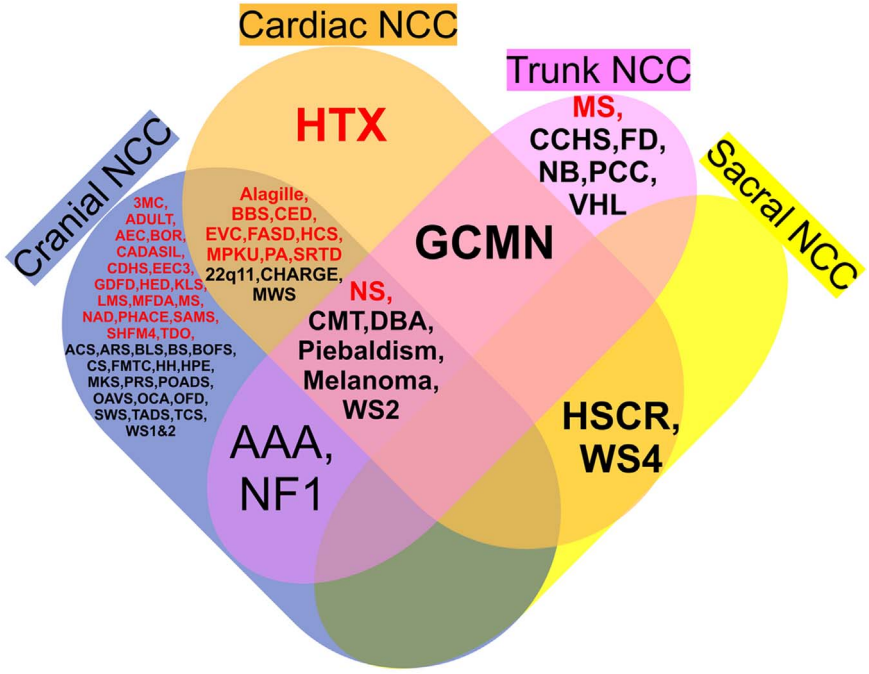

Fig. 2. Schematic representation of the contribution of each NCC population to NCP. NCP are classified based on the embryonic axial origin of the affected tissues or organs. The overlapping of the NCC derivatives affected clearly shows the multiple origins of some NCP (drawing with http://bioinformatics.psb.ugent.be). **Abbreviations of new NCP described in this article (red)**: **3MC**: 3MC Syndrome, **ADULT**: ADULT syndrome, **AEC**: AEC Syndrome, **Alagille**: Alagille Syndrome, **BBS**: Bardet-Biedl Syndrome 8, **BOR**: Branchio-Oto-Renal Syndrome, **CADASIL**; **CDHS**: Craniofacial-Deafness-Hand Syndrome, **CED**: Cranioectodermal dysplasia/Sensenbrenner syndrome, **EEC3**: EEC3 syndrome, **EVC**: Ellis-van Creveld syndrome, **FASD**: Fetal Alcohol Spectrum Disorder, **GDFD**: Growth Retardation, Developmental Delay, and Facial Dysmorphism, **HCS**: Hajdu-Cheney Syndrome, **HED**: Hypohidrotic Ectodermal Dysplasia, **HTX** Heterotaxy, **KFS**: Klippel-Feil Syndrome, **LMS**: Limb-Mammary Syndrome; **MFDA**: Mandibulofacial Dysostosis with Alopecia, **MPKU**: Maternal PKU syndrome, **MS**: Multiple sclerosis, **NAD**: Nager Acrofacial Dysostosis, **NS**: Noonan syndrome, **PA**: Peters Anomaly, **PHACE**: PHACE Syndrome, **SAMS**: SAMS disorder, **SHFM4**: Split-hand/split-foot malformation type 4, **SRTD**: Short-Rib Thoracic Dysplasia 10, **TDO**: Tricho-dento-osseous syndrome. **Abbreviations of classical NCP described in previews reviews (black)**: **22q11**: 22q11.2 Deletion Syndrome; **AAA**: Achalasia-Addisonianism-Alacrima Syndrome, **ACS**: Auriculo Condylar Syndrome, **ARS**: Axenfeld-Rieger Syndrome, **BLS**: Bamforth-Lazarus syndrome, **BOFS**: Branchio-Oculo-Facial Syndrome, **BS**: Binder Syndrome; **CCHS**: Congenital Central Hypoventilation Syndrome, **CHARGE**: CHARGE syndrome, **CMT**: Charcot-Marie-Tooth and Deafness Syndrome, **CS**: Craniosynostosis, **DBA**: Diamond Blackfan Anemia, **FD**: Familial dysautonomia, **FMTC**: Familial Medullary thyroid carcinomas, **GCMN**: Giant congenital melanocytic nevi, **HH**: Hypogonadotropic Hypogonadism, **HPE**: Holoprosencephaly, **HSCR**: Hirschsprung Disease, **Melanoma**; **MBS**: Moebius Syndrome, **MKS** Meckel-Gruber syndrome, **MWS**: Mowat Wilson Syndrome, **NB**: Neuroblastoma, **NF1**: Neurofibromatosis I, **OAVS**: Oculo-Auriculo-Vertebral Syndrome, **OCA**: Oculocutaneous Albinism, **OFD**: Orofaciodigital Syndrome, **PCC**: Pheochromocytomas, **Piebaldism**; **POADS**: Postaxial Acrofacial Dysostosis Syndrome, **PRS**: Pierre Robin sequence, **SWS**: Sturge-Weber syndrome, **TADS**: Tietz Albinism-Deafness Syndrome, **TCS**: Treacher Collins Syndrome, **VHL**: von Hippel-Lindau Syndrome, **WS**: Waardenburg Syndrome.

called Mandibulofacial Dysostosis with Alopecia (MFDA) (Section 3.1.16), Congenital Central Hypoventilation Syndrome (CCHS) (Section 3.3.1), Waardenburg Syndrome (Sections 3.1.29, 3.7.2 and 3.8.6) and Hirschsprung disease (Section 3.7.1).

3.1.3. Axenfeld-Rieger syndrome (ARS)

ARS is a rare autosomal dominant disorder. ARS includes changes in the colored part of the eye (the iris), and developmental anomalies of the anterior angle that lead to ocular hypertension. This disease is caused by an arrest in the development of NC derived tissues in the anterior structures of the eye. People with ARS often have a single central hole (pupil) that is off-center (corectopia) or extra holes in the iris that can look like multiple pupils (polycoria).

Elevated intraocular pressure and glaucoma develop in 50% of ARS patients (Lewis et al., 2017). Patients also show typical craniofacial signs such as widely spaced eyes (hypertelorism), maxillary underdevelopment or incomplete development (hypoplasia), missing teeth as a result of the failure of those teeth to develop (hypodontia), congenital absence of more than six teeth in primary, permanent or both dentitions (oligodontia) and one or more teeth that appear smaller than normal (microdontia) as well as umbilical anomalies. Mutations in the transcription factors *FOXC1*, *PITX2*, *CYP1B1*, or *PRDM5* genes have been shown to lead to ARS. Moreover, the chromosome locus 13q14 was also associated with ARS but its role remains unidentified yet (Li et al., 2017a; Song and Hu, 2017). *PI3K* in particular has been shown to be a key factor in NC cell proliferation and migration. This gene has been found to cross-talk to other pathways such as Rho GTPase signaling (Solheim et al., 2017).

3.1.4. Bamforth-Lazarus syndrome (BLS)

BLS is a congenital disease that is characterized by a partial or complete loss of function of the thyroid gland (hypothyroidism), spiky hair and a cleft palate, with or without blockage of the nasal passage (choanal atresia), and an epiglottis divided by a deep cleft (bifid) (Carré et al., 2014). Several *FOXE1* mutations have been reported in patients with BLS (Carré et al., 2014; Castanet and Polak, 2010; Kang et al., 2010). Foxe1 is a forkhead transcription factor involved in important processes during mouse development. Human and mice Foxe1 play important roles in thyroid and craniofacial development (Damante et al., 2001). In particular, homozygous *Foxe1*-null mice exhibit thyroid agenesis or ectopia and cleft palate (De Felice et al., 1998). Moreover, it was described in mice that *Foxe1* is required for correct hair follicle morphogenesis, indicating that the spiky hair defected in BLS is due to altered FOXE1 function in the hair follicle (Brancaccio et al., 2004). In the zebrafish model, *foxe1* plays an important role in chondrogenesis during the development of the pharyngeal skeleton, which is a known NC derivative. This was confirmed by knockdown of this gene, which produced a severe reduction in the expression of the *sox9a*, *colIIaI*, and *runx2b* genes, known to play roles in chondrocytic proliferation and differentiation (Nakada et al., 2009).

3.1.5. Binder syndrome (BS)

BS or maxillonasal dysplasia is a congenital malformation characterized by striking facial features such as short nose with flat bridge, a short columella (the bridge of tissue that separates the nostrils at the nasal base), an acute nasolabial angle, perialar flatness, and a convex upper lip. Critical features of the BS syndrome appear to be midfacial hypoplasia, lack of anterior nasal spine, and malocclusion. Although the majority of BS cases are sporadic, a familial recurrence in an autosomal dominant manner has been reported (Roy-Doray et al., 1997).

Throughout the medical literature, human pituitary deficiencies are frequently reported in association with numerous other defects of the forebrain and with premaxillary nasofrontal malformations. The craniofacial and forebrain defects of BS are associated with human pituitary defects (Etchevers et al., 2001a), as well as Kallman syndrome (Section 3.1.9), Axenfeld-Rieger Syndrome (Section 3.1.3), Moebius syndrome (Section 3.1.17), Oculo-Auriculo-Vertebral Syndrome (Section 3.1.22), EEC3 syndrome (Section 3.1.26.c) and CHARGE syndrome (Section 3.4.3). These defects and syndromes, all of which are somehow associated with cephalic NC developmental dysfunctions, support the hypothesis that facial dysmorphologies could be predictive of pituitary defects (DeMyer et al., 1964; Etchevers et al., 2001a).

The pituitary gland or hypophysis, which is probably the most important endocrine organ, is composed of the neurohypophysis and the adenohypophysis. The neurohypophysis arises from the neuroectoderm, while the adenohypophysis (anterior pituitary) originates from the adenohypophyseal placode. Placodes are formed at the border between the neural and non-neural ectoderm during early gastrulation, a territory that is later divided into the preplacode and the NC regions (Singh and Groves, 2016). Placode cell precursors interact with NC cells to form the placodal domain. It has been demonstrated that NCCs play a key role in pituitary vascularization, forming pericytes (Cheung et al., 2017; Davis et al., 2016; Etchevers et al., 2001b). NCCs also contribute to pituitary development by differentiating into all types of hormone-producing cell lineages in addition to pericytes (Ueharu et al., 2017).

In BS, the patients show a maxillonasal dysplasia similar to the *NAX* mice mutant for the *TTR* gene (Holmstrom, 1986). Interestingly, a familial BS recurrence in an autosomal dominant manner has been reported (Roy-Doray et al., 1997). With respect to the molecular mechanism underlying the onset of this disease, model organism research has proven Retinoic acid (RA) to be a key factor in the development of this pathology. RA in particular, which is a metabolic product of retinol, is essential for craniofacial morphogenesis, while *TTR* is a plasma protein delivering retinol to different tissues (Noguchi et al., 2002). Moreover, in the mutant *TTR* mouse model (*NAX*), excessive cell death was observed in the nasal placode.

3.1.6. Branchio-Oculo-Facial syndrome (BOFS)

BOFS is caused by a misdevelopment of the first and second branchial arches, which causes facial, ocular and cutaneous anomalies that include abnormal patches or segments of noncancerous facial growths of blood vessels under the skin (hemangioma), a gap or split in the structures that make up the eyes (coloboma), hypertelorism, abnormally small eyes (microphthalmia), upslanted palpebral fissures, broad nasal tip, and hearing loss. BOFS was initially described by Fujimoto et al. (1987). This disease is caused by a mutation in the transcription factor *TFAP2A*, which participates in several steps of NC development (Milunsky et al., 2011). Moreover, it has recently been found that *TFAP2A* is expressed in migratory human NCC (Yi et al., 2016). Recently, in Argentina, new phenotypes associated with this disease were found, including bifid uvula and tongue with partial central cleft, which had not been previously described for this clinical condition (Garcia Flores et al., 2015). Model organism research has shown that in *Tfap2a* $^{+/-}$ mice BOFS model the reduction in *Fgf8* gene dosage can attenuate the clefting pathology by generating compensatory changes (Green et al., 2015). Additionally, complementary investigations in zebrafish embryos have shown that *foxd1l* and *tfap2a* interaction is essential for the proper development of craniofacial structures (Balikova et al., 2010). More research with other model organisms will be essential to further pinpoint the molecular causes of BOFS.

3.1.7. Branchio-Oto-Renal (BOR) syndrome

BOR syndrome is a rare genetic disorder characterized by a distinct phenotype including branchial arch anomalies (branchial clefts, fistula, cysts), hearing impairment (malformations of the outer, middle, and inner ear, featuring auricle with preauricular pits, conductive or sensorineural hearing impairment), and renal malformations (urinary tract malformation, renal hypoplasia or agenesis, renal dysplasia and renal cysts) (Fraser et al., 1980; Izzedine et al., 2004; Stinckens et al., 2001). BOR is related to BOS (Branchio-Otic Syndrome) and has the same features as BOR syndrome but without renal involvement. BOR syndrome is transmitted in an autosomal dominant manner. Mutations within the *EYA1* gene have been detected in 40% of the patients affected with this disease (Chang et al., 2004; Klingbeil et al., 2017; Sanchez-Valle et al., 2010). EYA1 functions as a protein phosphatase and as a transcriptional co-activator whose role is important during embryogenesis. Other pathogenic variants of the BOR syndrome include mutations in the *SIX5* and *SIX1* genes, which makes up 5% and 4% of all cases, respectively (Krug et al., 2011). Moreover, it has been shown that the products of these genes interact directly with the *EYA1* gene product, forming transcription factor complexes. Therefore, *SIX1* mutations cause BOR syndrome by disruption of the EYA1–SIX1–DNA complexes (Ruf et al., 2004).

As to the possible mechanism of this disease, it could be argued that auricular pits or tags, and lateral branchial sinuses, fistulas or clefts could reflect missdevelopment of the first and second branchial arches. However, sensorineural hearing loss observed in some patients with BOR syndrome cannot be explained only as a branchial arch malformation. Abnormal development of NCCs, which affects the migration of NC-melanocytes precursors to the cochlear stria vascularis of the inner ear and/or to the middle ear, could account for the combination of sensorineural hearing loss and branchial arch malformations seen in the BOR syndrome (Gimsing, 1987; Konig et al., 1994; Nishio et al., 2015).

Whether the renal malformations of the BOR syndrome can also be attributed to a defective NCC function is still an open question, but the association between disturbances of the auditory and renal system are well known and structural similarities are documented (Moody et al., 2015).

3.1.8. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

CADASIL syndrome is characterized by migraine, transient restriction in blood supply to tissues (ischemic attacks) and poor blood flow to the brain (strokes), cognitive decline, and psychiatric symptoms. CADASIL is caused by *NOTCH3* gene mutations that result in vascular smooth muscle cell (VSMC, in which *NOTCH3* is highly expressed), and pericytes degeneration (Joutel et al., 1996). Most VSMC that ensheath blood vessels in the brain region are of NCC origin (Majesky, 2007; Wang et al., 2017). Similarly, Notch is an essential regulator of NCC during cardiovascular development and smooth muscle differentiation (see Alagille Syndrome, Section 3.4.2) (High et al., 2007).

Mechanistically, the mutation in *Notch3* causes the aggregation of the Notch3 extracellular domain into extracellular deposits of granular osmiophilic material, thus producing the breakdown of VSMC (Masek and Andersson, 2017). Recently, the generation of knockout mice and the analysis of other animal models have provided new insights regarding Notch function in the development of CADASIL (Joutel, 2011). Moreover, several lines of research have helped in the development of possible treatments for this disease, based on limiting the expression of the mutated *Notch3* domains by cysteine-corrective exon

Table 1
Neurocristopathies: Defects in the Formation, Migration or Differentiation of NCC.

Name Of NCP	Function in NC development	NC Derivatives	Genetic Changes	OMIN ID	Frequency	Patient Support and Advocacy Resources
22q11.2 Deletion Syndrome	Trunk Migration	Heart. Immune system: thymus, parathyroid glands, bone marrow. Calcium Level: parathyroid (C cells). Hearing bones, choanal atresia, Striated muscles	PITX2/TBX1, COMT, Cxcr4/ Cxcl12; Sdf1	188400	1 in 1000 births	http://www.22q.org/; http://22qcentral.org/, https://www.22q11ireland.org/
3MC Syndrome	Differentiation	Craniofacial bone	COLEC11, MASP1/3	265050, 248340, 257920	unknown	http://www.thearc.org/
ADULT Syndrome	Migration and Differentiation	dentine, melanocyte, lacrimal glands, adenohypophysis	TP63	103285	1 in 1000000	
AEC Syndrome	Migration and Differentiation	Melanocytes, dentine, lacrimal and salivary gland, craniofacial bones,	TP63	106260	1 in 100,000 newborns	www.cleftline.org/
Alagille Syndrome	Differentiation	Heart. Head bones. VSMC in the Brain, Schwann cells of Langerhans' islet	JAGGED1, NOTCH2	118450	1 in 70,000 newborns	https://www.alagille.org/
Allgrove Syndrome	Migration and Differentiation	Endocrine: Adrenal glands. Lacrimal glands	ALADIN (nuclear pore complex)	231550	8800 cases identified	https://aboutgimotility.org/disorders-of-the-esophagus/achalasia.html
Auriculo-Condylar Syndrome	Migration	First and second pharyngeal arches	PLCB4, GNAI3, EDN1	602483	50 cases identified	
Axenfeld-Rieger Syndrome	Differentiation	Adenohypophysis, Craniofacial bone, dentine, eye	FOXC1, PITX2, CYP1B1, PRDM5	180500	1 in 200,000	http://www.glaucoma.org/
Bamforth-Lazarus Syndrome	Migration and Differentiation	Endocrine: thyroid gland. Spiky hair, choanal atresia, cleft palate.	FOXE1	241850	1 in 4000 newborns	https://www.thyroid.org/
Bardet -Biedl Syndrome 8	Cranial and Cardiac Migration	craniofacial bones, enteric nervous system	BBS8	615985	1:140,000	http://www.ciliopathyalliance.org/
Binder Syndrome	Migration	Craniofacial bones, eye	TTR, NEUROG1 (5q31.1)	155050	1 per 10,000 live births	
Branchio-Oculo-Facial Syn.	Cranial NC Migration	Craniofacial bones, cornea,	TFAP2A	113620	1 per million newborns	http://www.aboutface.ca/ http://www.ameriface.org/
Branchio-oto-renal Syndrome	Migration	Branchial arches	EYA1, SIX1, SIX5	113650	1 in 40,000 infants	
CADASIL	Differentiation	VSMC in the Brain	NOTCH3, FOXC1, PITX2, TIMP3, vitronectin, LTBP – 1	125310	1 in 50,000	http://www.cadasilfoundation.org/ http://curecadasil.org/
Charcot-Marie-Tooth	Differentiation	Schwann cells	*PMP22*, *MPZ*, *LITAF*, *EGR2* and *NEFL*	118300	1 in 2500	
CHARGE Syndrome	Trunk Migration	coloboma, eart, choanal atresia, inner ear and face bones, cleft palate, thymus, adenohypophysis	CHD7	214800	1 in 8500 newborns	https://www.chargesyndrome.org/
Congenital Central Hypoventilation Syndrome	Differentiation	**Sympathetic** Glia, Schwann-cells in the Islets of Langerhans, **Endocrine**: adrenal gland. Pharyngo cephalic	RET, GDNF, EDN3, TRK/ BDNF, PHOX2A and B, GFRA1, BMP2, ECE1	209880	1000 individual identified	http://cchsnetwork.org
Cranioectodermal dysplasia/ Sensenbrenner syndrome	Migration and Differentiation	Odontoblasts, cranial sutures	WDR35, IFT122, WDR19, IFT43	218330	40 cases reported	
Craniofacial-Deafness-Hand Syndrome	Differentiation	Craniofacial bone	PAX3	122880	unknown	http://www.aboutface.ca/
Craniosynostosis	Induction and Differentiation	Chondroblasts and osteoblasts	SOX9, FGFR2, FGFR3, TWIST1, MSX2, EFNB1, POR, RAB23, RECQL4, GLI3	101200, 123150, 123500, 123790, 604757	1 in 2500 births	
Diamond Blackfan Anemia Syn.	Induction and Specification	Craniofacial and cleft palate. Septo-cardiac defects. HPC progenitors.	At least 14 Ribosomal proteins including: RPL5, RPL11, RPS19	105650	5–7 cases per Million live births. 1:200,000 ete abrogati	http://dbafoundation.org; https://www.dbar.org
EEC3 Syndrome	Migration and Differentiation	Lip, melanocyte, dentine, salivary glands, craniofacial bones, cornea, thymus,	TP63	129900	1 in 10,000	http://nfed.org/ www.ectodermaldysplasia.org

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Table 1 *(continued)*

Name Of NCP	Function in NC development	NC Derivatives	Genetic Changes	OMIN ID	Frequency	Patient Support and Advocacy Resources
		adenohypophysis				
Ellis-van Creveld syndrome	Migration and Differentiation	Odontoblasts, craniofacial bones	EVC, EVC2	225500	1 in 60.000–1 in 200.000	
Frontonasal Dysplasia	NCC proliferation	craniofacial bones (Craniosynostosis)	GLI1 ALX3 (FND1), ALX4 (FND2), ALX1 (FND3), EFNB1, Kif3a	136760	100 cases	http://www.ccakids.com/frontonasal-dysplasia.html
Familial dysautonomia	Differentiation	Root and sympathetic ganglia	*IKBKAP* *ELP1*	223900	1:3700 (Ashkenazi Jewish people)	https://rarediseases.org/rare-diseases/dysautonomia-familial/
Giant Congenital Melanocytic Nevus	Differentiation	Melanocytes	BRAF/NRAS, SOX10, MITF	137550	1 in 100 births	http://www.nevus.org
Growth Retardation, Developmental Delay, And Facial Dysmorphism	Cranial Migration	craniofacial bones	FTO	612938	unknown	
Hajdu-Cheney Syndrome	Differentiation	Neurological, cardiovascular	NOTCH2	102500	100 affected individuals have been described	https://rarediseases.org/rare-diseases/hajdu-cheney-syndrome/
Heterotaxy Syndrome	NCC differentiation	Heart	Pkd2, PKD1L1	617205	1:10,000	https://rarediseases.info.nih.gov/diseases/10875/heterotaxy
Hirschsprung	Trunk NC Migration and Differentiation	PNS: Parasympathetic Nervous System). Ganglion of submucosal enteric plexus. Anterior part of the eye	RET, GDNF, ARAD, NTN, EDNRB/EDN3, PHOX2B, L1CAM, SOX10, SIP1, HASH1, HAND2, PATCH1/NOTCH	142623	1 in 5000 births worldwide	https://iffgd.org; http://www.bgk.org.au
Hypogonadotropic Hypogonadism.	Differentiation	Adenohypophysis, Craniofacial bone, dentine	FGF8, PROK2, PROKR2, CHD7, WDR11, FGFR1	612370 308750	1 in 30,000	http://www.hormone.org/ https://www.pituitary.org.uk/
Hypohidrotic ectodermal dysplasia	Migration and Differentiation	Melanocyte, dentine, salivary gland	EDA1, EDAR, EDARADD, and WNT10A	305100	1 in 17,000	https://rarediseases.org/rare-diseases/hypohidrotic-ectodermal-dysplasia/
Hypohidrotic Ectodermal Dysplasia	Differentiation	Craniofacial bone, dentine	EDA	305100	unknown	http://www.aboutface.ca/
Klippel-Feil Syndrome	Differentiation	Craniofacial bone	MEOX1, GDF3, GDF6	118100	1 in 40,000	http://www.climb.org.uk/ http://kfsalliance.org/
Limb-Mammary	Migration and Differentiation	dentine	TP63	603543	1 in 1000000	
Meckel-Gruber Syndrome	Migration and differentiation	Craniofacial	MKS1	249000	1 in 14,000 to 1 in 140000	
Medullary Thyroid Carcinomas	Migration and Differentiation	Endocrine: parathyroid glands	MEN1, RET, CDKN1B	171400, 162300, 155240	1 in 30,000	https://www.cancer.org/
Melanoma	Trunk NC Migration and Differentiation	Melanocytes	BRAF/NRAS, SOX10, MITFA, Trk/NT, CDKN2A, MCIR, CDK4, BRN3A	155600	unknown	https://www.melanoma.org
Mandibulofacial Dysostosis with Alopecia	Differentiation	Craniofacial bone	EDNRA	616367	unknown.	https://www.worldcf.org/
Moebius Syndrome	Migration	Adenohypophysis, sensory and motor neurons	HOX, PTCH1, TUBB3, NEUROG1, etc	157900	1 per 50,000	http://moebiussyndrome.org/
Mowat Wilson Syn.	Cranial and Cardiac NC Migration	Craniofacial bones, heart and enteric plexus	ZEB2/SIP1	235730	200 individual identified	https://mowat-wilson.org
Neuroblastoma	Trunk NC Migration and differentiation	PNS, sympathetic ganglia. Adrenal glands	PHOX2B, TRK/NT	256700	1 in 100,000	http://www.cncfhope.org
Neurofibromatosis I	Differentiation	Ciliary glia. VSMC in the Brain. Melanocytes. Schwann cells. Endocrine: Chromaffin cells of	NF1	162200	1 in 2000 births	http://www.ctf.org; http://www.nfnetwork.org

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Table 1 *(continued)*

Name Of NCP	Function in NC development	NC Derivatives	Genetic Changes	OMIN ID	Frequency	Patient Support and Advocacy Resources
		the adrenal medulla				
Noonan syndrome	Premigratory	Melanocytes, heart	Aortic arch arteries	151100	200 cases have been reported	https://rarediseases.org/rare-diseases/leopard-syndrome/
Oculo-Auriculo-Vertebral Syndrome	Induction, Migration and Differentiation	Craniofacial bones, adenohypophysis	SKI	164210, 182212	1 in 5600 and 1 in 26,550 newborns	http://www.thearc.org/
Oculocutaneous Albinism	Differentiation	Melanocytes	TYR (OCA1,2), TRP1 (OCA3), MATP, SLC45A2 (OCA4)	203100	1 in 20,000 newborns worldwide	http://www.albinism.org/ http://www.visionofchildren.org/
Orofaciodigital Syndrome I	Cranial Migration	craniofacial bones	CXORF5	311200	1:50,000	
Paragangliomas	Differentiation	Carotid Body,Adrenal medulla	SDHB, SDHC, SDHD	168000		
Peters Anomaly	Differentiation	Eye, Craniofacial bone, cardiac	PAX6, PITX2, FOXE3, FOXC1	604229 261540	1 in 15,000	http://www.ameriface.org/
PHACE	Differentiation	Craniofacial bone,		606519	unknown	
Phenylketonuria	Differentiation	Outflow tract and aortic arch. Coloboma	PAH	261600	1 in 10,000 births	https://npkua.org/ https://pkunews.org
Pheochromocytomas	Differentiation	Endocrine: Adrenal medulla	VHL, RET, SDHB, SDHD	171300	1 in 500,000	http://www.pheoparatroopers.org/ http://www.pheochromocytoma.org/
Piebaldism	Trunk NC Migration	White spotting, megacolon,	KIT, SNAI2	172800	unknown	http://www.albinism.org
Pierre Robin sequence	Migration and Differentiation	Craniofacial bones	SOX9, MED13L	261800	1 in 8500	
Postaxial Acrofacial Dysostosis Syndrome	Induction and Specification	Cheek and lower jaw bones. Cleft palate and cleft lip. coloboma	DHODH	263750	1 per million newborns	https://rarediseases.org
SAMS	NCC specification	Craniofacial bones	GSC	138890/ 602471		
Short-Rib Thoracic Dysplasia 10	Cranial Migration	craniofacial bones, heart, intestine	IFT172	615630		http://www.ciliopathyalliance.org/ http://www.lpaonline.org/
Split-hand/ split-foot malformation 4	Migration and Differentiation	dentine	TP63	605289	1 in 90,000	
Sturge-Weber Syndrome	Differentiation	Cornea, sclera, melanocytes	GNAQ	185300	1 in 20,000 births	http://swscommunity.org; http://sturge-weber.org; https://birthmark.org
Tietze's Syndrome	Differentiation	Ear bones, melanocytes	MITF	103500	5000 Tietze Netherland's patients	http://www.albinism.org; http://www.asha.org/
Treacher Collins Syndrome	Induction and Specification	Craniofacial hypoplasia, choanal atresia and cleft palate. Coloboma	TCOF1, POLR1C, POLR1D	154500	1 in 10,000 births	http://www.cleftline.org/who-we-are/what-we-do/publications/treacher-collins/
Tricho-dento-osseous Syndrome	Cranial Migration and Differentiation	Dentine of the teeth (dental follicle)	DLX3	190320	12 families identified	https://rarediseases.org/rare-diseases/tricho-dento-osseous-syndrome/
Von Hippel-Lindau Syndrome	Differentiation	Adrenal medulla, carotid body, Schwann Cells	VHL	193300	1 in 36,000	https://vhl.org
Waardenburg Syndrome	Induction-Specification and Trunk NC Migration, Differentiation	PNS: Ganglion cells of enteric plexus. Melanocytes. Sensory Neurons	PAX3 (WS1,3). MITF (WS2A) SNAI2 (WS2D), EDNRB/EDN3, SOX10 (WS4)	193500, 148820, 193510, 609136	1 in 40,000 births	http://deafchildren.org

skipping (Rutten et al., 2016).

3.1.9. Combined pituitary hormone deficiency (CPHD)

During development, placodes form the pituitary, eye, ear, nose and cranial ganglia. The developmental programs controlling their formation involve common genetic pathways. Mutations in genes expressed in the prospective head, hypothalamus, and/or pituitary gland cause Combined Pituitary Hormone Deficiency (CPHD). Moreover, several genes associated with craniofacial abnormalities also cause pituitary deficiency (syndromic CPHD) while the genes expressed in the hypothalamus or exclusively in the pituitary gland cause nonsyndromic CPHD. To date, about 30 genes have been reported to be involved in the pathogenesis of CPHD (i.e. *GLI2, HESX1, LHX3, LHX4, OTX2, POU1F1, PROP1,* and *SOX2*), which are reviewed in (Castinetti et al., 2015; Fang et al., 2016; Flemming et al., 2013). Based on the clinical phenotypes, other endocrine disorders such as Hypogonadotropic Hypogonadism (HH), Kallmann Syndrome (KS), Axenfeld-Rieger Syndrome (Section 3.1.3), Binder Syndrome (Section 3.1.5), Moebius Syndrome (Section 3.1.17), Oculo-Auriculo-Vertebral Syndrome (Section 3.1.22), CHARGE syndrome (Section 3.4.3),

Holoprosencephaly (Section 4.1.1.a) and Isolated Growth Hormone Deficiency (IGHD) (Blustajn et al., 1999; Stagi et al., 2015) are also identified as NCP. In particular, CPHD and HH have overlapping genetic causes, and mutations in many genes are implicated in both pathologies (*FGF8*, *PROK2*, *PROKR2*, *CHD7, WDR11*, and *FGFR1* (Dode and Rondard, 2013; Ha et al., 2017; Kim et al., 2010). These facts highlight the complexity of discerning new NCP from diseases that have already been identified and call for an improved method of genetic testing to diagnose different pathologies.

Gonadotropin-releasing hormone (GnRH) expressing neurons originate from the NC and from the olfactory placode. These neurons migrate from the olfactory placode to the hypothalamus along the axons of developing olfactory nerves (Barraud et al., 2010). Defects in the development of GnRH neurons, either in their migration or in GnRH secretion, cause congenital HH, which is a rare developmental disorder characterized by delayed or absent puberty. In particular, if HH is characterized by defects in the sense of smell, the condition is termed Kallmann Syndrome (KS). Despite these recent advances, the genetics of congenital HH is still complex and heterogeneous. Although several genes have been implicated in the etiology of congenital HH, still about 65% of the cases remain with no identified genetic cause (Mitchell et al., 2011). However, several mutations have been implicated in the development of KS, and include the genes *KAL1, FGF1, FGF8, PROK2, PROKR2, CHD7, SOX10*, and *WDR11* (Dode and Rondard, 2013; Kim et al., 2010; Pingault et al., 2013).

3.1.10. Craniofacial-deafness-hand syndrome (CDHS)

CDHS is a rare disorder that was first described in a three-generation family (Sommer and Bartholomew, 2003). Individuals with CDHS have severe hearing impairment, a lateral displacement of the inner canthi of the eyes (dystopia canthorum), hypertelorism, flat facial profile, opening between the eyelids down positioned in an oblique direction (downslanting palpebral fissures), depressed nasal bridge, small mouth, ulnar deviation and contractures of the hand, hypoplasia of the nasal bones and a hypoplastic ulnar styloid. By imaging findings and by a distinct facial feature this disease can be distinguished from Waardenburg syndrome type 3 (Section 3.1.29). Mechanistically, CDHS is caused by a *PAX3* mutation which affects its paired box domain (Asher et al., 1996). This highlights the role of the mouse model in the discovery of the underlying causes of NCP.

3.1.11. Craniosynostosis (CS)

Craniosynostosis is a primary abnormality of skull growth involving premature fusion of the cranial sutures such that the growth velocity of the skull often cannot match that of the developing brain. This causes skull deformity and, in some cases, raises intracranial pressure, which must be treated promptly to prevent permanent neurodevelopmental disability (Cohen and MacLean, 2000; FitzPatrick, 2013). Most CS syndromes are associated with mutations in *COL2A1* (Stickler syndrome), FGF receptors (FGFR) 21, 22, and 23, as well as with mutations in the genes *TWIST* (Saethre Chotzen syndrome), *MSX2* (Boston-type CS), and *EFNB1* (craniofronto-nasal dysplasia) (Farlie et al., 2016). Since the cranial skeleton includes mesoderm- and NC-derived structures, an altered migration and boundary formation between these cell populations is a potential mechanism for the pathogenesis of CS. In this regard, it is currently known that cranial NCCs contribute to the majority of cartilages and bones of the head and face (Fig. 1). This contribution is marked by the expression of the *Sox9* gene, which activates the expression of the *Col2a* gene, as it has been shown in mice (Bi et al., 1999). In particular, a missense mutation in the mouse *Col2a* gene causes spondyloepiphyseal dysplasia congenita (an inherited bone growth disorder that results in short stature (dwarfism), skeletal abnormalities, and problems with vision), hearing loss, and retinoschisis (abnormal splitting of the retinal neurosensory layers) (Donahue et al., 2003). Therefore, this mice model could provide insights into the mechanisms of skeletal development dependent on Col2a1 and its role in fibril formation and cartilage template organization.

The differentiation of the chondrocyte lineage is also achieved by inhibiting the osteoblast-promoting gene *β-catenin* (Day et al., 2005). On the other hand, the determination of the bone lineage is produced by the stimulation of the expression of *Runx2* by *Sox9* (Eames et al., 2004). In addition to this genetic cascade, many other signaling pathways influence the expression of *Runx2*, including TGFb, BMP, Hh and FGF (Komori, 2007). Research in the *Xenopus* model has provided useful insights into the mechanisms underlying human craniofacial anomalies, making this amphibian species a simplified model system for the study of cranial ossification and suture patterning (Slater et al., 2009). This organism has also provided evidence of the preponderant role that metalloproteases exert in the remodeling of cartilage into bone (Harrison et al., 2004; Slater et al., 2009). Thus, it will be interesting to elucidate the intrinsic mechanisms that underlie the formation of these boundary structures.

3.1.12. Familial medullary thyroid carcinomas (FMTC)

FMTC is a malignant tumor of the NC-derived calcitonin-secreting parafollicular C cells of the thyroid that occurs sporadically or as a component of the multiple endocrine neoplasia type 2 (MEN2)/familial medullary thyroid carcinoma (FMTC) syndromes (Maliszewska et al., 2013; Santoro and Carlomagno, 2013). Thyroid cancer derived from follicular epithelial cells is referred to as nonmedullary thyroid cancer and comprises several subtypes. Gain of function mutations of the *RET* (rearranged during transfection) gene are associated with a limited number of patients affected with isolated or syndromic autosomal dominant FMTC (Mulligan, 2014). The RET proto-oncogene encodes a tyrosine kinase transmembrane receptor (RTK) which is mainly expressed in NC-derived cell lineages such as parafollicular C cells, adrenal medullary cells and parathyroid cells. This RET receptor plays a pivotal role in regulating cell proliferation, migration, and differentiation (Manié et al., 2001).

Another gene involved in FMTC is *PITX2*, which encodes a paired-like homeodomain transcription factor. *PITX2* is expressed in NCC and has been associated with tumorigenesis and with Wnt/b-catenin signaling (Maliszewska et al., 2013). *PITX2* has also been associated with the onset of the Axenfeld-Rieger Syndrome (Section 3.1.3), CADASIL (Section 3.1.8), 22q11.2 Syndrome (Section 3.4.1) and Peter anomaly (Section 3.4.6). Further investigations will be required to fully understand the factors involved in the development of FMTC.

3.1.13. Growth retardation, Developmental delay, and Facial dysmorphism (GDFD)

The GDFD syndrome is characterized by severe conscious movement retardation (psychomotor), poor overall growth and dysmorphic (different body structure) facial features. Additional features may include cardiac malformations and deafness (Daoud et al., 2016; Osborn et al., 2014). In humans, homozygous mutations in the *FTO* gene result in severe developmental defects including developmental delay, postnatal microcephaly, craniofacial dysmorphism and early lethality (Boissel et al., 2009; Daoud et al., 2016). This suggests that *FTO* plays a vital role during the onset of this syndrome. In zebrafish, loss of *Fto* also leads to developmental defects such as growth retardation, craniofacial dysmorphism and aberrant NCC migration (Osborn et al., 2014). Moreover, in this model, *Fto* is required for canonical Wnt signaling while its loss results in short, absent or disorganized cilia leading to *situs inversus*, renal cystogenesis, NC defects and microcephaly. On a molecular level, it has been found that FTO is a protein-regulator of the balanced activation between canonical and non-canonical branches of the Wnt pathway (Osborn et al., 2014). This study therefore puts the Wnt signaling in a central position during the onset of several NCP.

3.1.14. Hypohidrotic ectodermal dysplasia (HED)

HED is a syndrome characterized by a triad of signs comprising sparse hair (hypotrichosis), abnormal or missing teeth (anodontia or hypodontia), and inability to sweat (anhidrosis or hypohidrosis). The dental phenotype allows early diagnosis and consists of oligodontia with other dental abnormalities (moderate oligodontia, conical incisors, and delayed dental eruption). The HED syndrome is caused by mutations of the genes involved in the Ectodysplasin (*EDA*)-NF-κB pathway, which is essential in skeletogenic NCC differentiation, migration and osteoclast differentiation (Clauss et al., 2008a; Zhang et al., 2011). Specifically, the mutated genes are ectodysplasin (*Eda*) (Clauss et al., 2008b; Li et al., 2017b), the *TNF* ligand, its receptor *Edar* (van der Hout et al., 2008), the intracellular adapter protein *Edaradd* (Cluzeau et al., 2011), and *Wnt10A* (Cluzeau et al., 2011; Zeng et al., 2016). The diagnosis of mild HED is established by identification of a heterozygous *EDA*, *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant (Haghighi et al., 2013; Lexner et al., 2008; Megarbane et al., 2008). Additionally, HED patients and the mouse model lines Tabby (*Ta*), Downless (*Dl*) and Crinkled (*Dr*) show defects in the teeth and hair as well as in the salivary, lacrimal, and sweat glands (Thesleff and Mikkola, 2002). Further studies in these mouse models will reveal more mechanistic details regarding the onset of this syndrome.

3.1.15. Klippel-Feil syndrome (KFS)

KFS (or XXY syndrome) is characterized by a congenital fusion of any of the seven neck (cervical) vertebrae. Patients with this disease also show cardiovascular, craniofacial, hearing, ocular, laryngeal cartilage, limb, digital, and urogenital defects, with an incidence of up .5% of live births (Clarke et al., 1998; Fantasia, 2014). The NC-derived part of the skeleton is specifically affected in human KFS (Matsuoka et al., 2005). Mutations in the *MEOX1*, *GDF3* and *GDF6* genes are responsible for the onset of KFS (Markunas et al., 2013; Mohamed et al., 2013; Tassabehji et al., 2008). Model organism research performed on the GDF6 knockout mice and on *the gdf6* morpholino knockdown in *Xenopus* have shed light into the pathogenesis of KFS. In particular, the defects observed in theses model systems are consistent with a role for GDF6 in the etiology, diversity and variability of KFS (Settle et al., 2003; Tassabehji et al., 2008).

3.1.16. Mandibulofacial dysostosis with alopecia (MFDA)

The main features of the MFDA syndrome are micrognathia, cleft palate, dysplastic zygomatic arch, thickened malar bones, absent or hypoplastic lateral margin of the orbits, short nose with broad nasal tip, dysplastic ears, hearing loss, sparse eyelashes and hypoplasia of the eyelids, and loss of hair from part of the head or body (alopecia) (Cushman et al., 2005; Gordon et al., 2015; Zechi-Ceide et al., 2010). MFDA is caused by mutations in *EDNRA* (Endothelin Receptor type A) gene (Gordon et al., 2015). As it has been shown in several model organisms, EDN1-EDNRA cell signaling plays a critical role in the specification of mandibular identity in post-migratory NCCs (Bonano et al., 2008; Gordon et al., 2015; Sabrautzki et al., 2016).

3.1.17. Moebius syndrome (MBS)

MBS, or congenital ophthalmoplegia, is a rare neurological condition that is characterized by specific cranial nerve defects including the trigeminal (V), abducens (VI) and facial (VII) nerves together with partial facial paralysis (paresis: a condition of muscular weakness caused by nerve damage), hypertelorism and affected eye movements. Many people with MBS are born with micrognathia, microstomia and cleft palate.

Cranial nerves govern sensory and motor information exchange between the brain, head and neck tissues, and different organs. Cranial nerves are derived from two specialized cell populations, cranial NCCs and ectodermal placode cells (V, VII, VIII, IX, X; (Nishio et al., 2015; O'Rahilly and Müller, 2007; Park and Saint-Jeannet, 2010; Schlosser, 2010). Defects in either cell type can result in cranial nerve developmental defects. A recent mouse model study has correlated the MBS phenotype with elevated Shh signaling (Kurosaka et al., 2015). The enhanced Shh signaling suppressed canonical Wnt signaling in the cranial nerve region, critically affecting the survival and migration of cranial NCCs and the development of placodal cells as well as the integration between NC and placodes.

Additionally, mutations in the *MBS1*, *MBS2*, and *MBS3* gene loci have all contributed to the development of MBS. On the other hand, the *HOX* family of genes coding for homeobox domains has also been implicated in the abnormal development of the human brain. *HOXA1* is involved in hindbrain development, specifically in rhombomere 5. Its role in the migration of NCCs may also affect the development of the embryo vascular system. Therefore, mutations in homeobox genes or downstream genes may both result in MBS with varying phenotypes (Kadakia et al., 2015).

Another gene, *TUBB3*, is reportedly expressed transiently in NCCs destined to become neurons. Therefore, it plays a role in nasal patterning by altering the development of neural elements within the nasal placode. Mutations of *TUBB3* (E410K) in particular have been associated with MBS (Chew et al., 2013; Patel et al., 2017). Similarly, affected individuals with a mutation in *TUBB3* also present Kallmann syndrome (Section 3.1.9). Other genes involved in the onset of MBS are *GSH1*, *CDX2*, *CRBP1*, *PBX2*, *SOX14*, *EGR2* (*Krox-20*) and the above-mentioned *HOXB1* gene (Kremer et al., 1996; Uzumcu et al., 2009; Webb et al., 2012). Altogether, these various genes that participate in the development of MBS could play a pivotal role in the future development of new therapies against this disease.

3.1.18. Nager acrofacial dysostosis (NAD)

NAD, also known as Nager syndrome, first described in 1948, is an autosomal dominant genetic disease that is the prototype for a group of disorders collectively referred to as acrofacial dysostosis (abnormal development of bones in the skull and the hands or feet) (Chemke et al., 1988). Patients commonly present features such as micrognathia, downslanted palpebral fissures, midface retrusion (a tooth or the jaw is posterior to its proper occlusal position), malar hypoplasia, and limb deformities. Mutations affecting the *SF3B4* gene are the only known cause of the Nager syndrome, which affects over 50% of clinically diagnosed patients. The *SF3B4* gene encodes the spliceosome-associated protein 49 (SAP49), which participates in the assembly of spliceosomal complexes (Bernier et al., 2012; Cassina et al., 2017; Petit et al., 2014). Recently, the first animal model for Nager Syndrome was established by specifically knocking down *sf3b4* gene in *Xenopus* embryos (Devotta et al., 2016). These *sf3b4*-depleted embryos showed defects in the formation of NCC progenitors in craniofacial cartilages, while the pigmented cells were unaffected. Mutant zebrafish embryos for the *sf3b1* gene, another component of the SF3B complex, also showed defects in cranial NC derivatives by a disruption in the processing of *sox9b* and *snai1b* (An and Henion, 2012).

Additionally, missense mutations in EFTUD2 have been reported in individuals with NAD who had no mutations in *SF3B4* (Bernier et al., 2012; Lines et al., 2012). Interestingly, patients with differential diagnoses of NAD, Treacher Collins syndrome (Section 3.1.27), CHARGE syndrome (Section 3.4.3) or oculoauriculovertebral spectrum (Section 3.1.22) have been found to have *EFTUD2* mutations (Bernier et al., 2012; Gordon et al., 2012; Luquetti et al., 2013). The *EFTUD2* gene encodes the U5-116kD GTPase, a highly conserved spliceosomal protein with a striking sequence similarity to the ribosomal translation elongation factor EF-2 (Fabrizio et al., 1997). Due to this fact, NAD has been proposed as a ribosomopathy. However, these are not the only genes which have been linked to the onset of NAD. Mutations in genes encoding components of the spliceosome such as *SNRPB* and *TXNL4A* also cause craniofacial disorders (Lynch et al., 2014; Wieczorek et al., 2014).

3.1.19. Pierre Robin sequence (PRS)

PRS is a set of craniofacial abnormalities affecting the head and face, consisting of a small lower jaw (micrognathia), a tongue that is placed further back than normal (glossoptosis), and blockage (obstruction) of the airways. PRS leads to life-threatening obstructive apnea and feeding difficulties during the neonatal period. Most people with PRS are also born with cleft palate. Some people have the features of PRS as part of a syndrome that affects other organs and tissues in the body. When PRS occurs by itself, it is described as nonsyndromic or isolated. Approximately 20–40% of cases of PRS are isolated (Caouette-Laberge et al., 1994). This condition is described as a "sequence" because one of its features, underdevelopment of the lower jaw (mandible), sets off a sequence of events before birth that cause the other signs and symptoms. Specifically, having an abnormally small jaw affects the placement of the tongue, and the abnormally positioned tongue can block the airways. In addition, micrognathia and glossoptosis affect formation of the palate during development before birth, which often leads to cleft palate.

SOX9 protein regulates the activity of other genes, especially those that are important for development of the NC-derivative skeleton, including the mandible in mammalian, bird, frog and fish organisms (Liu et al., 2013; Wakamatsu et al., 2014). Changes in the chromosome environment near the *SOX9* gene are the most common genetic cause of isolated PRS. PRS cases may result from developmental misexpression of *SOX9* due to the disruption of very long range cis-regulatory elements (Benko et al., 2009; Cote et al., 2015). It is likely that changes in other genes such as *MED13L* (Utami et al., 2014) are also involved in the condition. Further investigations are needed to pinpoint more causes underlying this disease.

3.1.20. PHACES syndrome

PHACES (**P**osterior fossa malformations–**H**emangiomas–**A**rterial anomalies–**C**ardiac defects–**E**ye abnormalities–**S**ternal cleft and supraumbilical raphe) syndrome is the association of hemangiomas and congenital anomalies, such as posterior fossa malformations, cerebral arterial anomalies, coarctation of the aorta, eye anomalies and sternal defects (Frieden et al., 1996). Cephalic NC provides mesenchymal cells to the arteries in the cardio- and cerebrovascular regions, while the endothelium of all the vessels in the body, including the brain, originates in the mesoderm. Moreover, NCC serve as neuronal and glial precursors. Therefore we can speculate that some of the phenotypes observed in the PHACES syndrome are caused by an abnormal NC development. However, the role of NCC in the pathogenesis of PHACES vascular anomalies has not yet been studied in detail. Despite this fact, cerebrovascular anomalies were found in 56% and cardiovascular anomalies in 41% of the patients with PHACES syndrome, stressing the role of NC during PHACES onset (Hess et al., 2010). Recently, mutations of *RNF213* and *ACT2* genes have been suspected as responsible for the phenotypic features of PHACES syndrome (Schilter et al., 2017). The concurrence was proposed of cardio- and cerebrovascular diseases through cephalic NC embryology (Komiyama, 2017).

3.1.21. Postaxial acrofacial dysostosis syndrome (POADS)

POADS (or Miller syndrome) is characterized by a combination of craniofacial anomalies including orofacial clefts, malar hypoplasia, micrognathia, cup-shaped ears, coloboma of the lower eyelid and postaxial limb deformities. This syndrome is caused by mutations in the dihydroorotate dehydrogenase gene (*DHODH*), which is involved in pyrimidine biosynthesis (Ng et al., 2010). One of these pyrimidine is the uracil monophosphate, which is a constituent base of RNA, therefore being critical for ribosome biogenesis. Taking into account these evidences, POADS could be considered as a ribosomopathy (Yelick and Trainor, 2015). In mouse embryos, it has been shown that this gene is required for the development of the pharyngeal arches, forelimbs, hindlimbs and somites (Rainger et al., 2012). Additionally, treatment with the DHODH inhibitor leflunomide in zebrafish embryos produced a disruption in the expression of NC specification markers such as *foxd3* and *sox10* (White et al., 2011). This inhibitor will be an interesting tool for future studies aimed at understanding the molecular mechanisms that produce POADS. Altogether, these studies corroborate the hypothesis that POADS originates from a defect in NC induction and specification.

3.1.22. Oculo-Auriculo-Vertebral syndrome (OAVS)

People affected with OAVS (also called Goldenhar Syndrome) present hemifacial microsomia (abnormal smallness of body structures) with maxillary or mandibular hypoplasia affecting one side of the face and noncancerous (benign) growths in the eye called epibulbar dermoids. Additionally, patients have a congenital deformity where the pinna (external ear) is underdeveloped (microtia) (Landgren et al., 1992; Shrestha and Adhikari, 2015). Other conditions described in OAVS patients include upper eyelid colobomas, a falling of the upper eyelid (ptosis), varying degrees of microphthalmia, and cardiac defects (Nakajima et al., 1998). In particular, the cardiac conditions consist of truncus malformations and teratology of Fallot. These are thought to be the result of a disturbance of NC development (Kirby and Stewart, 1983). Moreover, the core malformations of the OAV syndrome are related to the development of the first and second branchial arches and, interestingly, their NC components have been implicated in the pathogenesis of the condition (Beauchamp and Knepper, 1984).

It has been postulated that iris and/or retinal colobomas associated with OAVS may represent a subgroup within the OAVS spectrum with autosomal dominant inheritance. Since microtia can result from aberrant migration of NCCs into the first and second branchial arches during early embryonic development and a concomitant deficient NC migration into the developing eye can lead to ocular coloboma and or iris heterochromia, it could be argued that the eye conditions observed in this syndrome are due to a failure in NC development. (Beck et al., 2005; Murialdo et al., 2016). Altogether, the above evidence strongly supports the idea that OAVS is an NCP. However further studies will be needed to assert the role of NC in the pathogenesis of OAVS.

3.1.23. Oculocutaneous albinism (OCA)

OCA is a form of albinism caused by incomplete melanocyte differentiation. It results from a mutation in the *TYR* gene that participates in melanin synthesis. Melanocytes originate from mammalian and bird NCCs, which migrate and then differentiate into pigment cell types during embryonic development (Joshi et al., 2017). Amphibians, fish and reptiles, in contrast, have a class of cell called chromatophores (Kelsh et al., 2009). This particular mutation produces the subtype OCA1, a condition characterized by reduced melanin pigmentation in the eye and skin. There are two forms of OCA1. In OCA-1A there is a lack of functional tyrosinase and thus a lack of melanin, whereas in OCA-1B the individuals produce a certain amount of melanin (Grønskov et al., 2007). A particular subclass of this disease is characterized by a temperature sensitive mutation that renders the gene inactive at temperatures above 35ºC. Therefore, darker hair appears on cooler parts of the body, whereas in warmer areas hair is white by a loss of the TYR function. Other genes that are mutated in OCA are the *P* gene, *TRP1* and *MATP* genes (Rundshagen et al., 2004).

Genome-wide association analysis performed on horses with oculocutaneous albinism (OCA) found 24 individuals harboring the candidate gene *SLC24A5*, with known roles in pigmentation in humans, mice, and zebrafish (Mack et al., 2017). Genetic studies in *Xenopus* and zebrafish have successfully analyzed polymorphisms and mutations, thereby addressing the functional relationships between gene function and the development of pigmentation deficiencies in order to further understand the mechanisms that trigger this disease (Ishibashi et al., 2012; Tsetskhladze et al., 2012). On the other hand, the mouse model has proved to be an essential tool for developing therapies against OCA. It has been shown that increasing the plasma

concentration of the tyrosine degradation inhibitor Nitisinone caused an increase in pigmentation in OCA-1B mice, improving their phenotype (Onojafe et al., 2011). This provides new possibilities for the treatment of this disease.

3.1.24. Sturge-Weber syndrome (SWS)

SWS is a condition that affects the development of certain blood vessels, causing abnormalities in the brain, skin, and eyes (coloboma). SWS has four major features: a red birthmark called a port-wine birthmark, a brain abnormality consisting in a bright red nodule of extra blood vessels in the meninges (called a leptomeningeal angioma), and increased eye pressure (glaucoma) (Dutkiewicz et al., 2015). In SWS, the cutaneous vascular lesions observed along the distribution of the trigeminal nerve that follow the lines of normal cell development in the skin (lines of Blaschko) represent the migratory pathways of rhombencephalic NCCs. These pathways are followed by NCCs to form both nerve sheaths and small blood vessels. (Sarnat and Flores-Sarnat, 2005). The involvement in the angiomas in the face and scalp of the trigeminal nerves branches associated with cutaneous vascular lesions was suggested / hypothesized (Roach and Miller, 2004). These nerve branches / vascular lesions / angiomas are colonized by the NCCs that surround them.

Another symptom of SWS, epilepsy, can result from microangiomatous malformations in the cranial meninges, which are of NC origin (Decimo et al., 2012; Dutkiewicz et al., 2015). These results indicate that NCCs are important contributors to the development of SWS.

This condition has been reported to be associated with a specific somatic activating mutation of *GNAQ*, which encodes a G-protein alpha subunit that mediates signal transduction between G-protein coupled receptors and downstream molecules (Nakashima et al., 2014; Shirley et al., 2013). Somatic mutations in *GNAQ*, other than those detected in capillary malformations, have been reported in melanocytic neoplasms, uveal melanoma, congenital hemangiomas (rapidly involuting congenital hemangioma [RICH] and non-involuting congenital hemangioma [NICH]), and phakomatosis pigmentovascularis (Ayturk et al., 2016; Shirley et al., 2013; Thomas et al., 2016). These mutations increase proliferation and inhibit apoptosis by increasing signaling through RAS effector pathways. Moreover, GNAQ is implicated in cell growth by signal transmission through cell membrane receptors via MAP kinases. In fact, recent findings have found that an activating mutation increases signaling via this pathway, which may therefore lead to the capillary malformations observed in SWS (Higueros et al., 2017).

3.1.25. Tietz Albinism-Deafness syndrome (TADS)

TADS is a rare hypopigmentation disorder characterized by fair skin, light-colored hair, and profound congenital hearing loss, which is inherited in a fully penetrant autosomal-dominant fashion. As mentioned above, melanocytes originate from NCCs and migrate through the developing embryo to specific locations within the skin and hair follicles and to other sites in the body (Mort et al., 2015). The neurosensory hearing loss of this syndrome is the result of a lack of melanocytes in the cochlear stria vascularis, another NC derivative, secondarily causing degeneration of the auditory nerve (Grill et al., 2013; Price and Fisher, 2001; Sandell et al., 2014). With respect to the molecular etiology of TADS, *MITF* mutations have been found in affected patients (Grill et al., 2013; Léger et al., 2012; Shigemura et al., 2010). Moreover, mice lacking the *Mitf* gene have white coats due to the absence of melanocytes (Steingrimsson et al., 2004). MITF is a transcription factor that regulates melanocyte development. *Mitf* was also reported as an important melanocyte survival factor in the cochlear environment, reinforcing the fact that NC are involved in the pathogenesis of TADS (Ni et al., 2013).

3.1.26. TP63-related disorders

In this section we will present a range of NCP that are caused by mutations in the same gene, the tumor protein *p63* (*TP63*) gene. TP63-related disorders comprise six overlapping diseases: AEC syndrome (which includes Rapp-Hodgkin syndrome), ADULT syndrome, EEC3 syndrome, Limb-mammary syndrome and SHFM4 syndrome. The *TP63* gene is a key regulator of ectodermal, orofacial and limb development. This protein, which acts by activating the transcription of specific target genes, is involved in metabolism, affecting cellular proliferation, energy metabolism, and tumor suppression activities (Candi et al., 2017). Multiple transcript variants of the *TP63* gene, produced by alternative splicing and the use of different promoters, are responsible for eliciting the mentioned functions of TP63. These transcripts encode six different isoforms, with the full length protein being 448 residues long (Sutton and van Bokhoven, 2015).

Orodental anomalies are often present in syndromes involving p63 mutations. These anomalies include ectodermal dysplasias (AEC syndrome, EEC3 syndrome, HEDs (Section 3.1.14) and SHFM4 syndrome, among others), abnormal tooth number (missing teeth) and shape (conical crown, taurodont molars-vertically enlarged pulp chamber at the expense of the roots), and a hardening of the enamel (enamel hypoplasia) (Laugel-Haushalter et al., 2012). With respect to their development, teeth have a dual origin (endodermal or ectodermal epithelium), with the oral ectoderm for the enamel organ (which makes up the normally visible part of the tooth, covering the crown), the derived ameloblasts synthesizing the enamel matrix, and the ectomesenchyme originating from the cephalic NCCs. The ectomesenchyme, which is the part in the center of a tooth made up of living connective tissue, forms the mesenchymal part of the tooth including pulp tissues, odontoblasts (part of the outer surface of the dental pulp) and the periodontium (the specialized tissues that both surround and support the teeth, maintaining them in the maxillary and mandibular bones). The interactions between the oral epithelium and the underlying NC derived mesenchyme are mediated by secreted signaling molecules from the major signaling families (FGF, TGF-β, WNT and Hh) (Klein et al., 2013). Next we will provide a detailed description of the different syndromes that are caused by a mutation in the *TP63* gene.

3.1.26.1. ADULT syndrome. The Acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome includes intensive freckling, frontal alopecia (a condition in which hair is lost from some or all areas of the body), lacrimal duct atresia (a condition in which an orifice or passage in the body is closed or absent), primary hypodontia, loss of permanent teeth, ectrodactyly (deficiency or absence of one or more central digits of the hand or foot), syndactyly (a condition wherein two or more digits are fused together), finger- and toenail dysplasia (presence of cells of an abnormal type within a tissue), and hypoplastic breasts and nipples (Otsuki et al., 2016; Slavotinek et al., 2005). Mutational analysis of the *p63* gene showed heterozygous mutations N6H, G173D, R337G, R337Q in patients with the ADULT syndrome (Sutton and van Bokhoven, 2015).

3.1.26.2. AEC syndrome. The **A**nkyloblepharon-**e**ctodermal defects-**c**left lip/palate (AEC) syndrome is a form of ectodermal dysplasia, a group of about 150 conditions characterized by the abnormal development of ectodermal tissues including the skin, hair, nails, teeth, and sweat glands. The most common features of the AEC syndrome are missing patches of skin, changes in skin coloring, malformed or missing teeth, and a reduced ability to sweat. Hearing loss is common, occurring in more than 90% of the children affected with this disease. Additional features of the AEC syndrome include small jaws, a narrow space between the upper lip and nose (philtrum), digestive problems, absent tear duct (lacrimal duct atresia) and limb abnormalities (syndactyly, camptodactyly –a medical condition that causes one or more fingers to be permanently bent- or ectrodactyly) (Barbaro et al., 2012; Gonzalez et al., 2017; Wang et al., 2009). The mouse mutant delta-N-p63-alpha (DNp63a) expresses the P63 protein that lacks its N-terminal domain, which acts in a dominant-negative

fashion. This mutant mimics the phenotype of severe skin erosions, delayed terminal differentiation, and basement membrane abnormalities (Koster et al., 2009). In particular, mutation analysis of the *p63* gene in this syndrome showed the mutations Q9X*, Q11X*, Q16X*, I549T, S580F, S580P, S580Y and 1976DelA in patients (Sutton and van Bokhoven, 2015).

3.1.26.3. EEC3 syndrome. This form of **E**ctrodactyly-**e**ctodermal dysplasia-**c**left lip/palate syndrome-3 is termed the EEC3 syndrome. Besides the three main cardinal signs of the syndrome, there are abnormalities in several ectodermal structures including skin (hypopigmented and dry skin, skin atrophy hyperkeratosis -thickening of the outer layer of the skin), hair (fine and sparse hair and eyebrows), teeth (small, absent or dysplastic teeth), nails (nail dystrophy) and exocrine glands (reduction/absence of sweat, sebaceous and salivary glands). Other associated clinical features include abnormalities such as choanal atresia, absent lacrimal puncta, corneal ulcerations and gland abnormalities (e.g. hypoplastic thymus, hypopituitarism, defective growth) (Phan et al., 2016). Mutation analysis of the *p63* gene showed the heterozygous mutations R243L, R243Q or R243W; R266Q, R318C, R318H, R318Q, R319C, R319H, R319S, R343P, R343Q, R343W, R325G in the patients (Ehrlich et al., 2008; Sutton and van Bokhoven, 2015).

3.1.26.4. Limb-Mammary syndrome (LMS). LMS, like EEC3, AEC and ADULT, is caused by mutations in the *p63* gene. The symptoms include lacrimal duct atresia, nail dysplasia, hypohidrosis (diminished sweating in response to appropriate stimuli), hypodontia, and cleft palate with or without bifid uvula (a piece of tissue hanging down over the tongue toward the back of the mouth, a part of the soft palate). The ELA syndrome is an acronym of the EEC/limb–mammary syndrome/ADULT syndromes, which are united into a single entity (Prontera et al., 2011; Yin et al., 2015). Mutation analysis of the *p63* gene in the LMS syndrome showed the heterozygous mutations G115W, S129W, 169DelTT, 1860Del AA, K671X in the patients (Sutton and van Bokhoven, 2015). A recent study of differential expression of genes in EEC and LMS syndromes showed that peripheral blood cytokines may represent promising clinical biomarkers for the diagnosis of these syndromes (Yin et al., 2015).

3.1.26.5. Split-hand/split-foot malformation type 4 (SHFM4). SHFM4 is a limb malformation syndrome involving the central rays of the autopod (the most distal part of the tetrapod limb) and is characterized by syndactyly, median clefts of the hands and feet, and aplasia (failure of an organ or tissue to develop normally) and/or hypoplasia of the phalanges, metacarpals, and metatarsals. Some patients with SHFM4 have been found to have mental retardation, ectodermal alterations, and orofacial clefting (Elliott and Evans, 2006; Sivasankaran et al., 2016; Wei et al., 2012). Mutation analysis of the *p63* gene showed the heterozygous mutations R97C#, K232E, R319C, R319H, Q673X, 678X in patients with this disease (Sutton and van Bokhoven, 2015).

3.1.27. Treacher collins syndrome (TCS)

TCS or Mandibulofacial Dysostosis is a congenital craniofacial disorder characterized by downward-sloping palpebral fissures, hypoplasia of the mandible, a zygomatic complex, cleft palate, coloboma of the lower eyelids and abnormalities of the external ears and middle ear ossicles that result in conductive hearing loss (Dixon, 1996). Orofacial clefting is the result of improper outgrowth or fusion of the facial prominences and/or palatal shelves, which are NC derivatives from the maxilla of the first pharyngeal arch (Sakai et al., 2016).

The mutations responsible for causing TCS are located in the genes *TCOF1*, *POLR1C* and *POLR1D*. The alteration in the expression of the *TCOF1* and *POLR1D* genes cause the disease in an autosomal dominant manner, whereas the mutation in *POLR1C* is autosomal recessive (Dauwerse et al., 2011). These genes encode three proteins that are involved in the process of ribosome biogenesis. In particular, human *TCOF1* encodes the nucleolar phosphoprotein Treacle which interacts with other proteins to stimulate transcription of ribosomal DNA (Valdez et al., 2004). *Tcof1* is expressed broadly throughout the mouse embryo, with particularly strong activity in the NC-derived frontonasal and pharyngeal arch mesenchyme. Moreover, *Tcof1* heterozygous mice (*Tcof1*$^{+/-}$) display severe craniofacial defects that mimic the symptoms of TCS in humans (Dixon et al., 2006; Jones et al., 2008). Analysis of a *Tcof1*$^{+/-}$ mouse model of TCS determined that this disorder arises through extensive apoptosis of neuroepithelial cells (Sakai and Trainor, 2016), and a deficiency in the generation and proliferation of NCCs, which are the precursors of the craniofacial skeleton (Fig. 1).

Deficient ribosome biogenesis can cause nucleolar stress activation of *p53* and, consistent with this mechanism, stabilization of the *p53* protein and activation of *p53*-responsive pro-apoptotic genes (self-destruction) are observed in the neuroepithelium and facial bones of *Tcof1* $^{+/-}$ embryos (Sakai et al., 2016). Based on this evidence, TCS has also been included in a disease subclass called ribosomopathies (Narla and Ebert, 2010). Additionally, research in the zebrafish model organism was essential to increase understanding of the molecular basis of TCS (Weiner et al., 2012). Moreover, this model was particularly useful to successfully reproduce the pathology and to find potential target genes that participate in the development of the TCS phenotype (Weiner et al., 2012). These results highlight the importance of animal models in the study of NCP and in the development of future therapeutic options.

3.1.28. Richo-Dento-Osseous (TDO) syndrome

The TDO syndrome is characterized by an inherited defect in tissues arising from an abnormal epithelial-mesenchymal interaction. This syndrome affects primarily the hair, teeth and bones from which the condition derives its name (Jain et al., 2017). Mutations in the *DLX3* homeodomain transcription factor gene are associated with the TDO syndrome. Five mutations in *DLX3* have been associated with this syndrome, all of them with an autosomal dominant mode of inheritance. The clinical observations associated with the different mutations in *DLX3* reported so far are associated with highly penetrant tooth defects, and with more variable defects in hair and bone (Nieminen et al., 2011; Wright et al., 2008). In mouse, the specific NC deletion of *Dlx3* in odontoblast differentiation produces a downregulation of the expression of the dentin sialophosphoprotein *Dspp*, and ultimately a defective dentin deposition/mineralization (Duverger et al., 2012).

3.1.29. Waardenburg syndrome (WS) types I and III

WS is characterized by depigmented (hypopigmented) cutaneous patches (partial albinism), blue eyes, hearing loss and rarely by spina bifida (Banerjee, 1986). There are four recognized types of WS, which are distinguished by their physical characteristics and by their different genetic cause. WS types I and II have very similar features, although people with type I almost always have eyes that appear widely spaced while those with type II do not. In addition, hearing loss occurs more often in people with type II than in those with type I. Type III (sometimes called Klein-WS) includes abnormalities of the arms and hands in addition to hearing loss and changes in pigmentation. Type IV (also known as Waardenburg-Shah syndrome) is characterized by signs and symptoms of both WS and HSCR (Section 3.7.1) disease (Pingault et al., 2013). The genes responsible for the pathogenesis of the different classes of this syndrome are *PAX3, SNAI2, EDN3, EDNRB* and *SOX10* . Types I and III are caused by mutations in the *PAX3* and *SOX10* genes. Another gene that is important for the establishment of the WS

is *MITF*.

All the typical craniofacial features observed in WS type I can be explained by NC defects: a) hair hypopigmentation is due to the lack of hair follicle melanocytes in the distribution of prosencephalic NC; b) the tubular nose owing to hypoplasia of the lateral portions of the nose (alae nasi) with a hyperplastic (with increased tissue amount), broad, and high nasal bridge that gives the pleasant feline facies are present in nearly all patients with WS type I and suggest a defect in prosencephalic NC; c) finally, the neurosensory hearing loss is the result of lack of melanocytes in the cochlear stria vascularis, another NC derivative (Sandell et al., 2014; Sarnat and Flores-Sarnat, 2005). WS type IV is a different disease, characterized by congenital hypomyelinating neuropathy, and defects in Schwann cell function, which is another NC derivative (Donkervoort et al., 2017).

A molecular cause for the pigmentation phenotype in the different WS has been attributed to the role that *Pax3* exerts on the proliferation of melanocyte progenitor cells, and also to the role of *Mitf* in the survival of the committed melanoblasts (Hornyak et al., 2001). *Sox10* is another important player in this process that when deregulated can lead to this syndrome. More specifically, this transcription factor, which is important in the survival of mice migratory melanocytes, is expressed in humans in the migratory enteric NCCs (Touraine et al., 2000). Recently, a novel mouse model has been identified that possesses a mutation in the *Pax3* gene. This model will provide several useful tools for analyzing the biological processes involving *Pax3* function, and particularly the development and migration of NCCs and melanocytes (Ohnishi et al., 2017).

3.2. Neurocristopathies originated from cardiac NCC

3.2.1. Heterotaxy syndrome (HTX)

HTX, a condition in which the internal organs are abnormally arranged in the chest and abdomen, consist of a constellation of defects defined primarily by abnormal lateralization of thoracic and abdominal organs across the left–right (L-R) axis of the body. HTX alters the structure of the heart, including the attachment of the large blood vessels that carry blood to and from the rest of the body. This condition can also affect the lungs, liver, spleen, intestines, and other organs (Grimes et al., 2016). Its etiology lies in the failure to establish a normal organ asymmetry along the left-right axis. In vertebrates, the establishment of L-R asymmetry occurs during early embryonic development and involves complex signaling transduction cascades that involve the NODAL protein (Collignon et al., 1996; Zhou et al., 1993; Zhu et al., 2006). Whereas the activation of the *NODAL* gene in the left lateral plate mesoderm results in a normal positioning of internal organs, an absent or abnormal activation of NODAL can produce heterotaxy (Sutherland and Ware, 2009). Approximately 80% of individuals affected with heterotaxy have complex congenital heart disease (CHD) (Peeters and Devriendt, 2006).

The genetic causes of laterality defects in humans are highly heterogeneous. Heterotaxy with complex CHD can be caused by defects in a number of genes including *ZIC3* (Gebbia et al., 1997; Megarbane et al., 2000), *LEFTYA* (Kosaki et al., 1999a), *CRYPTIC* (Bamford et al., 2000), *ACVR2B* (Kosaki et al., 1999b), *MMP21* (Guimier et al., 2015; Perles et al., 2015), and *PKD1L1* (Vetrini et al., 2016). These genes encode components or modifiers of the nodal signaling, which plays an important role in mesoderm and endoderm formation and subsequent organization of L-R axial structures in different animal models (Kamura et al., 2011; Levin, 2005; Vogel et al., 2010). Animal experiments have demonstrated that the ablation of NC in chick embryos may results in TGA (transposition of great arteries), which mimics in part the heterotaxy phenotype (Calmont et al., 2009; Manner et al., 1998). TGA is rarely associated with syndromes such as Noonan (Section 3.8.5), CHARGE (Section 3.4.3), 22q11.2 deletion syndrome (Section 3.4.1, (Marble et al., 1998; Melchionda et al., 1995; Van Mierop and Kutsche, 1986), Williams syndromes (Barnett et al., 2012; Makeyev and Bayarsaihan, 2013) and Turner syndrome (Richards and Garg, 2010). Further studies in animal models will be needed to elucidate the physiological characteristics of heterotaxy.

3.3. Neurocristopathies originated from Trunk NCC

3.3.1. Congenital central hypoventilation syndrome (CCHS)

This disorder is characterized by a dysregulation in the autonomic nervous system, a shallow breathing and the development of cancer such as neuroblastoma (Section 3.3.3, (Amiel et al., 2003)). The hallmark of CCHS is the mutation in the gene *PHOX2B* which is normally expressed in the central nervous system, PNS and in the NCC of the gut (Pattyn et al., 1999). *PHOX2B* alterations are single gene mutations that are either classified as PARM (**P**oly**A**lanine **R**epeat expansion **M**utations) or Non-PARM (NPARM) mutations. PARM mutations are extension mutations (patient gets extra poly-alanine codons) while NPARM can be produced by base substitution (missense and nonsense) or deletion mutations (Di Zanni et al., 2017).

Research in the *Phox2b*$^{-/-}$ mouse mutant has shown that neither neurons nor glia developed in the pancreas. It has also been shown that in this model *Nkx2.2* expression was markedly upregulated in the epithelium and proliferation of insulin-expressing cells and insulin-positive area were increased (Hennewig et al., 2008). This observation was also made in patients presenting the combination of congenital hyperinsulinism and CCHS (Hennewig et al., 2008; Hopkins et al., 2017). During pancreatic mouse development, *Phox2b* and *Nkx2.2* genes form a non-cell-autonomous feedback loop that links the NCC to the development of the pancreatic epithelium (Nekrep et al., 2008; Plank et al., 2011). In particular, adult islets of Langerhans are innervated by sympathetic, parasympathetic, and nociceptive neurons, and are encapsulated by a sheath of peri-islet Schwann cells, all derived from NC progenitors (Reinert et al., 2014; Shimada et al., 2012). *RET* expression, which is essential during development of the intestinal innervation, is orchestrated by different transcription factors such as PHOX2A, PHOX2B, MASH1, HOX11L1, SOX10, EDN3, TRK/BDNF and PAX3 (Bolk et al., 1996; Mulligan, 2014). These mutational analyses indicate an overlap in gene mutation between CCHS and Hirschsprung's disease (Section 3.7.1). Moreover, this illustrates the reiterated use of the same signaling molecules in multiple aspects of NCC development and the diverse variety of NCP that arise from similar perturbation in gene function. To corroborate this evidence, previous research has shown that up to 50% of CCHS patients will have Hirschsprung's disease, and approximately 20% of CCHS/Hirschsprung patients will also have neuroblastoma (Section 3.3.3, (Croaker et al., 1998).

3.3.2. Familial dysautonomia (FD)

FD is a progressive peripheral neuropathy that is characterized by tachycardia (a heart rate that exceeds the normal resting rate), blood pressure lability, autonomic vomiting and decreased pain and temperature sensation (Jackson et al., 2014; Kim et al., 2014; Zeltner et al., 2016). As described previously, the vertebrate PNS derives primarily from the NC, which among other derivatives gives rise to the dorsal root and sympathetic ganglia. This particular disease arises from a failure in the process of sensory neurogenesis.

FD is caused by mutations in the *IKBKAP*, *IKBKB* and *ELP1* genes. *IKBKAP* plays a key role in the development of sympathetic and sensory neurons by affecting the function of NC-derived DRG progenitors, and in particular in the proliferation and survival of Pax3 + cells but not the migration of trunk NCC (George et al., 2013). Mechanistic insights for this disease have been put forward by studies in the mouse embryo. Conditional mutant studies in mouse have shown that the Elp1 protein is required for the survival of post-migratory sensory and sympathetic neurons originated from trunk NCC (Jackson et al., 2013). Moreover, experiments in zebrafish have shown that Ikbkap knockdown results in aganglionosis and a reduced number of neurons in the

enteric nervous system (Cheng et al., 2015). All together, these results have proven that FD is not caused by impaired neuronal migration but by neuron death caused by the absence of the IKBKAP and ELP1 proteins in the NC.

3.3.3. Neuroblastoma (NB)

NB is a neuroendocrine tumor that arises from the embryonic sympathoadrenal lineage of the NC. It is associated with an excessive production of catecholamines by the adrenal medulla, which is derived from the NC and is the most common cancer in infancy (Caputi et al., 2017). This neuroendocrine lineage derives from the NCCs that migrate away from the neural tube early during embryogenesis along the ventrolateral pathway (Betters et al., 2010; Vega-Lopez et al., 2017). Different gene modifications characterize this cancer, including amplification of *MYCN*, mutations in *ALK* and segmental chromosomal alterations (Matthay et al., 2016; Schramm et al., 2015). The *MYCN* oncogene plays a major role in NB tumorigenesis and defines an aggressive subset of tumors. Well-defined transgenic mouse models confirm that deregulated *MYCN* expression targeted to the NC is sufficient to drive tumorigenesis with high penetrance (Hansford et al., 2004; Weiss et al., 1997). Additionally, activating mutations of *ALK* (Anaplastic Lymphoma Kinase) are also implicated as oncogenic drivers of NB (Ardini et al., 2010). Recent studies performed in the chick embryo have linked *ALK* to the development of sympathetic neurons and to the survival of migratory NCC and find it essential for neurogenesis (Reiff et al., 2011).

Approximately 4% of sporadic NB cases have been associated with a germline mutation of the paired-like homeobox 2b (*PHOX2B*) gene, an important regulator of neurogenesis (Mosse et al., 2004; Trochet et al., 2004). This mutation results in abnormal NCC development and in the emergence of NB, CCHS (Section 3.3.1), and Hirschsprung disease (Section 3.7.1, (Louis and Shohet, 2015). Recently, *PHOX2B* loss-of-function mutations have been shown to block NB differentiation by preventing the differentiation of immature sympathetic neurons (Wang et al., 2014b). Epigenetic changes and aberrant splicing in transcription factors and key signaling proteins (*DNMT3B*, *ALK*, *CHD5*, *DOCK8* and *PTPN14*) have also been described as oncogenic pathways that promote NB (Ostler et al., 2012; Schramm et al., 2015). Finally, the above advances in NB research have allowed the development of therapeutic strategies for this disease. These therapeutic solutions include intensive chemotherapy, surgery, radiation therapy, and myeloablative chemotherapy with autologous stem cell transplant (Applebaum et al., 2017). Recently, inhibition of the Histone deacetylase *HDAC8* has been shown to reduce NB growth in vitro and in vivo, thus becoming a potential treatment against this disease (Rettig et al., 2015). In addition, *ALK* kinase has become amenable to drug targeting, since potent *ALK* inhibitors are already in clinical trials for the *ALK*-mutant NB (Louis and Shohet, 2015).

3.3.4. Pheochromocytomas (PCC)

PCC and paragangliomas (PGL) are neuroendocrine tumors arising from chromaffin cells, which originate from the NC. These tumors arise in the adrenal medulla in the case of PCC and in the paraxial autonomic ganglia, as it the case for PGL (Maguire et al., 2015; Martucci and Pacak, 2014). PGLs arising from these parasympathetic sites account for up to 70% of extra-adrenal paragangliomas, the most common site of origin being the carotid body (CB). This tissue, a neural-crest-derived paired organ, is located in the carotid bifurcation and acts as the main arterial chemoreceptor in mammals facilitating reflex hyperventilation during hypoxia (Annese et al., 2017; Wieneke and Smith, 2009).

The above tumors can occur sporadically or within familial syndromes. The major hereditary syndromes associated with PCC/PGL are multiple endocrine neoplasia types 2A and 2B (MEN2A/2B), the Von Hippel Lindau syndrome (Section 3.3.5), neurofibromatosis type 1 (Section 3.5.2) and familial PCC/PGL syndrome. MEN2A/2B is associated with underlying mutations in the *RET* proto-oncogene. In particular, the RET protein is a receptor tyrosine kinase that regulates cellular proliferation and apoptosis (Karasek et al., 2013). On the other hand, the von Hippel-Lindau Syndrome (VHL) syndrome is characterized by mutations in the *VHL* gene (Latif et al., 1993), which regulates the activity of hypoxia-inducible factor alpha (HIFα) (Maxwell et al., 1999). The familial PCC/PGL syndromes are attributable to loss-of-function mutations in the succinate dehydrogenase (*SDH*) genes, including the four subunits of SDH (A-D) (Astuti et al., 2001; Baysal et al., 2000), and SDH assembly factor 2 (*SDHAF2*) (Hao et al., 2009). Because of its role as the mitochondrial complex II in both the Krebs cycle and the electron transport chain, *SDH* mutations severely disrupt cellular metabolism (Martucci and Pacak, 2014). In many cases the genetic basis of sporadic PCC/PCL is similar to hereditary PCC/PGL, with somatic mutations identified in genes associated with other hereditary syndromes of NC tumors. These genes include *RET, NF1, VHL, SDHA-D*, and *RAS* family members (Crona et al., 2013; Maguire et al., 2015; Welander et al., 2012).

3.3.5. von Hippel-Lindau syndrome (VHL)

VHL Syndrome is an autosomal dominant disorder with identical prevalence in both genders. VHL patients develop tumor from the vascular system (hemangioblastomas) of the central nervous system (CNS) and/or retina, endocrine neoplasia (abnormal tissue growth) of the adrenal gland (pheochromocytoma, Section 3.3.4), clear cell renal cell, carcinomas, low-grade adenocarcinomas (tumors formed from glandular structures in epithelial tissue) of the temporal bone, also known as Endolymphatic Sac Tumors (ELST), epididymal or broad ligament cystadenomas (benign cystic neoplasm), and/or pancreatic tumors (Maher, 2004). The VHL Syndrome is caused by germline mutations in the tumor suppressor gene *VHL* on chromosome 3p25 (222). VHL syndrome can occur with (type 2) or without (type1) pheochromocytomas (Nordstrom-O'Brien et al., 2010).

3.4. Neurocristopathies arising from cranial and cardiac NCC

3.4.1. 22q11.2 deletion syndrome

The 22q11.2 deletion syndrome (Velocardiofacial syndrome or DiGeorge syndrome) is a subset of conditions which include cardiac defects such as interrupted aortic arch (heart defects), an hypoplastic thymus, mild craniofacial defects, and parathyroid gland abnormalities, including hypothyroidism (Scuccimarri and Rodd, 1998). The name 22q11.2 stems from the fact that most patients have a “deletion or duplication” in the 11.2 region of the chromosome 22 which includes the location of the gene *TBX1* (Jerome and Papaioannou, 2001). The expression pattern of *Tbx1* in murine embryos suggests that it has a potential role in the early remodeling of the pharyngeal arch artery, and although not expressed by NCC, Tbx1 influences the expression of other genes implicated in NCC migration. In particular, this gene acts in NC development by controlling the expression of *Gbx2*, which ultimately disrupts the migration of the cardiac NCC, possibly through the downregulation of the Slit2 ligand (Calmont et al., 2009; Karpinski et al., 2014; Toritsuka et al., 2013). The use of a Tbx1 mutant mice has shown that β-catenin expression was increased when Tbx1 was inactivated, suggesting that there may be a negative feedback loop between canonical Wnt and Tbx1 in the anterior heart field to allow the formation of the cardiac outflow tract (Racedo et al., 2017). To sum up, the diseases described above arise from alterations in the interactions that occur during NCC migration. NCP arising from these defects involve several signaling pathways that act both in a cell-autonomous and in a non-cell autonomous manner. Future investigations will be essential for the development of potential therapeutic strategies relevant for the treatment of these disorders.

A hypothesis that could explain the 22q11.2 Deletion Syndrome phenotype and the Kallman syndrome (Section 3.1.9) phenotype in patients with CHARGE syndrome (Section 3.4.3) considers that the

mutation in *CHD7* (ATP-dependent chromatin remodeller chromodomain-helicase-DNA-binding protein 7) is likely to exert its effect in the common precursor NCC. A recent discovery showed that the *chd7* gene in *Xenopus* leads to a reduction in *sema3a* expression, one of the identified class 3 semaphorins, also involved in Kallman syndrome and in CHARGE syndrome (Payne et al., 2015).

3.4.2. Alagille syndrome

The Alagille syndrome (or Arteriohepatic Dysplasia) is characterized by defects in the liver, ears, eyes, kidneys, pancreas, heart, vascular system, face and skeleton. One of the most easily observed hallmarks of the Alagille syndrome is the posterior embryotoxon (an opaque ring in the cornea) which is an irregularity of Schwalbe's line (a peripheral line found on the interior surface of the cornea) (Emerick et al., 1999). The cardiac specific phenotypes of the Alagille syndrome include defects in the heart outflow tract and aortic valve hyperplasticity, tetralogy of Fallot and valve calcification, most of them deriving from abnormal NC migration and differentiation (MacGrogan et al., 2016). Mechanistically, the Alagille syndrome is caused by a haploinsufficiency for the *Jag1* gene and is considered to be a Notch loss-of-function phenotype (Alagille et al., 1975; Li et al., 1997). Notch have been implicated in the developmental differentiation of cardiac NCC (Majewski et al., 2011; Manderfield et al., 2012; Masek and Andersson, 2017). A specific deletion of the *Jag1* in cardiac NCC using the *Pax3-Cre* conditional knockout method revealed that *Jag1* plays a key role in the induction of cardiac NC-derived vascular smooth muscle cell (VSMC) differentiation (Humphreys et al., 2012; Manderfield et al., 2012). In addition, inactivation of *Jag1* selectively in cells of the cranial NC phenocopies the abnormalities of the craniofacial skeleton that characterize the Alagille syndrome, confirming its association with impaired Notch signaling (Humphreys et al., 2012). Altogether, these observations support the classification of this disease within the NCP scope.

3.4.3. CHARGE syndrome

CHARGE syndrome is a multiple anomaly disorder defined by ocular coloboma, heart defects (conotruncal lesions), choanal atresia, retarded growth and development, urogenital and ear abnormalities (produced by a malformation of the cranial nerve VIII and ossicles) an cleft palate. Craniofacial dysmorphisms are also a common feature in CHARGE syndrome, and include square-shaped facies, facial asymmetry, external ear anomalies, cleft lip and/or palate, cranial nerve palsies (paralysis), and torticollis. It has been shown that CHARGE syndrome results from the abnormal development of different tissues which derive from the NC (Sanlaville and Verloes, 2007; Williams, 2005). With respect to the choanal atresia phenotype, it has been speculated that its specific etiology is the misdirection of NCC migration. This theory is supported by the fact that the Bamforth-Lazarus Syndrome (Section 3.1.4), *TP63*-related disorders (3.1.26), Treacher Collins (Section 3.1.27) and 22q11.2 Deletion Syndrome (Section 3.4.1) exhibit a high rate of choanal atresia (Nanda and Assa'ad, 2014; Wieczorek et al., 2009).

CHARGE syndrome is caused by mutations in the *CHD7* gene that encodes the chromodomain helicase DNA binding protein 7, a chromatin remodeling protein. In humans, mouse, chick, *Xenopus* and zebrafish embryos, the *CHD7* gene is essential for the proper organization of NC-derived craniofacial cartilage and trachea structures (Bajpai et al., 2010; Balow et al., 2013; Schulz et al., 2014; Sperry et al., 2014). In particular, *Xenopus chd7* is essential for the activation of the NC transcriptional circuitry, including *sox9, twist and slug* (*snai2*) (Bajpai et al., 2010). Moreover, the role of CHD7 in the onset of this disease has been verified by modeling CHARGE syndrome from patient-induced pluripotent stem cells (patient-iPSCs). These results stress the fact that CHARGE syndrome patients exhibit defects in NC migration, and provide the first application of patient-derived iPSCs in modeling NC disorders (Okuno et al., 2017).

CHARGE syndrome is also considered to be a ribosomopathy, since Chd7 has been shown to play a role in ribosome biogenesis. Studies performed in human and mouse cell lines have shown that Chd7 binds to rDNA and enhances rRNA expression (Van Nostrand and Attardi, 2014; Zentner et al., 2010). Moreover, Chd7 loss-of-function induces *p53* expression in embryos, triggering cell-cycle arrest and apoptosis during development to cause CHARGE phenotypes. The importance of this protein in the origin of the CHARGE syndrome has also been corroborated in other model organisms such as the zebrafish model (Patten et al., 2012; Schulz et al., 2014).

3.4.4. Hajdu-Cheney syndrome (HCS)

This syndrome is characterized by osteoporosis and progressive focal bone destruction, renal cyst formation, heart defects, defective craniofacial development and hearing deficits. HCS is driven by the production of a stabilized NOTCH2 protein lacking a functional PEST degradation domain (Majewski et al., 2011). This is caused by a gain-of-function mutation in the *NOTCH2* gene (Canalis and Zanotti, 2014). Model organisms studies have shed light on the underlying mechanisms driving the appearance of this disease and the multitude of organs that are affected by the mutation in the *NOTCH2* gene (reviewed in (Masek and Andersson, 2017). In particular, Notch signaling has been implicated in the differentiation of cardiac NCC (Majewski et al., 2011; Manderfield et al., 2012; Masek and Andersson, 2017). A perturbation of Notch activity in the developing cranial skeleton or its systemic inactivation in adult mice leads to craniofacial abnormalities or enamel defects, respectively (Humphreys et al., 2012; Jheon et al., 2016).

3.4.5. Mowat-Wilson syndrome (MWS)

The MWS is characterized by microcephaly, mental retardation, distinct facial phenotype with or without HSCR disease (Section 3.7.1), corpus callosum agenesis, epilepsy, congenital heart defects, and genitourinary anomalies (Teraishi et al., 2017). Approximately 43% of patients diagnosed with MWS also have HSCR (Coyle and Puri, 2015). The MWS is produced by a mutation in the *SIP1* gene (also named *ZFHX1B* or *ZEB2*). In human embryos, the expression pattern of this gene is consistent with a role in NC development. Its transcripts are detected in the neural tube, pharyngeal arch mesenchyme, cranial ganglia, dorsal root ganglia, sympathetic ganglia and in the enteric nervous system (ENS) (Bassez et al., 2004; Ghoumid et al., 2013). The *SIP1* gene encodes the SMAD-interacting protein-1 (SMADIP1 or SIP1), a transcriptional co-repressor involved in the TGF-b signaling pathway. Specifically, SMAD proteins play an important role in BMP signal transduction. In this context, BMP signaling is essential during early NCC induction and migration, and in later steps of NC development by promoting autonomic neuronal differentiation (Chang and Harland, 2007; Liem et al., 1995; Mayor and Aybar, 2001). SIP1 family members have been involved in inducing the epithelial-to-mesenchymal transition (EMT), a process that is essential for NCC migration. Therefore, embryos harboring homozygous deletions of the *SIP1* gene exhibit compromised development of the peripheral nervous system as well as craniofacial tissue, heart and gastrointestinal malformations (Van de Putte et al., 2007; Wu et al., 2016). Additionally, a study in *Xenopus* animal caps has shed light on the intrinsic molecular mechanism of MWS development (Verstappen et al., 2008). They showed that an aberrant form of the Sip1 protein is unable to recruit NuRD subunits and therefore displays reduced transcriptional repression activity on the *xbmp4* gene promoter, a target of the *sip1* gene. Despite these great advances, extensive research is required to reach an understanding of the molecular mechanisms that will allow the development of successful therapeutic strategies aimed at treating this disease.

3.4.6. Peters anomaly (PA)

PA is a congenital condition characterized by central corneal opacities and dysgenesis of the anterior eye segment (corneal posterior

stroma, endothelium and Descemet's membrane). Peters anomaly has been subdivided into PA type I, which is characterized by a central corneal opacity with iridocorneal adhesions, and PA type II, characterized by a central corneal opacity with cataracts or corneal lenticular adhesions. Additionally, another form of this disease is the Peters-plus syndrome involving PA, featuring congenital cardiac defects, craniofacial dysplasia, cleft palate, abnormal ears, mental retardation and skeletal dysmorphologies (Bhandari et al., 2011).

The corneal endothelial layer is derived from NCC and is absent in PA, probably by a defective NC migration that precludes NCCs from reaching the central cornea (Harissi-Dagher and Colby, 2008; Kivlin et al., 1986; Shabeeb et al., 2017). The systemic anomalies that occur in PA include congenital cardiovascular disease, cleft palate and craniofacial anomalies (Maillette de Buy Wenniger-Prick and Hennekam, 2002; Ohkawa et al., 2003).

Mutations in *PAX6*, *PITX2*, *FOXE3* and *FOXC1* genes have been found to be responsible for PA (Bhandari et al., 2011; Dahl et al., 1997; Iseri et al., 2009). In addition, Peters-plus syndrome is produced by mutations in *B3GLCT* (previously *B3GALTL*), which encodes a β1,3-glucosyltransferase, and is thus a congenital glycosylation disorder (Lesnik Oberstein et al., 2006; Weh et al., 2014). Recently, it has been shown that *Adamts9*-null mice are models of PA, and that Adamts9 modification by B3glct is required for its secretion and proper functioning (Dubail et al., 2016).

3.5. Neurocristopathies arising from Cranial and Trunk NCC

3.5.1. Achalasia-Addisonianism-Alacrima syndrome (AAA)

Triple A syndrome (or Allgrove syndrome) is an inherited condition characterized by three specific features: achalasia, Addison's disease, and alacrima. Achalasia is a disorder that affects the ability to move food through the esophagus. This is a genetic syndrome associated with a decreased number of enteric neurons/ganglia (Panza et al., 2012), also called hypoganglionosis, which presents similar clinical conditions to HSCR (Section 3.7.1). Enteric plexuses, in particular, are derived from colonization of the gut by enteric NCC–derived cells. Addison's disease, on the other hand, is a rare autosomal recessive disease characterized by adrenocorticotropic hormone resistance, which predisposes individuals with this syndrome to severe (lethal) hypoglycemic episodes. This disease is derived from the NC as the adrenal medulla (of the adrenal gland) is derived from NCCs. Finally, alacrima is produced by a reduced ability to secrete tears. Lacrimal glands arise from the NC (de la Cuadra-Blanco et al., 2003; Garg and Zhang, 2017; Williams and Bohnsack, 2015) under the control of FGF signaling. This syndrome is frequently associated with progressive neurologic disease, including pupil and cranial nerve abnormalities, optic atrophy, autonomic neuropathy and upper and lower motor neuron signs. Dermatologic abnormalities have also been reported (Gershon and Ratcliffe, 2004). Etiologically, triple-A syndrome is caused by mutations in the *AAAS* gene, which encodes a WD-repeat family regulatory protein (547 aa) termed ALADIN (Tullio-Pelet et al., 2000). ALADIN has an important role in nucleocytoplasmic transport as it is part of the nuclear pore complex (Cronshaw and Matunis, 2003). Recent studies have shown that ALADIN is involved in the oxidative stress response leading to alteration in steroidogenesis in human adrenocortical cells (Jühlen et al., 2015), which sheds light on the mechanism causing the variable symptoms observed in this disease.

3.5.2. Neurofibromatosis I (NF1)

NF1 (Recklinghausen disease or *café-au-lait* spots) is a condition characterized by changes in skin coloring (pigmentation). Individuals with this disorder have increased susceptibility to the development of benign or malignant tumors along nerves in the skin, brain, and other parts of the body. The most common malignancies seen in individuals with NF1 involve defects in the development of NC-derived chromaffin cells of the adrenal medulla, astrocytes and myeloid cells (Ratner and Miller, 2015). NF1 is caused by germline mutations in the *NF1* gene (Wallace et al., 1990), which encodes a guanosine triphosphatase–activating protein involved in multiple signaling cascades that are important for cell growth and differentiation. The molecular cloning of the *NF1* gene led to the identification of biallelic NF1 mutations in patient-derived tumors, which in turn led to the classification of *NF1* as a tumor suppressor gene (Cawthon et al., 1990; Wallace et al., 1990). The *NF1* gene in particular codes for the protein neurofibromin, which contains a GTPase activating protein (GAP)-related domain (NFI-GRD) and functions as a negative regulator of small G proteins, including Ras (Ballester et al., 1990; Martin et al., 1990; Xu et al., 1990). The hyperactivation of Ras that results from the loss of neurofibromin is thought to contribute to the various types of lesions that are prevalent in NF1 (Cichowski et al., 2003; The et al., 1993).

Some features support the hypothesis that the pathogenesis of NF1 is indeed a result of defective NC development. First, the *café-au-lait* and depigmented spots are caused by abnormal differentiation of melanocytes derived from rhombencephalic NCCs. Second, neurofibromas and schwannomas of peripheral nerves, including small cutaneous and subcutaneous nerves, are benign nerve sheath growth disorders of NCC origin. Third, an increased incidence of hypertelorism is found in patients with NF1, a minor dysmorphism indicating involvement of prosencephalic NCC (Cung et al., 2015; Wolters et al., 1986). Finally, the meningiomas over the cerebral convexities and nerve sheath tumors can be directly attributed to a defective NC formation, with the *NF1* gene also increasing the predisposition of patients to suffer from different neoplasias (Sarnat and Flores-Sarnat, 2005).

3.6. Neurocristopathies arising from cardiac and trunk NCC

3.6.1. Giant Congenital Melanocytic Nevi (GCMN)

GCMN (also called dark hairy nevus syndrome, congenital melanocytic hairy nevi, giant hairy nevus, garment hairy pigmented nevus, nevomelanocytic nevus, melanocytic nevus, and Becker hairy nevus) is a skin condition characterized by an abnormally dark, noncancerous skin patch (nevus). It is present from birth (congenital) or is noticeable soon after birth (Lucia and Salvador , 2016). Individuals with GCMN have an increased risk of developing an aggressive form of cancer called melanoma. Patients with GCMN also tend to have a characteristic facial appearance, including wide or prominent forehead, periorbital fullness, small short nose with narrow nasal bridge, round face, full cheeks, prominent premaxilla, and everted lower lip (Kinsler et al., 2012, 2008).

As with other primary neurocutaneous syndromes, all forms of epidermal nevus syndromes fall into the category of NCP because most of the affected cells arise from the NC and dermal appendages such as cutaneous nerves, melanocytes, adipocytes, elements of eccrine or sweat glands and apocrine or sebaceous glands, and cutaneous blood vessels (Flores-Sarnat, 2013; Sarnat and Flores-Sarnat, 2005).

In severe clinical phenotypes involving the skin, somatic mosaicism for genes is lethal in the germline and has recently been found to be the cause of several conditions like GCMN. Somatic oncogenic missense mutations on the *NRAS* and *BRAF* genes were observed in patients with GCMN. These mutations result in constitutive activation of both genes. It has been suggested that the mutation probably occurs in the developing NC or neuroectoderm (Kinsler et al., 2013). Additionally, perturbations in mouse migration, proliferation and differentiation of NC-derived melanoblasts may be linked to the *C-met* proto-oncogene, which controls the expression of the tyrosine kinase receptor *Met* (Kos et al., 1999).

3.7. Neurocristopathies arising from cardiac and sacral NCC

3.7.1. Hirschsprung disease (HSCR)

HSCR is a developmental disorder characterized by the absence of enteric neurons of the enteric nervous system (ENS) in the myenteric and submucosal plexuses of the gut (megacolon). HSCR is caused by a failure of enteric NCCs to colonize different portions of the distal intestine. The male to female ratio of this disease is 3.3:1 (Bradnock et al., 2017). HSCR also occurs as a feature of several syndromes including CCHS (Section 3.3.1), Mowat-Wilson Syndrome (Section 3.4.5), Triple A syndrome (Section 3.5.1), Waardenburg Syndrome (Sections 3.1.29 and 3.7.2) and also, in rare cases, OAVS (Section 3.1.22).

Mutations in different genes have been associated with the onset of this disease, which includes *RET, EDNRB, EDN3, PHOX2B* and *SOX10* (Heanue and Pachnis, 2007). The mechanistic interplay of these genes during NC development has been elucidated by recent efforts using the mouse embryo as a model system. These studies found that *Sox10* and *Phox2b* stimulate the expression of *Ret,* whereas the Edn3/Ednrb signaling pathway has been proved to have a defined genetic interaction with both *Sox10* and *Ret* (Carrasquillo et al., 2002; Stanchina et al., 2010). HSCR-associated *RET* mutations seem to act mostly by a loss-of-function mechanism. The RET protein is crucial for the migration and differentiation of NCC-derived enteric neuron progenitors, which therefore affects the development of the ENS (Lake and Heuckeroth, 2013). Similarly, the Hedgehog and Notch signals have been implicated in mediating the proliferation and differentiation of enteric NCCs. A recent study showed that *PTCH1* (which encodes a receptor for the Hedgehog ligands) and *DLL3* (which encodes a receptor for Notch) play a key role in the induction of gliogenesis (Ngan et al., 2011). Recent studies have also established a novel HSCR model in chick embryo that allows the testing of non-genetic modifiers to alter the HSCR phenotype (Gasc et al., 2015). Therefore, these complex interactions stress the fact that HSCR is still an incompletely characterized disease which requires more in-depth studies to enable the development of effective therapies.

3.7.2. Waardenburg Syndrome type IV (WS4)

WS4 or Waardenburg-Shah syndrome is a rare NC disorder characterized by comorbidity (the presence of one or more additional diseases or disorders co-occurring with a primary disease or disorder) with Hirschsprung disease (Section 3.7.1). WS4 is a genetic condition that can cause hearing loss, changes in coloring (pigmentation) of the hair, skin, and eyes, and megacolon. This disorder is marked by an absence of neural ganglia in the distal colon, which causes functional intestinal obstruction. Mutations in three genes are known to be involved in this condition: *EDN3, EDNRB,* and *SOX10* (Wang et al., 2014a). The mouse model organism named Spot has been instrumental in defining the molecular mechanisms that govern the development of this disease, providing phenotypic confirmation that premature gliogenesis can be a cause of aganglionic megacolon in postnatal mice (Bergeron et al., 2016).

3.8. Neurocristopathies arising from cranial, cardiac and trunk NCC

3.8.1. Charcot-Marie-Tooth (CMT) and Deafness syndrome

CMT is the most common inherited neuropathy. CMT is a chronic demyelinating disease of the PNS that especially affects the peroneal nerve. CMT disconnects the brain and spinal cord from muscles and sensory cells. The majority of CMT syndromes are of demyelinating type (demyelinating CMT) caused by an alteration in Schwann cell development (Kitani-Morii et al., 2017).

The majority of the peripheral nervous system (PNS) components, including the glial cells, are derived from the NC. The NC-derived cells that align along outgrowing peripheral nerve bundles of motor and sensory neuron axons will give rise to myelinating and non-myelinating Schwann cells (Bhatheja and Field, 2006; Kidd et al., 2013; Mirsky et al., 2008). A recent global gene expression analysis of iPSC-derived NCC has shown that a glutathione-mediated detoxification pathway is involved in demyelinating CMT, while pathways involved in the production of reactive oxygen species were increased in demyelinating CMT (Kitani-Morii et al., 2017).

The many different types of CMT are distinguished by age of onset, inheritance pattern, severity, and whether or not they are linked to defects in axon or myelin development. These are called CMT1, CMT2, CMT4 and CMTX. Altogether, more than 30 genes have been implicated in Charcot-Marie-Tooth disease. With respect to the different CMT diseases, it has been established that CMT1 is caused by damage to the myelin sheath covering nerves, and that it is produced by mutations in the following genes: *PMP22* (CMT1A and CMT1E), *MPZ* (CMT1B), *LITAF* (CMT1C), *EGR2* (CMT1D), and *NEFL* (CMT1F). CMT2 is caused by direct damage to the nerve axon itself in contrast to CMT1, which results from damage to the myelin sheath insulating the axon. CMT2 can result from alterations in many genes, including *MFN2* and *KIF1B* (CMT2A); *RAB7A* (CMT2B); *LMNA* (CMT2B1); *TRPV4* (CMT2C); *BSCL2* and *GARS* (CMT2D); *NEFL* (CMT2E); *HSPB1* (CMT2F); *MPZ* (CMT2I and CMT2J); *GDAP1* (CMT2K); and *HSPB8* (CMT2L). CMT4 presents more severe symptoms than CMT1 or CMT2. In general, CMT4 is caused by defects in the myelin sheath that insulates the axon. Additionally, CMT4 is caused by mutations in the following genes: *GDAP1* (CMT4A), *MTMR2* (CMT4B1), *SBF2* (CMT4B2), *SH3TC2* (CMT4C), *NDRG1* (CMT4D), *EGR2* (CMT4E), *PRX* (CMT4F), *FGD4* (CMT4H), and *FIG. 4* (CMT4J). Finally, CMTX is caused by mutations in the gene for connexin 32 (*Cx32* in the X chromosome), which normally codes for a protein located in myelin, the insulating sheath that surrounds nerve fibers.

3.8.2. Diamond Blackfan anemia (DBA)

DBA is characterized by anemia, reticulocytopenia, macrocytosis, a reduction in the number of erythroid precursors, craniofacial and cardiac defects, cleft palate and microtia. A possible explanation for this complex array of symptoms is the consideration that NC participates in the development of different hematopoietic precursors, thereby producing anemia in the patient. Moreover, the migration of cranial NCCs is also affected in this condition, resulting in craniofacial, cleft palate, microtia, and the failure of cardiac structures. This disease, which is considered a ribosomopathy, is caused by mutations in at least 14 ribosomal proteins: *RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPL5, RPL11, RPL27, RPL35A, RPL27, TSR2, L5, L11* and *GATA1* (Lipton and Ellis, 2009).

Hematopoietic stem cells (HSC) and their lymphoid progenitors are supported by the adult bone marrow (BM) microenvironmental niches composed of various stromal cells, sympathetic non-myelinating glial Schwann cells and sympathetic nerve fibers. Since NCCs contribute to the development of all three, they are present in the human adult BM to generate or regulate HSC (Coste et al., 2017; Isern et al., 2014; Jiang et al., 2016). Additional research has also shown that Schwann cells invade the bone marrow and serve as a component of the hematopoietic stem cell niche (Yamazaki et al., 2011). Moreover, recent investigations have proven that erythropoietin production is originated in NCCs during primitive erythropoiesis (Suzuki et al., 2013).

Different studies in model organism have been carried out to understand the etiology of DBA. Knock-down and mutations of the *rpl11* (*Rpl11*) and *rps19* (*Rps19*) genes in zebrafish and mouse have produced reduced hemoglobinization, an increase in mean corpuscular volume (MCV), decreased RBC counts, a decrease in adult BM cellularity, and increased p53 activity (increased apoptosis), which suggests a reduction in the number hematopoietic stem cells (Jaako et al., 2012; Morgado-Palacin et al., 2015; Payne et al., 2012). Another intrinsic mechanism involved in the etiology of DBA could be a downregulation of the *SNAI2* gene. This was confirmed by the fact that *Snai2* deficient mice showed a white forehead blaze, patchy

depigmentation of the ventral body, tail and feet, macrocytic anemia and infertility, suggesting a potential role for Snai2 in melanocyte, germ cell and hematopoietic stem cell development (Pérez-Losada et al., 2002).

Additionally, experiments aimed at addressing a possible treatment for this disease have successfully rescued the phenotype by inhibiting the p53 protein (Jaako et al., 2011; Pérez-Losada et al., 2002; Song et al., 2014; Wan et al., 2016).

Recently, in a *Xenopus tropicalis* DBA model, it was shown that this disease is associated with ribosome production (Robson et al., 2016). In agreement with this, a previous work showed that L-leucine treatment is effective to treat anemia in some DBA patients, possibly by stimulating ribosome biogenesis (Pospisilova et al., 2007). More recently, bone marrow failure and severe anemia in Rps19-deficient mice were cured with enforced expression of RPS19 driven by the Elongation factor-1a short promoter (Debnath et al., 2017).

3.8.3. Piebaldism

Piebaldism is an autosomal dominant disorder characterized by the congenital absence of melanocytes in specific areas of the skin and hair that lack pigmentation due to mutations of the *KIT* and *SNAI2* genes (Giebel and Spritz, 1991; Sánchez-Martín et al., 2003), which affects the differentiation, migration and survival of melanoblasts from the NC (Agarwal and Ojha, 2012). Other congenital pigmentary disorders are the Waardenburg syndrome (Section 3.8.6), and the disorders of melanin synthesis in the OCA syndrome (Section 3.1.23).

As mentioned in the previous section, molecular analyses have suggested that *KIT* may act upstream of *SNAI2* (Pérez-Losada et al., 2002). With respect to model organism research, it has been found in mice that the *Kit* transcription factor is expressed in melanocyte precursors whereas the *Kitl* gene is expressed in the dorsal dermatome in the trunk NCC (Aoki et al., 2015; Keshet et al., 1991). Piebaldism occurring in domesticated animals will also serve as a model tool to unveil the molecular mechanisms of the human disease (Finch et al., 2017).

Recently, several therapeutic approaches have been used to treat Piebaldism. One of these treatments consists in autologous punch grafting for repigmentation, which has been performed in selected individuals (Lommerts et al., 2017). Another option is autologous cell suspension transplantation using a cell extraction device (Komen et al., 2015). Nevertheless, further molecular analyses are required to gain a better insight of the role of Kit signaling in the migration and differentiation of melanocytes to further develop better therapeutic strategies.

3.8.4. Melanoma

Melanoma is a cancer consisting of an alteration in melanocytes, which are pigment-producing cells derived from the embryonic NC lineage (Chance et al., 2015; Mort et al., 2015). Even though melanoma accounts for only 4% of all skin cancer incidences, this cancer is the most aggressive and malignant of all, producing 80% of all skin cancer deaths (Miller and Mihm, 2006). Melanoma is treatable and curable when it is localized and resected completely but remains largely incurable once it has spread, even when treated with new therapies. Recent advances in the chick model organism have provided alternatives to analyze the metastatic behavior of melanoma cells (Jayachandran et al., 2015). Moreover, melanophore infiltration behavior has been studied using *Xenopus laevis* embryos (Haynes-Gimore et al., 2015), a system that recapitulates many facets of mammalian tumorigenesis. Mutations in *CDKN2A*, *BRAF* and *NRAS* are common in melanoma (Ghosh and Chin, 2009), and somatic mutations have also been identified in genes encoding the transcriptional machinery that drives NC and melanocyte development (Mort et al., 2015) like the MAPK/MITF pathway (Cheli et al., 2010; Tsao et al., 2012) and SOX10 (Shakhova et al., 2012), which activate the transcription of *TYR*, *TRP1* and *TRP2*. Furthermore, *SOX10* silencing in human melanoma cells suppresses NC stem cell properties, counteracts proliferation and cell survival, and completely abolishes in vivo tumor formation. Thus, *SOX10* represents a promising target for the treatment of melanoma in human patients (Shakhova et al., 2012).

3.8.5. Noonan syndrome (NS)

The characteristic features of NS include brown skin spots called lentigines that are similar to freckles, heart defects, widely spaced eyes (ocular hypertelorism), a sunken chest (pectus excavatum) or protruding chest (pectus carinatum), and short stature. This syndrome is also called LEOPARD syndrome, the acronym referring to its major features: Lentigines, ECG conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness. Approximately half of all Noonan syndrome cases are caused by heterozygous mutations in *PTPN11*, a gene encoding the protein–tyrosine phosphatase SHP2 (Tartaglia et al., 2011). SHP2 positively regulates the RAS and mitogen-activated protein kinase (MAPK) signal transduction pathway. Mouse studies have shown that *Shp2* is important for the normal development of cardiac NCC. Ablation of *Ptpn11* specifically from the premigratory NCCs results initially in normal migration and proliferative patterns, but cardiac NCCs fail to enter the developing outflow tract. Embryos with this genotype display persistent truncus arteriosus, septal defects and abnormalities of the great vessels (Nakamura et al., 2009). A recent study identified a role for *Shp2* in NC specification and migration in zebrafish embryos expressing mRNA for NS alleles. *Shp2* was also shown to prevent *p53*-mediated apoptosis of NCC (Stewart et al., 2010). Other altered genes in this disease include *SOS1*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, *SHOC2*, *MEK1* and *CBL*, all of which affect RAS–MAPK signaling.

3.8.6. Waardenburg syndrome type 2 (WS2)

The Waardenburg syndrome is characterized by dystopia, sensorineural hearing loss and heterochromia iridum type II. This disease arises due to a mutation in the *MITF*, *SNAI2* and *SOX10* genes (Liu et al., 1995). In addition to melanocyte development, these genes are important for the development of nerve cells in the large intestine. Mutations in one of these genes result in hearing loss, changes in pigmentation, and intestinal problems related to Hirschsprung disease (Section 3.7.1). It has recently been found that a heterozygous missense variation in *EDNRB* is also an important cause of the development of WS2 that accounts for 6% of the cases (Issa et al., 2017; Kawasaki-Nishihara et al., 2011; Pla et al., 2005).

4. Novel causal mechanisms of neurocristopathies

In this section we will outline some diseases which, although not originally classified as NCP, we consider should be included among these pathologies on the basis of molecular and cell lineage analyses. With respect to this form of classification, we consider that many congenital and genetic diseases are the product of an abnormal development not only of the NC, but also of the surrounding tissues. Therefore, some diseases that at first glance may not seem to be of NC origin turn out to be NCP because they involve one or more cell populations that harbor a particular mutation that affects the specification, migration and differentiation of the NC. In line with this observation, in this section we will also consider the epigenetic mechanisms that govern the development of the NC and thus become an important factor in the pathology of NCP. A third approach to classify diseases within the NCP spectrum will be the consideration of environmental factors that could affect the proper development of the embryo. Lastly, we will consider ciliopathies. This group of diseases arises from defects in the cellular machinery required for the proper assembly of primary cilia during development. The pathology of a subset of these diseases is characterized by alterations in the differentiation of NC-derived tissues. Thus, we will discuss some ciliopathies

that could be considered to be NCP. In summary, we will suggest the inclusion of new diseases within the NCP spectrum and classify them according to the axial origin of the affected NC population, as in the previous section.

4.1. Disease incorporation into NCP based on NC phenotype resulting from improper development of NC-adjacent populations

4.1.1. NCP originated from Cranial NCC

4.1.1.1. Holoprosencephaly (HPE). Holoprosencephaly (HPE) arises due to a mutation in the *SHH* gene. The HPE eye phenotype ranges from cyclopia, anophthalmia (absence of one or both eyes) and microphthalmia to coloboma. Several syndromes have been associated with HPE, including the Kallmann syndrome (Section 3.1.9, (Vaaralahti et al., 2012) and the CHARGE syndrome (Section 3.4.3, (Lin et al., 1990). At least 11 different mutations can produce a similar cerebral dysgenesis due to failure of prosencephalic cleavage and arrhinencephaly (absence of the rhinencephalon, or olfactory lobe of the brain). The NC origin of HPE could be accounted for by analyzing the midfacial hypoplasia and facial dysmorphism phenotype. These phenotypes in particular could be explained by the extension of the genetic rostrocaudal gradient to the embryonic mesencephalon produced by impaired NC formation and migration (Sarnat and Flores-Sarnat, 2001).

With respect to the etiology of this disease, a 12 bp deletion in SHH has been implicated in isolated colobomatous microphthalmia affecting the iris and retina, stressing the importance of genotype-phenotype specificity (Gregory-Evans et al., 2004). *Six3* is directly required to activate *Shh* expression in ventral midline floor plate cells. It has recently been show that variations in Six3 dosage result in different forms of mouse HPE (Geng et al., 2016). Thus, based on these mouse phenotypes and on the fact that Shh is required for the survival of the NC (Marcucio et al., 2011), it would be interesting to consider a possible inclusion of HPE as an NCP. Moreover, mice with a hypomorphic mutation in *Fgf8* have a variable phenotype, including reduction in the size of the pituitary anterior lobe (NCCs contribute to pituitary development, Section 3.1.5), loss of the pituitary posterior lobe, and neural ectoderm midline defects, including HPE (McCabe et al., 2011).

4.1.1.2. SAMS disorder. Another recently discovered NCP is the disorder consisting of Short stature, Auditory canal atresia, Mandibular hypoplasia, and Skeletal abnormalities (SAMS). This disease has been previously reported as a rare, autosomal-recessive developmental disorder with unique rhizomelic skeletal anomalies (Parry et al., 2013). Recent studies attributed the syndrome to a null mutation of the Goosecoid homeobox protein gene (GSC), Parry et al., 2013, (Blitz et al., 2016; Gottlieb et al., 1998; Twigg and Wilkie, 2015). Goosecoid, which is expressed during gastrulation in some vertebrates embryos (Blum et al., 1992; Cho et al., 1991; Schulte-Merker et al., 1994), at later stages is expressed in craniofacial regions, ventral body wall and limbs (Gaunt et al., 1993; Schulte-Merker et al., 1994; Wakamiya et al., 1997) and acts cell autonomously in mesenchyme-derived tissues forming craniofacial structures (Rivera-Perez et al., 1995, 1999). Based on the phenotype, Goosecoid could be considered as a downstream effector of the regulatory network that defines pharyngeal arches patterning in mammals, thereby supporting the consideration of SAMS disorder as an NCP (Parry et al., 2013). ET-/- mice embryos exhibit craniofacial malformations due in part to the absence of the Goosecoid transcription factor (Clouthier et al., 2010). In *sucker* (*suc/Edn1-/-*) mutant zebrafish embryos, NC forms and migrates normally, ;edn1 −/− mutants, but later expression of gsc is reduced in the ventral arches (Miller et al., 2000). Moreover, in the Ednra1-Ednra2 double morphant embryos, *Goosecoid* expression is strongly reduced in the ventral mandibular and hyoid arches (Nair et al., 2007), indicating that its relationship with the Endothelin cell signaling in craniofacial development is conserved. Additionally, Goosecoid-like is a gene deleted in the 22q11.2 syndrome (Section 3.4.1), (Gottlieb et al., 1998).

4.1.2. NCP originated from Trunk NCC

4.1.2.1. Multiple sclerosis (MS). A seminal study has provided strong evidence to support the claim that Multiple Sclerosis (MS) could be an NCP, based on the fact that certain neurological disorders are found in association with this disease. These disorders include hypertrophic peripheral neuropathy, cerebral glioma and NF1. Most of them are of NC origin and some are associated with abnormalities of the Schwann cell lineage (Behan and Chaudhuri, 2010).

4.2. Disease incorporation into NCP based on epigenetic mechanisms controlling NC development

The current state of knowledge of the NC formation by a gene regulatory network (GRN) is based on interactions between transcription factors and signaling molecules, and does not consider additional levels of regulation such as those elicited by epigenetic, post-transcriptional or post-translational control. In line with the above, the direct effect of the action of transcription factors and signaling molecules in the development of NC has been extensively studied. Nevertheless, the expression of some of these genes is under the control of regulatory non-coding elements of the genome and under the effect of epigenetic modifications. This could be the reason why there is a gap in our full comprehension of the complexity of the mechanisms that govern NC development and thereby the underlying pathology of NCP. During the past few years, numerous investigations have been conducted to determine the role of these molecular mechanisms in the development of human diseases. Genome-wide association studies (GWAS) and whole-genome sequencing, in particular, have provided new information regarding the implications of noncoding DNA regions in human disease, complemented with data obtained by the epigenome mapping consortia (Ward and Kellis, 2012). Recent studies have demonstrated the role of conserved non-coding elements (CNEs) of the genome in the development of NCP. Here, a variation in a CNE located in an intron of the *RET* proto-oncogene was recently identified as a frequent hypomorphic allele in HSCR (Section 3.7.1), WS2 (Section 3.8.6) and WS4 (Section 3.7.2), (Amiel et al., 2010).

With respect to epigenetic modifications of the genome, a study published in 2010 showed that chromatin modification is crucial for the regulation of a number of NC specifier genes (Strobl-Mazzulla et al., 2010). Moreover, recent evidence has stressed out the importance of chromatin remodeling in the positional identity of NC. In this study, mouse cranial NC subpopulations have been shown to maintain a broad patterning competence through chromatin epigenetic regulation. This regulation ultimately affects the transcriptional output of the cell (Minoux et al., 2017).

Histone methylation has also been shown to have a key role during developmental processes. These modifications are elicited by a group of proteins called histone methyltransferases. Some important developmental genes that regulate the proper specification and migration of the NC have been shown to be regulated at the genome level. Examples of these are *Snai2, Pax3, Sox10* and *Mitf* genes, which are epigenetically modified by a combination of two histone marks, active (H3K4me3) and repressive marks (H3K27me3). These signatures are poised epigenetic marks commonly found in specific cell-lineage genes in different model organisms (Zhu et al., 2013). Since these marks are

established by two different protein complexes, the polycomb repressive complex 2 (PRC2) and the trithorax group, it will be interesting to study whether an alteration in these proteins could be involved in the onset of some NCP. Supporting this approach for the analysis of diseases, a previous study has shown that a mouse mutant of *Aebp2*, which participates in histone modification, presents an NCP similar to the one found in humans: HSCR (Section 3.7.1) and WS4 (Section 3.7.2) (Kim et al., 2011). Additionally, in *Xenopus* and zebrafish it has been found that another histone demethylation protein, *phf8*, regulates NC development as well as the formation of craniofacial structures (Qi et al., 2010). Finally, PRC2 has been shown to regulate the differentiation of cranial NCCs into chondrocytes (van der Velden et al., 2013). Moreover, chicken knockdown of DNA methyltransferases protein (DNMT3A) blocks NC specification markers (Hu et al., 2012). This same mutation in humans can cause the immunodeficiency-centromeric instability-facial anomalies syndrome (ICF) (Ehrlich et al., 2008).

Histone acetylation is a complex process that renders the chromatin accessible for transcription. These modifications are carried out by histone acetyltransferases (HATs) and histone deacetylases (HDACs), which are involved in the activation and silencing of transcription, respectively. HDAC4 is involved in NC related diseases and syndromes. During human development, haploinsufficiency of HDAC4 produces brachydactyly mental retardation syndrome, characterized by craniofacial and skeletal abnormalities (Williams et al., 2010). Other HDACs involved in NCP formation are HDAC3 and HDAC8. HDAC3 is crucial for the control of smooth muscle differentiation and cardiac outflow tract formation during cardiac NC development in mouse (Singh et al., 2011). HDAC8 participates in skull morphogenesis by repressing the homeobox transcription factors *Otx2* and *Lhx1*, in cranial NC-derived cells (Haberland et al., 2009). In zebrafish embryos, *hdac1* is required for NC derivatives formation, during craniofacial (mandibular, hyoid and branchial arches) and peripheral neuron (enteric and DRG neurons) development (Ignatius et al., 2013). Even though HDACs are known to be involved in transcriptional repression, they have also been associated with the activation of certain genes when acting in concert with HATs (Wang et al., 2012; Zupkovitz et al., 2006). It has recently been shown that HDAC1 and HDAC2 bind to promoter regions and promote differentiation of NCCs to peripheral glia (Jacob et al., 2014).

Chromatin remodeling can also be caused by ATP-dependent protein complexes such as SWI/SNF (mating type switching/sucrose nonfermenting), ISWI (imitation switch), and CHD (chromodomain helicase DNA-binding). These proteins regulate gene expression by changing the structure of higher order chromatin, creating nucleosome-free regions to facilitate transcriptional activity. (Smith and Peterson, 2004). The CHD7 protein promotes the specification of embryonic stem cells into NCCs (Bajpai et al., 2010). An alteration in the function of CHD7 in early NC development is related to the CHARGE syndrome (Section 3.4.3), a known NCP (Zentner et al., 2010). Taken together, these studies show that the scientific community is focusing on a new direction in which the function of NC epigenetic modulation should be correlated with the development of NCP.

4.3. Disease incorporation into NCP based on ciliopathies related to NC differentiation

Primary cilia are essential components of vertebrate cells, which receive and process molecular and mechanical signaling cues. Ciliopathies are a group of diseases that arise due to a defect in the proper assembly of ciliary proteins. Moreover, primary cilia, which are non-motile organelles that participate in signal transduction, are required for NCC specification, migration proliferation and differentiation (Chang et al., 2015). Besides, NCCs utilize primary cilia throughout their development to interpret and process signals emitted by the surrounding environment and by the NC cells themselves. Many research studies performed in model organisms have analyzed the role of primary cilia in NC specification, survival, migration and differentiation (Chang et al., 2015; Grimes et al., 2016; Walentek and Quigley, 2017). The syndromes and diseases that are thus produced by a lack or malfunction of primary cilia which affect these NC processes could thereby be considered to be NCP. Examples of these conditions are the Orofaciodigital Syndrome (Section 4.4.1.a), Meckel–Gruber syndrome (Table 1, Section 4.4.1.b) (Barker et al., 2014), the Bardet–Biedl syndrome (Table 1, Section 4.4.2.a) (Tobin et al., 2008), Short-Rib Thoracic Dysplasia 10 (Section 4.4.2.b), Cranioectodermal dysplasia/Sensenbrenner syndrome (Section 4.4.2.c, (Walczak-Sztulpa et al., 2010) and the Ellis–van Creveld syndrome (Section 4.4.2.d) (Caparros-Martin et al., 2015).

4.3.1. Ciliopathic NCP originated from cranial NCC

4.3.1.1. Orofaciodigital syndrome type I (OFD). OFD is characterized by malformations of the face, oral cavity and digits and is transmitted as an X-linked dominant condition with lethality in males. The central nervous system may also be involved in as many as 40% of the cases (Toriello, 2009). The *OFD1* gene (also named *CXOF5*) is mutated in this syndrome. The majority of the mutations (65.5%) have been located in exons 3, 8, 9, 13, and 16 (Scolari et al., 1997; Thauvin-Robinet et al., 2006). The gene product of *Ofd1* is a centrosomal protein located at the basal body of the primary cilia. In both mouse and zebrafish it was demonstrated that *Ofd1* is required for normal ciliary formation (Ferrante et al., 2009, 2006). Mutation analyses of 100 individuals with *OFDS1* (Prattichizzo et al., 2008) showed that most mutations occur in the first half of the gene, generally causing a truncated protein, and thus a loss-of-function mechanism.

4.3.1.2. Meckel-Gruber syndrome (MKS). The MKS syndrome is caused by a mutation in the *MKS* gene. It is characterized by skeletal malformation of the cranial base among other numerous abnormalities of the brain and spinal cord (Kjær et al., 1999). Another characteristic symptom of this ciliopathy is a cleft lip and palate in almost 45% of the cases. This clefting is accompanied by tongue malformations including ankyloglossia (Rehder and Labbé, 1981). Both patients with ciliopathies and ciliopathic animal models often have dysmorphic NC-derived craniofacial skeletons. A study using the murine mutant ciliopathic model Msk^{krc} has shown that these embryos exhibit misshapen skulls and a decrease in frontal and parietal bone ossification. As to the mechanistic etiology of the disease, it has been shown that the *MKS1* gene encodes a protein associated with the base of the cilium in vertebrates. This protein is involved in neural tube, bone and kidney development (Weatherbee et al., 2009).

4.3.2. Ciliopathic NCP originated from cranial and cardiac NCC

4.3.2.1. Bardet-Biedl syndrome 8 (BBS). BBS disorder is characterized by retinitis pigmentosa, obesity, postaxial polydactyly, hypogonadism, and developmental delay (Carré et al., 2014). At least 19 genes are associated with *BBS: BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LZTFL1 (BBS17), BBIP1 (BBS18),* and *IFT27 (BBS19)* (Forsythe and Beales, 1993). However, no known pathogenic variants were identified in approximately 20% of individuals with BBS, suggesting that additional *BBS* related genes have yet to be discovered (Haws et al., 2015). *BBS* genes have been associated with ciliary, basal body or centrosomal dysfunctions and some have been shown to disrupt intraflagellar transport (IFT) (Hernandez-Hernandez et al.,

2013). Recently, BBS has been linked to NCP. In a human and mouse craniofacial study, it has been demonstrated that BBS proteins are required for NCC migration in such a way that its alteration causes Shh-dependent craniofacial defects and gut motility disorder (Tobin et al., 2008).

4.3.2.2. Short-Rib thoracic dysplasia 10 (SRTD). SRTD refers to a group of autosomal recessive skeletal ciliopathies that are characterized by a constricted skeletal chest system. Non-skeletal phenotypes can include cleft lip/palate as well as anomalies of major organs such as the brain, eye, heart, kidneys, liver, pancreas, intestines, and genitalia (Halbritter et al., 2013). SRTD encompasses Ellis-van Creveld syndrome (EVC) as well as the disorders previously designated as Jeune syndrome or asphyxiating thoracic dystrophy (ATD), short rib-polydactyly syndrome (SRPS), and Mainzer-Saldino syndrome (MZSDS). Polydactyly is variably present, and there is a phenotypic overlap in the various forms of SRTDs, which differ in visceral malformation and metaphyseal appearance (Huber and Cormier-Daire, 2012; Schmidts et al., 2013).

Skeletal ciliopathies are frequently caused by mutations in intraflagellar transport (IFT) genes. Mutations in *IFT80*, *DYNC2H1*, *TTC21B*, *WDR19*, *NEK1*, *WDR35*, *WDR60*, *IFT140*, *IFT172*, *WDR34*, *CEP120*, *KIAA0586*, *DYNC2LI1*, *IFT52* and *TCTEX1D2* were found in this disease (Alby et al., 2015; Girisha et al., 2016; Shaheen et al., 2015). Work in animal models such as knockout mice suggests that defective IFT leads to impaired hedgehog signaling, which disturbs chondrogenic and osteogenic cellular proliferation and differentiation leading to chondrodysplasia phenotypes (Haycraft et al., 2007; Huangfu et al., 2003; Rix et al., 2011). Analysis of *Ift172* mouse mutants have shown several craniofacial phenotypes, including cleft secondary palate, suggesting aberrant NCC behavior (Friedland-Little et al., 2011). Additionally, research in zebrafish has shown that mutants of this protein present dysmorphology of craniofacial cartilages (Lunt et al., 2009).

4.3.2.3. Cranioectodermal dysplasia (CED). The CED (also called Sensenbrenner syndrome) phenotype includes frontal bossing, dolichocephaly (a relatively long head) due to an abnormal fusion of the skull bones. In addition, abnormal dentition is observed in the individuals with this disease along with skeletal disorders such as narrow thorax, shortened proximal limbs and brachydactyly. It has also been shown that CED has an autosomal recessive inheritance pattern (Walczak-Sztulpa et al., 2010). CED is a disease caused by a mutation in at least one of the genes encoding components of the ciliary intraflagellar transport complex: *IFT122, WDR35, WDR19* or *IFT43*. The mutation at the *IFT122* gene has been recognized as the most common one. In zebrafish morphants of the *ift122* gene, ciliary phenotypes correlating with those observed in human patients were found.

4.3.2.4. Ellis-van Creveld syndrome (EVC). The EVC syndrome, which is caused by mutations in the *EVC* and *EVC2* genes, is also known as chondroectodermal dysplasia. This disease is characterized by growth retardation, dysplastic nails, cardiac defects, dental abnormalities and polydactyly (Ruiz-Perez et al., 2003). The mutations described above produce an abnormally small, nonfunctional version of the EVC and EVC2 proteins. It is known that these two proteins regulate the output of the hedgehog signaling pathway during development by regulating the activation of the Smoothened protein (Yang et al., 2012). Recently, mouse genetics studies have shown that a mutation in the *Gli1* gene is associated with a phenotypic spectrum overlapping that of the EVC syndrome (Palencia-Campos et al., 2017). Studies performed in the mouse model have also corroborated the importance of the Evc proteins in the regulation of the Hh signaling pathway during the onset of this disease (Ruiz-Perez and Goodship, 2009).

4.4. Disease incorporation into NCP based on environmental factors affecting NC development

Environmental factors play a fundamental role during NC migration and differentiation. Moreover, some congenital diseases arise both from environmental conditions and from the presence of a wide variety of molecules or abuse drugs to which the embryo is exposed. It has been shown that ethanol exposure causes Fetal Alcohol Spectrum Disorder (FASD), characterized by a reduction in cranial and cardiac NC migration and by the reduction in cranial NCC numbers, reinforcing the conclusion that FASD is an NCP (Fainsod and Kot-Leibovich, 2017; Flentke et al., 2011). The Fetal Tobacco Syndrome is an important causative for fetal malformations during human development. One of the most important malformations is cleft lip/palate among several other disorders such as intrauterine growth restriction and susceptibility to respiratory diseases, clubfoot, gastroschisis, heart defects and Attention Deficit/Hyperactivity Disorder (ADHD) (Lie et al., 2008). NCCs are also affected by smoke exposure during development. However, the underlying molecular mechanisms of these processes are poorly understood. Recently, however, it was shown in mouse embryos exposed to cigarette smoke extract, which contains low levels of aryl hydrocarbon receptor (AhR) ligand compounds, that NC migration is affected by downregulating R-spondin1, a co-activator of Wnt signaling (Sanbe et al., 2009). Moreover, a recent study performed in *Xenopus* embryos and mammalian NCCs has shown that exposure to nicotine and aerosolized e-cigarette liquids induces a variety of defects, including median facial clefts and midface hypoplasia (Kennedy et al., 2017).

These two examples of environmental factors affecting NC development illustrate the sensibility of NC developmental processes to the presence of certain molecules. An extensive list of molecules, medicinal drugs, and teratogenic or fetotoxic agents also affect NC development (high glucose levels, retinoic acid, tetrahydrocannabinol, cocaine, morphine, LSD, ketamine, angiotensin-converting enzyme inhibitors, bosentan, chloramphenicol, carbamazepine, fluconazole, glyphosate herbicides, lithium compounds, methotrexate, phenobarbital, tamoxifen, thalidomide, toluene, trastuzumab, tretinoin, valproic acid, among others).

In this section we briefly described some environmental factors o teratogens implicated in the disruption of NC development. The particular consideration of the mechanisms of action and the effects produced by the whole range of agents affecting NCCs, as well as numerous factors that affect the proper establishment of the epigenome and microRNA expression and function (Resendiz et al., 2014), require further analysis and is beyond the scope and length of this review.

5. Future directions

Patients with NCP present various defects in NCC-derived anatomical structures. While genetic screening is considered the best approach to identify and diagnose genetic diseases in newborns, only a few causative genes have been identified and they only account for a minority of the patients. Therefore, identifying additional genes that also participate in the molecular mechanisms operating during normal development may uncover new causative genes that can be added to genetic screenings for newborns at risk. Great efforts using different animal models are being made to identify putative candidate genes. The functional testing of these candidates in an animal model with high genetic, protein and functional similarity to human is likely to rapidly

unveil the high priority candidates for diagnostic genome sequencing.

Acknowledgments

We are grateful to our colleagues for their helpful discussions. We also thank the anonymous reviewers for their careful reading of the manuscript and their many insightful comments. This publication was supported by grants from ANPCyT-Foncyt (to MJA PICT2013-1686 and PICT2015-1207; to CT, PICT2013-0219; to GAVL, PICT2016-0835), and by grants from CIUNT (to MJA, PIUNT 26/D506, and PIUNT2018). We specially thank Ms. Virginia Mendez for her proof-reading. We regret that a lot of specific publications dealing with the subject of this review could not be cited due to space limitations.

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