Mutation Research 785 (2020) 108319

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

A comprehensive analysis of *AHRR* gene as a candidate for cleft lip with or without cleft palate

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ARTICLE INFO

Article history:
Received 24 June 2019
Received in revised form 28 May 2020
Accepted 29 May 2020
Available online 5 June 2020

Keywords:
Craniofacial anomalies
Cleft palate
AHRR gene
Cleft lip and palate
Genetics
Genotype-phenotype correlation

ABSTRACT

Cleft lip and palate (CL/P) is among the most common congenital malformations and affects 1 in 700 newborns. CL/P is caused by genetic and environmental factors (maternal smoking, alcohol or drug use and others). Many genes and loci were associated with cleft lip/palate but the amount of heterogeneity justifies identifying new causal genes and variants. AHRR (Aryl-Hydrocarbon Receptor Repressor) gene has recently been related to CL/P however, few functional studies analyze the genotypephenotype interaction of AHRR with CL/P. Several studies associate the molecular pathway of AHRR to CL/P which indicates this gene as a functional candidate in CL/P etiology. Methods: Systematic Literature Review was performed using PUBMED database with the keywords cleft lip, cleft palate, orofacial cleft, AHRR and synonyms. SLR resulted in 37 included articles. Results: AHRR is a positional and functional candidate gene for CL/P. In silico analysis detected interactions with other genes previously associated to CL/P like ARNT and CYP1A1. AHRR protein regulates cellular toxicity through TCDD mediated AHR pathway. Exposure to TCDD in animal embryos is AHR mediated and lead to cleft palate due to palate fusion failure and post fusion rupture. AHRR regulates cellular growth and differentiation, fundamental to lip and palatogenesis. AHRR decreases carcinogenesis and recently a higher tumor risk has been described in CL/P patients and families. AHRR is also a smoking biomarker due to changed methylation sites found in smokers DNA although folate intake may partially revert these methylation alterations. This corroborates the role of maternal smoking and lack of folate supplementation as risk factors for CL/P. Conclusion: This research identified the importance of AHRR in dioxin response and demonstrated an example of genetic and environmental interaction, indispensable in the development of many complex diseases.

1. Introduction

Cleft lip with or without cleft palate (CL/P), and cleft palate only (CPO), are among the most common craniofacial anomalies [1,2] and affect approximately 1/700 live births worldwide [3]. Caused by breaks or gaps between orofacial structures [4], clefts affect not only speaking, hearing and appearance of the bearer [5] but also cause negative psychological and socioeconomic repercussions [6,7], which can also lead to a higher suicide rate [8]. Reducing the impact of craniofacial anomalies on the health of affected individuals requires treatment by a multidisciplinary team of surgeons, speech therapists, physiotherapists, nurses, psychologists, geneticists and other healthcare professionals [2]. It is estimated that five to ten years [9] of treatment, with an average cost of two hundred thousand American dollars per patient [10] are necessary to achieve satisfactory results. These lifelong morbidities, with extremely elevated costs to national healthcare centers, constitute an important public healthcare issue [9,11].

Even though there is a vast variation of phenotypic presentation, orofacial clefting is usually classified as a qualitative disorder, either present or absent, and characterized as to the degree of involvement [microform, cleft lip, cleft lip plus hard palate, cleft lip plus hard and soft palate, cleft palate only (CPO)] [12]. However, recent literature suggests individuals with cleft are only part of a much larger spectrum of phenotypes that includes not only CL/P and CPO but also multiple subclinical characteristics that could be

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http://dx.doi.org/10.1016/j.mrrev.2020.108319
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present in non-affected relatives [13,14]. These characteristics may include craniofacial measurement alterations, dental anomalies [tooth agenesis, microdontia and hyperdontia (extranumerary teeth)], structural brain anomalies, *orbicularis oris* muscle defect, cleft microform, bifid uvula, submucous cleft palate and velopharyngeal insufficiency [14].

Cleft lip is a result of the failure of the union between the maxillary prominence of the affected with the merged medial nasal prominences [15,16]. This improper fusion of the primary palate may cause the palatal shelves to be mispositioned and therefore could interfere with the fusion of the secondary palate. This explains why cleft lip can occur with or without cleft palate (CL/P) [17]. On the other hand, several pathogenic mechanisms have been proposed to be involved in the development of CPO. Palatogenesis depends on several steps which include growth, shelf elevation, contact and fusion [18]. Therefore the proposed mechanisms leading to CPO include failure of palatal elevation, growth perturbations and failure of fusion of the palatal shelf, all mechanisms that could prevent the mesenchymal masses of the lateral palatal process to meet and fuse with each other and/or with the nasal septum, causing a secondary palate cleft [17,19]. Another mechanism proposed by Kitamura suggests that the palate could also be ruptured after being completely fused, resulting in cleft palate [15].

Although most clefts are unilateral and affect the left side twice as often as the right side [12,20], a minority of patients have bilateral clefts [12]. While cleft lip is more prevalent among male individuals, cleft palate is more frequent in female individuals [2,21].

Clefts can be classified as syndromic and non-syndromic [22]. The syndromic forms of clefts are associated to other structural, developmental or cognitive anomalies [11], and represent 30 % of CL/P and 50 % of CPO cases [14,16,23–26]. Although syndromic forms are caused by a large group of conditions, about 75 % of the genetic etiology of syndromic CL/P and CPO is known [2,14,27]. On the other hand, non-syndromic forms of clefts are caused by numerous genetic and environmental factors with smaller roles in an intricate mechanism [12,27,28]. Some predisposing environmental factors during pregnancy include maternal smoking [29,30], alcohol use [31,32], advanced maternal age (above 40 years-old) [33], lack of folate supplementation during the first trimester [34] and use of medications such as anti-inflammatory drugs, antibiotics and anticonvulsants [35–38].

Although sharing several morphological phenotypes, CL/P and CPO have been considered two distinct conditions with separate etiologies since the first genetic study by Fogh-Andersen, due to different embryological origins of the lip and the palate [39,40]. Nonetheless, some families have both CL/P and CPO cases, suggesting some etiological overlap [41], especially in families with etiologic mutations in the genes know as tumor protein 63 (*TP63*), msh homeobox 1 (*MSX1*), interferon regulatory factor 6 (*IRF6*) and fibroblast growth factor receptor 1 (*FGFR1*) [12].

Many other genes and chromosomal regions have been associated with a greater risk of non-syndromic CL/P (NSCLP), however they represent only part of the genetics behind this condition [42–44]. The lack of inheritance pattern or incomplete penetrance found in some case reports could be partially explained due to the phenotypic variability and subclinical manifestations in affected families, which would cause an incorrect identification of all affected family members [14]. Better knowledge of the genetic background in CL/P could result in improved prevention, treatment and prognosis for individuals with these conditions [12]. But, no validated genetic markers are currently available, so the roles of additional candidate genes must be investigated to better define the genetics underlying the condition. While some genes and *loci* have well known associations with CL/P, such as for the genes *IRF6*, *VAX1 (Ventral Anterior Homeobox 1), MAFB (MAF BZIP Transcription Factor B)*, *ABCA4 (ATP Binding Cassette Subfamily A Member 4)* and the 8q24 chromosomal band, other genetic *loci* have insufficient supporting data correlating with NSCLP [44,45]. Most genetic variations were found by a variety of approaches including GWAS (genome wide association studies), target-based genetic screening and linkage studies. In a recent study by Leslie and colleagues, the role of low frequency protein coding genetic variants in individuals with orofacial clefts predisposition. The study identified *AHRR (Aryl-Hydrocarbon Receptor Repressor)* as one of the genes related to NSCLP [45]. Although this is the first report in literature to directly correlate *AHRR* variants to increased NSCLP risk, the signaling pathway involving *AHRR* and its genomic locus have been described in several CL/P genetic studies [44,45]. This could indicate *AHRR* has perhaps been overlooked as a candidate gene in CL/P.

In this work, we performed a systematic literature review to compile and evaluate current findings associating the *AHRR* gene with cleft lip phenotype. We first describe the genetic structure of the *AHRR* gene, known splicing isoforms and gene expression levels per tissue. We describe the 3D protein structure encoded by the *AHRR* gene, and how it interacts at both the gene and protein levels with other molecules known to be associated with cleft lip. Finally, we discuss all the findings associating the gene *AHRR* with known cleft lip phenotypes.

2. Methods

The method used to execute this systematic literature review (SLR) was based on the protocol developed by Kitchenham and Charters [46]. The main objective was to identify and synthesize the state of the science vis-à-vis of the *AHRR* gene and associated cleft palate characteristics, including molecular, cellular and clinical phenotypes. In the following sections, the steps considered by this SLR will be described in detail.

2.1. Research questions

The development of this SLR was primarily focused on the research question: What is the correlation between *AHRR* gene and cleft lip/palate? This question was then subdivided into the following research questions: What is the correlation between the *AHRR* gene and cleft lip/palate molecular phenotypes? What are the genetic variants in *AHRR* associated with cleft lip/palate.

2.2. Exclusion and inclusion criteria

The inclusion criteria were included: i) articles published before May 2019, ii) articles published in the English language, iii) articles that consider cleft lip/palate and *AHRR* and *AHRR* related genes, and iv) articles that describe genetic variants found in individuals with cleft lip/palate. The exclusion criteria were: i) articles that used *AHRR*, *AHHR* and *AHH* initials for a different purpose.

2.3. Search databases

PubMed was used as database for an electronic search. PubMed is a search-free resource, developed and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institute of Health (NIH). PubMed covers portions of life sciences, behavioral sciences, chemical sciences and bioengineering through more than 25 million citations and summaries from the fields of biomedicine and health (https://www.ncbi.nlm.nih.gov/pubmed/).

2.4. Search strategies

To obtain as many articles as possible, we sought to use the terms and their synonyms for: cleft lip, cleft palate, orofacial cleft, *AHRR*, aryl-hydrocarbon receptor repressor. Subsequently, we obtained keywords that composed the following search string: ((((((((((((((cleft lip[Title/Abstract]) OR cleft palate[Title/Abstract]) OR orofacial cleft[Title/Abstract]) AND ahrr[Title/Abstract]) OR Aryl Hydrocarbon Receptor Repressor[Title/Abstract]) OR Aryl-Hydrocarbon Receptor Repressor[Title/Abstract]) OR Class E Basic Helix-Loop-Helix Protein 77[Title/Abstract]) OR AhR Repressor [Title/Abstract]) OR BHLHe77[Title/Abstract]) OR Aryl Hydrocarbon Hydroxylase Regulator[Title/Abstract]) OR Aryl Hydrocarbon Receptor Regulator[Title/Abstract]) OR Dioxin Receptor Repressor [Title/Abstract]) OR KIAA1234[Title/Abstract]) OR BHLHE77[Title/Abstract]) OR AHHR[Title/Abstract]) OR AHH[Title/Abstract]. Although BHLHe77 and KIAA1234 are known aliases for AHRR, these terms were not found in PubMed. The composition of the keywords resulted in 1325 combinations of terms used for research. Firstly, a triage was carried out by title, followed by analysis of abstracts, resulting in respectively 29 and 1007 articles eliminated due to initials AHH having meanings other than Aryl Hydrocarbon Hydroxylase.

The remaining 289 articles containing information about *AHRR* gene and its pathway and were considered potentially relevant to the research. Two independent readers analyzed all potentially relevant studies which resulted in the inclusion of 37 articles (Fig. 1). In all cases, the inclusion and exclusion criteria previously presented were applied.

2.5. Gene isoforms and protein structure characterization

Gene isoforms were collected from UCSC genome browser (https://genome.ucsc.edu/cgi-bin/hgTracks) using as reference datasets the human reference genome (build Hg38) and a comprehensive transcriptome annotation created by Gencode (version 32) [47].

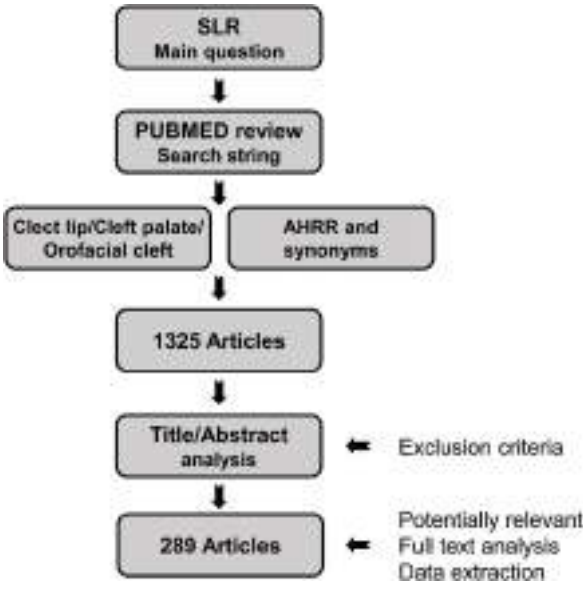

Fig. 1. Schematic representation of the systematic literature review (SLR). As a standard SLR protocol, it was performed the steps for the definition of the main research questions, the database search using key words and synonyms, and analysis of the reports by applying exclusion criteria to select the relevant manuscripts for complete analysis followed by data extraction.

The protein structure and corresponding interactions were collected from the Protein Data Bank (PDB) [48] and from specialized literature.

2.6. Genetic and protein interaction

The genetic interaction was performed using the software PathwayCommons (version 12) [49] that uses a collection of internal literature-based internal databanks to create a representative view of genetic interaction for a gene.

The protein-protein interaction network was created using the software String (version 11) [50]. Like PathwayCommons, it uses literature-based information to create a protein-protein interaction network, specifying the source of the information, including curated database, experimentally determined, text-mining, protein homology, co-expression.

2.7. Gene expression at single-cell and tissue level

Gene expression data at single cell level was collected from the databanks Panglao DB (https://panglaodb.se/index.html) [51] and EBI (https://www.ebi.ac.uk/gxa/sc/search?q=ahrr&species=Homo%20sapiens).

Tissue level expression data was collected from GPTEx and from the literature.

3. Results and discussion

To investigate whether the gene *AHRR* correlated with the known phenotypes presented by CL/P, we applied a protocol for a SLR to collect information from this gene, including cellular, molecular and phenotypic data that are related to known phenotypes of CL/P. In the next paragraphs, we describe the characteristics of the gene *AHRR*, its coded protein and corresponding protein domains and protein-protein interactors. We also show how AHRR gene interacts with other genes and proteins through protein molecular interaction networks. Finally, we performed a systematic literature-based investigation to describe the current findings of the *AHRR* gene and how it is associated with CL/P, at molecular and cellular levels, including environmental factors.

3.1. Genetic and protein characteristics of AHRR gene

AHRR gene is located on the short arm of chromosome 5 [5p15.3; genomic coordinates (GRCh38/hg38) chr5:304,176-438,291] [52] and is 134,116 bases long [53]. According to Gencode (v32), *AHRR* has 6 transcript isoforms, with the longest isoform having 10 exons, and the shortest having 4 exons (Fig. 2A).

Between these transcripts, there are three known protein isoforms annotated in the Uniprot protein databank. The first AHRR protein is considered canonical and has 701 amino acids (A9YTQ3-1). The second isoform (A9YTQ3-2) differs from the canonical isoform at position 240, where additional amino acids (LARGSQAWQLRLCCPEPLM) are inserted, making A9YTQ3-2 719 amino acids in length. The third isoform (A9YTQ3-3) has the same amino acid insertion and a deletion of the first four amino acids, changing its length to 715 amino acids [54,55]). Seven other computationally-predicted isoforms have been reported [D6RE68 (557 amino acids), D6RF73 (547 amino acids), E5RFG4 (157 amino acids), E5RGQ2 (81 amino acids), G3V143 (139 amino acids), H0YA43 (215 amino acids) and E5RHE0 (12 amino acids)] [54].

To investigate the expression of AHRR gene, an RNA-sequencing-based investigation of 27 distinct body tissue samples found expression of the gene *AHRR* in all analyzed samples [56]. In another work, Fagerberg et al. [57] analyzed distinct tissues from

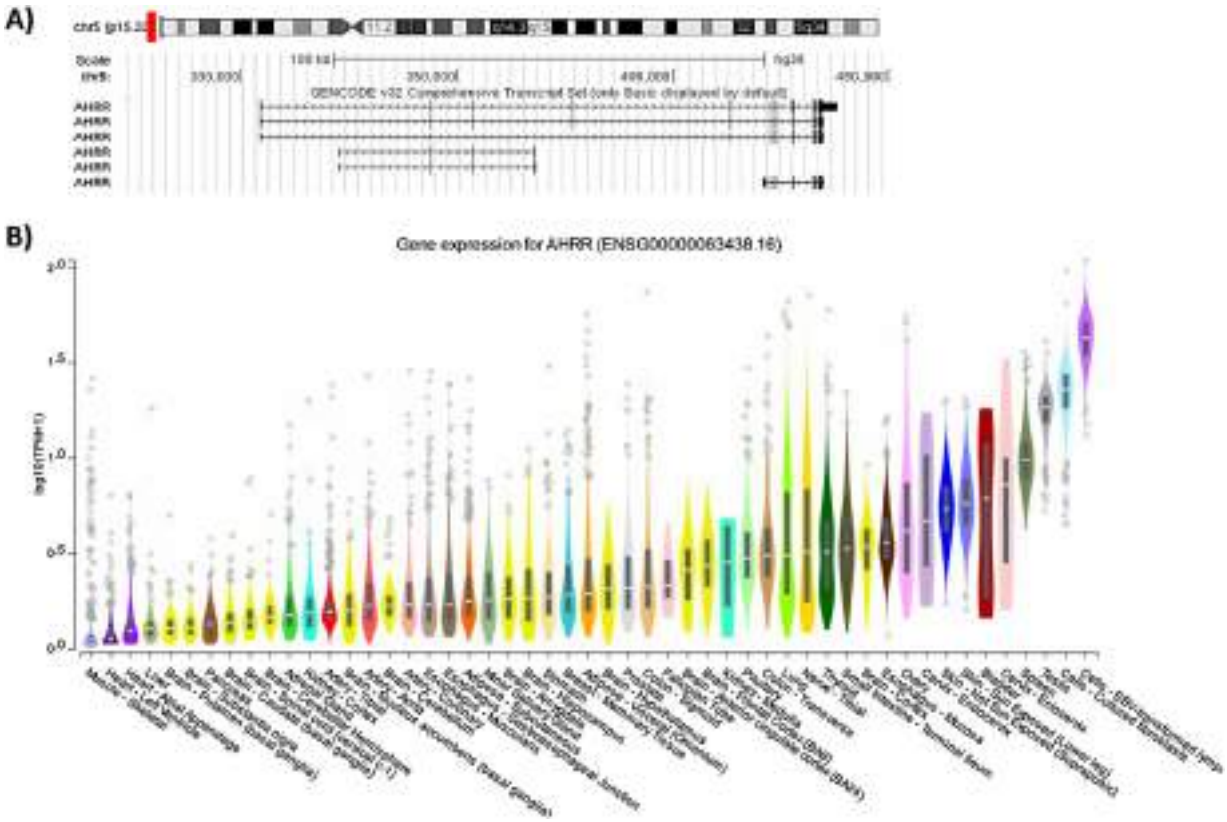

Fig. 2. Splicing isoforms of the gene *AHRR* and gene expression over human tissues. A) Splicing isoforms of gene AHRR are represented black lines (intronic regions) and black boxes (exonic regions: wider are protein coding regions, and narrow are untranslated regions). Arrows within isoform lines indicates gene strand, and the red box on top indicates the AHRR gene locus. B) AHRR gene expression as log scale 2 of TPM values (transcripts per million) over human tissues. Samples corresponding as expression outliers are represented as gray circles, and average values are indicated by horizontal white lines within the vertical bars for each tissue. Expression data were extracted from GTEx Portal (https://www.gtexportal.org/) [113].

human body, and found that testicular tissue presented the highest expression of *AHRR* followed by spleen, skin, placenta and ovaries. The highest expression in testicular tissue was also reported by other independent databanks, such as by the Illumina bodyMap2 transcriptome Project [58], and more recently by the Genotype-Tissue Expression (GTEx) project. According to GTEx, testis, spleen and skin are the tissues with highest expression of AHRR gene (Fig. 2B). In GTEx, when including all cell types and tissues, it is reported that cultured fibroblast has the highest expression of AHRR gene (Fig. 2B). Similar results are also reported by EBI Expression Atlas (https://www.ebi.ac.uk/gxa/home).

In single-cell data available at PANGLAODB database [59], we also found that *AHRR* gene is expressed by fibroblasts and testicular tissue cells (dendritic cells, endothelial cells, germ cells, spermatocytes).

Besides expression variation between distinct cell and tissue types, we also investigated inter-population variation in the *AHRR* gene to check whether individuals from specific ethnicities could be more prone to accumulation of higher number of potentially deleterious mutations. We verified the mutations classified as missense variants and the ones classified by gnomAD as pLof (predicted loss-of-function variation in a given gene) and supported by high coverage exome- and genome-based sequencing experiments (Fig. 3A). In *AHRR* gene, we found 571 mutations classified as missense (SNV and Indels) that are distributed over all protein coding exons of this gene (Fig. 3B and C, Supplementary material Table S1). Most these mutations are annotated as missense variants (507 in total), but other less frequent variant types are stop gain (16), stop loss (2), start loss (1), splice acceptor variant (3), splice donor variant (5), frameshift variant (30), in frame deletion (6) and inframe insertion (1). From the total mutations found, only 42 are classified as predicted loss of function (pLof) mutations, but none of them appears in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). These reported mutations are distributed over different populations, including Africans, Asians, Europeans and Latins, but we did not find any population-specific mutation considering these individuals (Supplementary material Table S1).

3.2. AHRR protein domains

AHRR codes for a protein also known as AHRR. There are two known AHRR domains, the bHLH and PAS (Fig. 4A). The domain bHLH (Myc-type, basic helix-loop-helix domain profile) starts at amino acid position 27 until 91 and acts in protein dimerization, enabling the non-covalent union of two identical or non-identical subunits creating a macromolecule. PAS domain [PAS repeat profile (Per-period circadian protein, Arnt-Ah receptor nuclear translocator protein and Sim-single-minded protein)] starts at position 115 up until 180 and interacts with signaling proteins as a responder to light, oxidation and other stimuli [60]. The two domains are also present in AHRR related proteins Aryl Hydrocarbon Receptor (AHR) and AHR Nuclear Translocator also called HIF-1β (ARNT) (Fig. 4B).

Besides these two domains, AHR and ARNT proteins contain an additional PAS domain and a transactivation bHLH domain (Fig. 4B). The bHLH domain in AHR allows its dimerization with ARNT, binding of DNA and interaction with chaperones like HsP90 (Heat Shock Protein 90). It is important for nuclear importation and exportation as well [61]. The PAS domain with two repeats is

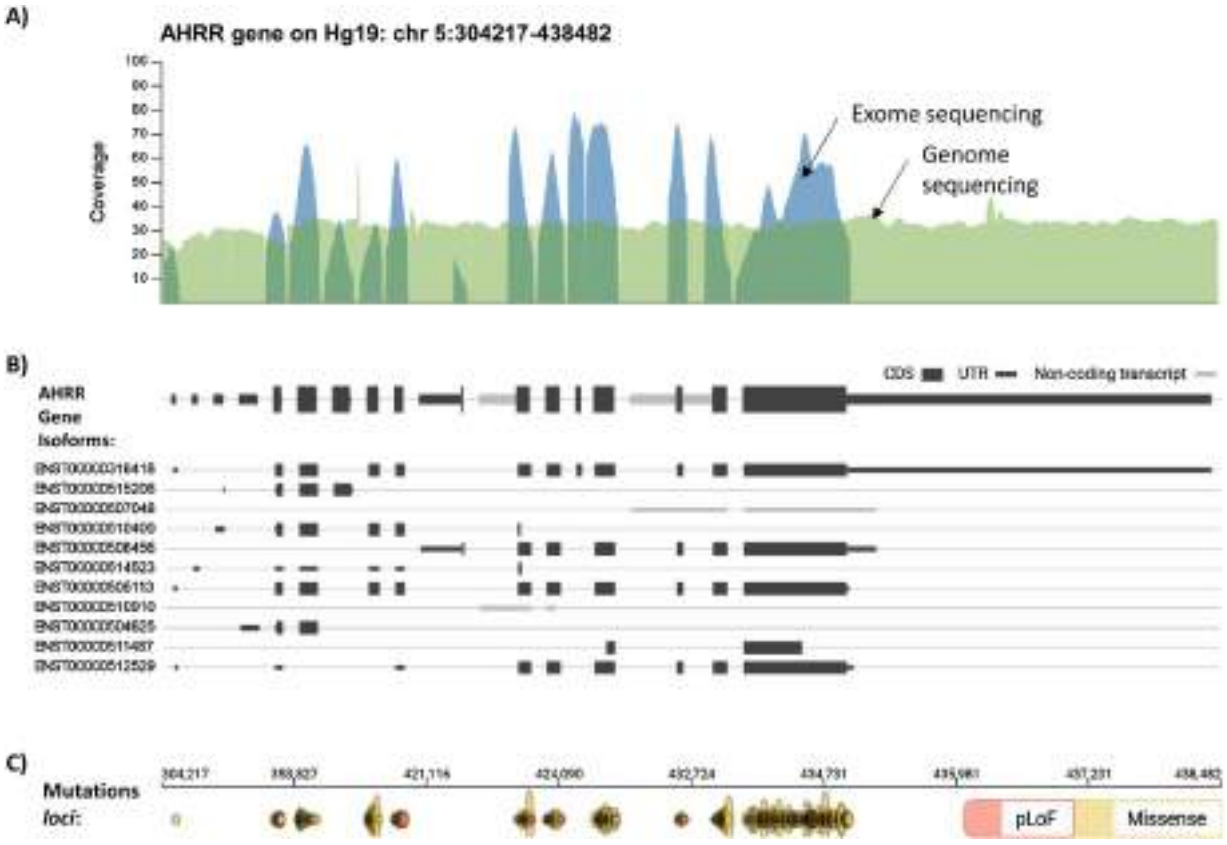

Fig. 3. Distribution of missense mutations and predicted loss of function mutations in AHRR gene isoforms covered by genome and exome sequencing. A) AHRR gene locus and the coverage indicated by exome (blue) and genome sequencing (green). B) AHRR gene isoforms and corresponding coding regions (CDS), untranslated regions (UTR) and transcribed non-coding regions. C) Distribution of missense and pLoF (predicted loss of function) mutations over AHRR gene *loci*.

involved with ARNT dimerization (PAS A) and allows ligand binding (PAS B). There is an extra C-terminal domain with three subdomains, one enriched with acidic residues, the second Q-rich (glutamine enriched) and the third serine, threonine and proline enriched (S/T/P). This domain is responsible for interactions with coactivators and corepressors [62,63]. The interaction between the 3D structures AHRR-ARNT forms a heterodimer (Fig. 4C) that reveals the structural basis of the repression of AHR-mediated transcription [64]. By regulating transcription, mutations in the genes that code for these proteins could alter their structure and their specific functional domains, thereby affecting their correct function and, consequently, phenotypes associated with CL/P.

3.3. Protein network interaction pathways involving AHRR

AHRR protein acts as a mediator of dioxin toxicity and is also involved in cellular growth regulation and differentiation. Most studies correlate the *AHRR* gene to different types of cancer. Zudaire et al. [65] reported that *AHRR* expression is consistently downregulated, mainly due to hypermethylation, in human malignant tissues as compared to healthy tissue from different sites, including colon, breast, lung, stomach, cervical, and ovarian, when compared with normal tissues of the same anatomical origin. These results correlate with the finding that the silencing of *AHRR* in human lung cancer cells led to a rise in cellular growth, both *in vitro* and in animal models [65–67]. A similar effect was observed in healthy human mammary epithelial cells [65]. Furthermore, the downregulation of *AHRR* in lung cancer cells also resulted in an increase in cell mobility, apoptosis resistance, *in vivo* angiogenesis and *in vitro* invasive potential [65,67]. On the other hand, ectopic expression of *AHRR* has decreased cellular growth rates and angiogenesis in tumor cells, which indicates the essential role *AHRR* has as a tumor suppressor in humans [65]. Another study by Zhang reported that overexpression of the RNA produced by AHRR in human monocytes enhances inflammatory gene expression, leading to higher levels of immune response transcription factor NF-kappaB [68]

In addition, *AHRR* has a role in xenobiotic metabolism through its regulation of the *AHR (Aryl Hydrocarbon Receptor)* gene, which interacts with the p450A1 cytochrome complex in the *AHR* pathway [69]. The *AHR* pathway (Fig. 5A) begins when a complex formed by ligand [TCDD(2,3,7,8-tetrachlorodibenzo-p-dioxin)], chaperone proteins (HSP90, XAP2 and p23) and importins bound to the AHR protein enters the cellular nucleus. Inside the nuclear structure, AHR binds to ARNT and forms a heterodimer. This AHR-ARNT dimer recruits coactivators CBP/p300 in order to create an activated complex that binds to XRE (xenobiotic response elements) and stimulates the synthesis of proteins CYP1A1 [Cytochrome P450 (CYP) 1A1] and AHRR [69] (Fig. 5A). CYP1A1 is one of the most important enzymes involved in cytochrome p450 drug metabolism and synthesis of cholesterol, steroids and other lipids. This CYP1A1 mediated metabolism pathway can generate reactive metabolites and lead to mutagenesis and tumor formation [70].

AHRR protein production autoregulates this pathway, because AHRR can also form a heterodimer with ARNT and, therefore, competes with AHR repressing its transcription. This process leads to protein SUMOylation and recruits other co-repressors like proteins, ANKRA2 (Ankyrin Repeat Family A Member 2), HDAC4 (Histone Deacetylase 4) and HDAC5 (Histone Deacetylase 5) to form a repressor complex that prevents CYP1A1 synthesis and the metabolic action of P450 cytochrome [69,71] (Fig. 5A). Disruption

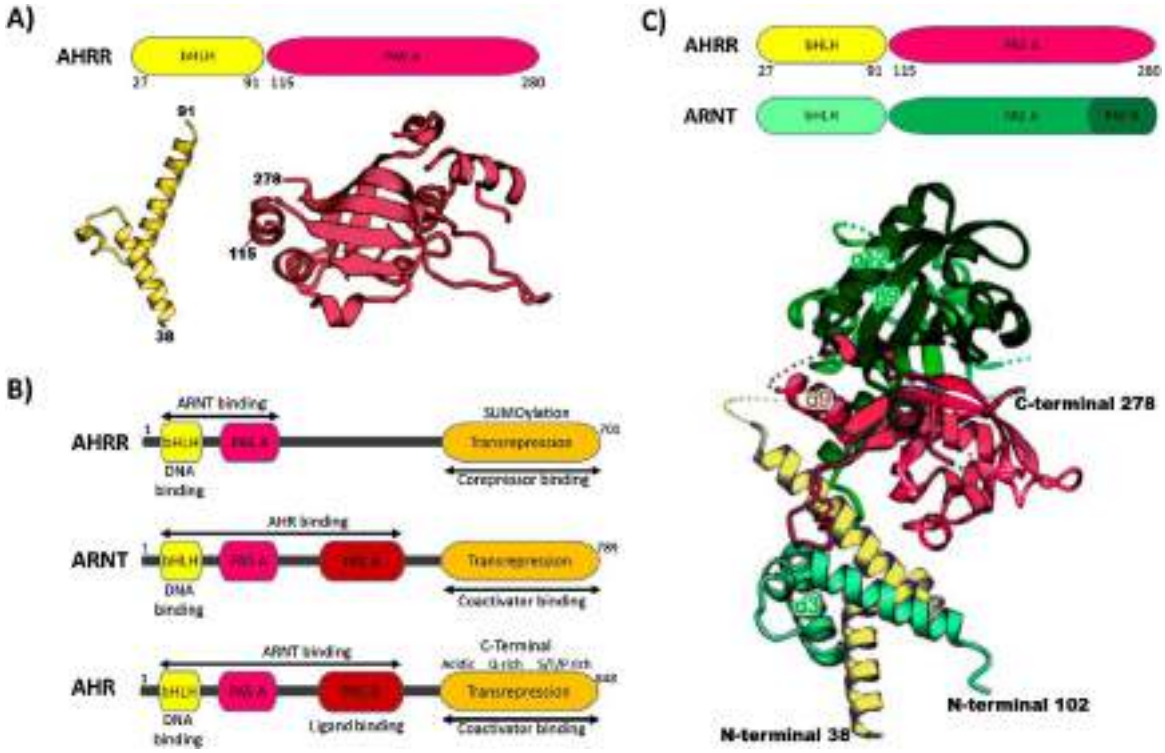

Fig. 4. AHRR, AHR and ARNT protein domains and structure. A) The proteins AHRR, ARNT and AHR have a bHLH domain and a PAS A domain, which are needed for DNA binding and dimerization (between AHR-ARNT and AHRR-ARNT). AHR has a PAS B domain, which binds ligands, such as TCDD. AHRR has a transrepressor domain, which binds to corepressors and undergoes SUMOylation. ARNT and AHR have a transactivator domain, which allows binding to coactivators. AHR has an additional C-terminal domain subdivided in acidic, Q-rich (glutamine enriched) and S/T/O rich (serine, threonine and proline enriched) subdomains. B) Crystal structure (3D) of the active AHRR protein domains bHLH (yellow) and PAS A (pink) complexes (bellow each domain it is represented the corresponding 3D protein structure). bHLH corresponds to the amino acid positions 27-91, and PAS A to the amino acid positions 115-280. C) Crystal structure (3D) of the active AHRR protein domains interacting with ARNT. *AHRR* (yellow and pink) and *ARNT* (green) gene structures (wide and narrow boxes) and below both 3D structures interaction. Yellow and light green represent bHLH while pink and green represent PAS A. The darkest shade of green represents PAS B. These figures were adapted from Sakurai et al. [64].

of this process can lead to transcription dysregulation and directly interfere in the phenotypes that are controlled by these genes as previously described.

Supporting data that also confirms the interaction between AHRR gene with other important genes and proteins discussed here have been documented in molecular interactome-type databases. According to the String: functional protein association database (https://string-db.org/), the interaction network of AHRR, at protein level, includes ARNT, ARNT2 (Aryl Hydrocarbon Receptor Nuclear Translocator 2), CYP1A1 (Cytochrome P450 family 1 subfamily A member 1), MYO1G (Myosin IG), ANKRD9 (Ankyrin Repeat Domain 9), FLYWCH1 (FLYWCH-Type Zinc Finger 1), F2RL3 (F2R Like Thrombin Or Trypsin Receptor 3), AHR, HIF1A (Hypoxia-inductible factor 1-alpha), EPAS1(Endothelial PAS domain-containing protein 1), EPHX1 (Epoxide Hydrolase 1) and F2 (Coagulation Factor II) (Fig. 5B) [50].

Additionally, some of the AHRR-related protein-protein interactions mentioned above are confirmed by an independent database of genetic interactions for the gene *AHRR*. Using PathwayCommons software [49], we found that the AHRR gene product interacts with the gene products of HDAC5, VIRMA (Vir Like M6A Methyltransferase Associated), ARNT, ANKRA2, HDAC4 and ESR1 (Estrogen Receptor 1) (interactions reported by HPRD-Human Protein Reference Database). AHRR also controls the expression of the gene products of TGFB1 (Transforming Growth Factor Beta 1), TIPARP [TCDD Inducible Poly(ADP-Ribose) Polymerase] and CYP1A1 (reported by Comparative Toxicogenomics Database and Reactome). AHRR also controls the state change of the gene products of CYP1A1 and AHR [Comparative Toxicogenomics Database (Fig. 5C)].

According to the protein interacting network, the proteins ARNT, ARNT2, RPL22 (Ribosomal Protein L22), XRCC6 (X-Ray Repair Cross Complementing 6), PNPO (Pyridoxamine 5′-Phosphate Oxidase), CYP1A1, CYP1B1 and MAP2K7 (Mitogen-Activated Protein Kinase Kinase 7) are members of the same complex as AHRR. ARNT, ARNT2 and AHRR are known to regulate *CYP1A1* expression, and AHRR can change the state of AHR and CYP1A1. Another important protein that might also modulate the expression of these proteins is TIPARP through the regulation of the expression of AHRR [49].

3.4. AHRR and cleft lip/palate

Due to the genetic heterogeneity of NSCLP, multiple genetic approaches have been applied to study either the whole genome or specific candidate genes. Some methods include linkage analysis with inbred or multiplex families, association studies with case-parent trios, identification of chromosomal anomalies, identification of microdeletions and CNVs (copy number variations) and direct DNA sequencing of probands [12].

In 2018, a study with probands from Brazil detected and compared different CNVs and identified multiple genomic *loci* related to NSCLP. The study described a duplication at the chromosomal band 5p15.33 that could predispose to an increased clefting risk [72]. In 2017, a study by Leslie and colleagues tested 1995 unrelated cases with NSCLP and 1626 unrelated controls selected from a larger set of cases, controls, and families recruited from 11 countries across North America, Latin America, Asia, and Europe. Cases included probands from unrelated families and unrelated individuals recruited as sporadic cases. Controls had no

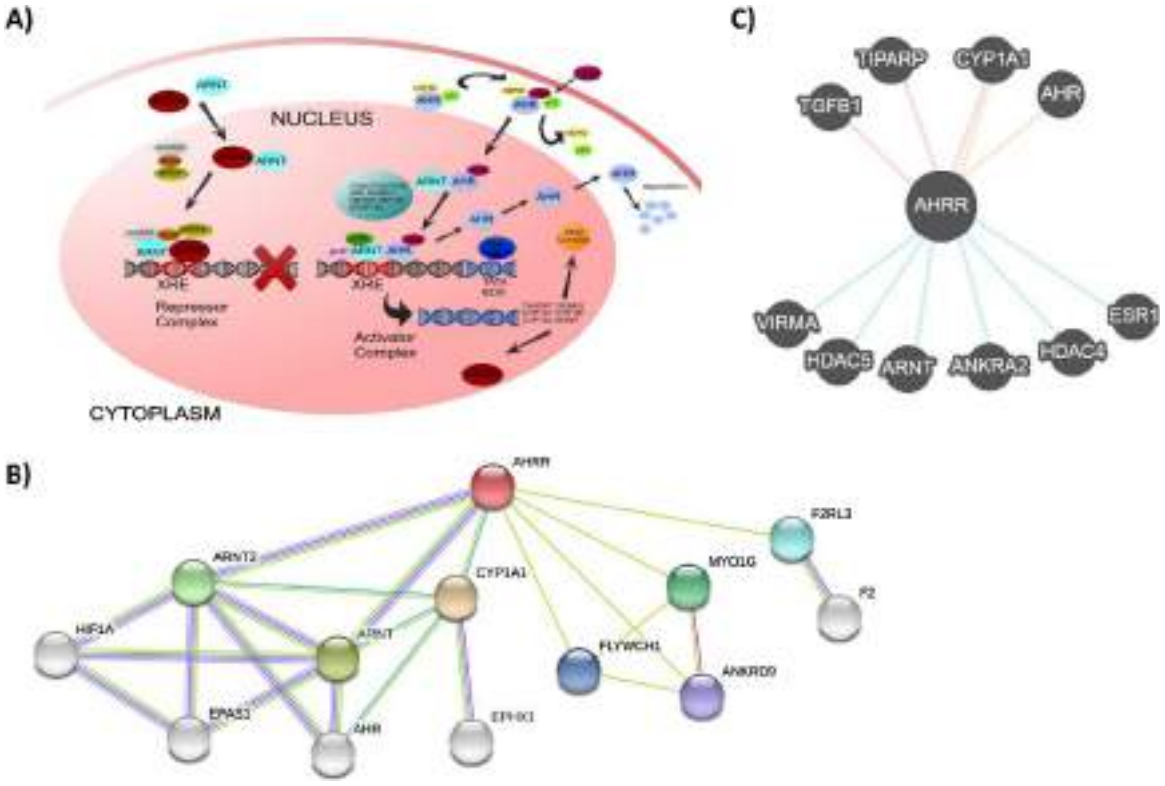

Fig. 5. Molecular pathways and genetic interactions of AHRR gene. A) When a ligand (TCDD) passes the plasma membrane through passive diffusion, it binds to AHR (PAS B domain). AHR usually exists in a dormant state within the cytoplasm associated with a complex of HSP90, p23 (co-chaperone) and other proteins. This ligand binding allows the dissociation of the ligand-AHR complex from HSP90/p23 complex and translocation of this complex into the cell nucleus. Inside the nucleus, the AHR complex binds to ARNT and forms a heterodimer. The AHR-ARNT dimer binds to XRE (xenobiotic response elements) a specific DNA sequence located in the promoter regions of target genes, and recruits components of the transcriptional machinery, such as CBP/p300 (cAMP response element-binding protein binding protein) and p/CIP (p300/CBP/CoIntegrator-associated Protein), as well as other transcriptional coactivators, such as RIP140 (Receptor Interacting Protein 140), pRb (retinoblastoma protein), SUMO1 (Small Ubiquitin Like Modifier 1), NEDD8 (neural precursor cell expressed, developmentally down-regulated 8) and ERAP140 (nuclear receptor coactivator 7). This process promotes the transcription of target genes *CYP1A1, CYP1B1, CYP1A2* and *AHRR*. ARNT forms a heterodimer with the synthesized AHRR, which enhances the SUMOylation of both proteins. SUMOylated AHRR recruits corepressors like ANKRA2, HDAC4, and HDAC5 creating a transcriptional repressor complex which also binds to XRE and represses the transcription of target genes. AHR is then exported and degraded in the cytoplasm by the proteasome. B) Protein-protein interaction network for AHRR in humans. Interactions identified in the String software [50]. The colored lines indicate known protein interactions that are determined by the following methods: experimentally determined (pink), curated databases (blue), predicted interactions with genes in the same neighborhood (green), text mining ((greenish yellow). **C)** Genetic interactions of AHRR gene with other known human genes. The genetic interactions depicted were generated using PathwayCommons software [49]. The blue line indicates that AHRR interacts with another gene, the pink line indicates that AHRR controls the expression of another gene, the orange line indicates that AHRR gene controls the state change of another gene.

known history of orofacial clefts and other craniofacial anomalies. This study analyzed low-frequency variants in a multiethnic population and then stratified them into three ancestry groups: Europeans, Latin Americans, and Asians. In the group of European population, six variants were reported in *AHRR*: rs111451538, rs200229746, rs111768223, rs35756515, rs61757546 and rs200762873 (Table 1). This was the first study to associate *AHRR* to an increased risk of NSCLP, even though there was no supporting evidence linking *AHRR* with a functional role in craniofacial development at the time [45].

Although the *AHRR* gene had not been connected to cleft lip/palate previously, the genomic pathway regulated by *AHRR* (TCDD-AHR pathway) had been linked with this condition [73]. By activating the AHR pathway, exogenous ligands, like TCDD, can induce dysregulation of tissue morphogenesis and insufficient differentiation of epithelial cells, causing not only cleft palate but

Table 1
Low frequency variants (MAF < 0.02) in AHRR gene found in a cohort of non-syndromic cleft lip with or without cleft palate individuals. Mutations were reported in a GWAS investigation (Leslie et al., 2017). The columns within table are described as follows: Gene is the gene name; CHR is the chromosome number; BP is the base position; SNP is the single nucleotide polymorphism code in SNPDB; A1 is the reference nucleotide; A2 is the alternative nucleotide; MAF is the minimum allele frequency; N is the absolute amount of individuals; Cases is the probands; Controls are the nonaffected individuals; Population is the geographic location of the individuals in which the study was conducted.

GENE	CHR	BP	SNP	A1	A2	Cases		Controls		Population
							MAF	N (Chrom.)	MAF	N (Chrom.)
AHRR	5	306807	rs111451538	A	G	0	1152	0.001796	1670	Europeans
AHRR	5	432995	rs200229746	A	G	0.000868	1152	0	1670	Europeans
AHRR	5	434146	rs111768223	T	C	0.01302	1152	0.00479	1670	Europeans
AHRR	5	434219	rs35756515	T	C	0.000868	1152	0	1670	Europeans
AHRR	5	434546	rs61757546	T	C	0.009549	1152	0.001198	1670	Europeans
AHRR	5	434581	rs200762873	G	C	0.003472	1152	0.000599	1670	Europeans

also other malformations in TCDD-exposed mice and zebrafish [74]. Furthermore, several known targets of AHR activation are important in the regulation of tissue and extracellular matrix (ECM) remodeling, which indicates that the AHR-pathway has an endogenous role in matrix metabolism and deposition. Besides the effects of the AHR pathway on ECM remodeling during the development, it is also critical for processes that require extensive remodeling such as wound repair and regeneration [75]. In zebrafish, it was demonstrated that expression and activity of proteases and ECM remodeling are required for full regeneration of tail fins after amputation [74,76]. Although indirect, this finding in zebrafish can suggest that rescuing any defect related to the misregulation of the molecules involved in ECM remodeling and proteases can play a role in the cleft lip phenotype.

TCDD administration to pregnant hamsters, mice and rats resulted in cleft palate in fetuses but did not result in cleft lip phenotypes [77]. In mice, the peak susceptibility period for the onset of cleft palate is between gestational days nine and twelve. According to Couture [78], TCDD administration to pregnant mice resulted in 93 % and 100 % incidence of cleft palate when given on gestational days 8 and 12, respectively. However, the incidence of cleft palate dropped to 40 % when TCDD administration occurred on gestational day 6 and no offspring had a cleft palate phenotype when administration occurred on gestational day 14. Interestingly, doubling of the TCDD dose on gestational day 6 produced 100 % incidence of cleft palate, indicating that high doses may expand the apparent window of susceptibility. On the other hand, the low incidence found in later periods did not depend on dosage and could be more related to palatogenesis completion timing [77–79].

In normal mouse development, palatal shelf elevation occurs from gestational day 14–14.25 and complete fusion ends by day 14.5. In TCDD exposed mice, not only is this process delayed by one day, but the fusion is less efficient and cleft palate is induced on gestational days 17−18. Even in successfully fused palate shelves, TCDD exposure on gestational day 15 leads to clefting on gestational day 17 in 5% of the fetuses, which suggests TCDD can disturb palatogenesis and induce post-fusional rupture of the palate [77,80]. According to Yamada [81], the best explanation of TCDD-induced cleft palate is medial edge epithelium disruption and fusional failure.

Also, palate shelf fusion initiates through periderm cells adhesion, as medial edge epithelial (MEE) palate shelf makes initial contact and adheres to the contralateral shelf. Afterwards, a medial epithelium seam is formed of periderms and MEE cells. This seam degenerates by cell death and the dying cells activate basal lamina degradation leading to mesenchymal confluence of the palate and completion of palatogenesis. According to Cuervo and Covarrubias, although the exact mechanism in which TCDD leads to cleft palate is unknown, one leading hypothesis is that TCDD impairs the growth of MEE cells in the palatal shelves [82–84].

In another study by Gao et al. [85], the effect of TCDD in cells isolated from human palate shelves were tested and revealed that TCDD promoted epithelial cell growth without effect on apoptosis. His results indicated cleft palate in TCDD-exposed embryos may be due to accelerated cell proliferation. Other studies have demonstrated cell-cycle-dependent effects of TCDD on gene expression and also AHR-dependent and AHR-independent effects of TCDD on cell-cycle progression [86,87]. Gao also, demonstrated that the proliferation of human palate shelve cells promoted by TCDD was mediated through an *AHR*-dependent activation of the PI3K/Akt pathway and its upstream components, like PDK1 and PTEN. The author suggests that changes in epithelium proliferation caused by TCDD may be responsible for the underlying mechanism by which TCDD induces palatal fusion failure, because cell death is an important aspect of palatogenesis [85].

Furthermore, when *AHR* is suppressed, TCDD exposure did not result in cleft palate, which indicates the important role of AHR in this pathologic process [76] and that most of the toxic effects of TCDD are mediated via *AHR* [88].

Considerable effort has been aimed at reducing levels of dioxins, like TCDD, in our environment. Different dioxins cause distinct levels of toxicity [77,89]. Nevertheless, dioxins levels should continue to be monitored, because even low level exposures can lead to a decrease in the threshold for multifactorial CPO pathogenesis [81]. In 2014, Yamada et al. [81] demonstrated that the mouse palatal bone is rich in AHR, which could enhance its sensitivity to TCDD. This study found an increase in AHR expression in muscle tissues, such as the tongue and masticatory muscles, after the administration of TCDD, suggesting a susceptibility to TCDD in osteogenesis and myogenesis [81].

In addition to the rodent studies described above, several investigations performed in humans also identified the *AHR* gene as a causative factor for CL/P. A whole exome sequencing (WES) study in a Honduran population correlated AHR to CL/P. The study used WES to identify CNVs in NSCLP multiplex families, which are families with two or more affected members. One of the analyzed families had two affected brothers, their unaffected mother, and unaffected grandfather. One of the brothers had complete bilateral cleft lip and palate while the other had complete unilateral cleft lip without cleft palate. Deletion of 13.3 kb and 23.6 kb in the region of AHR was found in the affected brothers. The CNV in AHR was identified in two affected siblings as well as their unaffected mother and maternal grandfather, consistent with an autosomal dominant mode of inheritance with incomplete penetrance [90].

Recent data has suggested that both CL/P patients and their first and second degree relatives are at an increased risk of developing malignant tumors [91,92]. In 2016, Dunkhase et al. [93] reported an overlap among genetic factors predisposing to clefts and cancer. This study identified multiple loci that were related to both pathologies and proposed that the genes in these regions may have a pleiotropic effect. Among the described regions was 5p15.33, associated with both NSCLP and lung cancer [93,94].

3.5. Smoking and alcohol associated with AHRR mutations and CL/P

Recent epigenetic studies have provided additional data supporting maternal tobacco exposure and lack of folate supplementation as risk factors for cleft palate. Prenatal maternal smoking and passive exposure to tobacco are known risk factors for CL/P [12] and preterm delivery, intrauterine growth restriction, low birth weight and potentially lifelong negative health consequences [95,96]. Cigarette smoke has numerous chemicals capable of penetrating the placenta such as polycyclic aromatic hydrocarbons, which bind to AHR and activate the AHR pathway [96,97]. Exposure to maternal smoking during pregnancy is associated with an increase in *AHRR* mRNA expression in cord blood mononuclear cells and is also associated with hypomethylation of the *AHRR* gene in umbilical cord blood, peripheral blood and buccal cells. The well described association between smoking and *AHRR* hypomethylation allowed this to become a biomarker for current and former smoking status [97–99]. A study by Fa et al. [99] tested whether exposure to maternal smoking in the first trimester changed DNA methylation and mRNA expression of *CYP1A1* and *AHRR*. This study detected two CpG sites in *AHRR* with an increase in methylation in placentas of female fetuses. Further, greater smoking exposure-associated mRNA expression was observed in first trimester fetal livers. Therefore, *AHRR* expression may be increased in fetal tissues, leading to *CYP1A1* repression, as a response to sustained maternal smoking and the long-term expression change can manifest as hypomethylation of specific CpGs within *AHRR* [99].

In 2018, Zhang et al. [100] published a comparison of DNA methylation in smoking and non-smoking African American

mothers and their newborns. The study confirmed epigenome-wide associations between maternal smoking and cord blood DNA methylation (DNAm) at multiple sites, including the *AHRR* gene and suggested that these DNAm changes related to smoking are present in whites and African Americans. This study also demonstrated that the adverse effect of maternal smoking on the newborn may vary according to sex and gene, with the male fetus more vulnerable to the impact of maternal smoking on DNAm than the female. Zhang et al. [100] also observed that some of these effects in DNAm can be partially mitigated by sufficient maternal folate levels, however, these investigators did not confirm that sufficient maternal folate levels can counteract the adverse effects of maternal smoking on child health [100].

Alcohol consumption is also associated with CL/P. In a large study of European individuals, multivariate analyses showed an increased risk of cleft lip (with or without cleft palate) associated with smoking and an increased risk of cleft palate associated with alcohol consumption [101].

In a similar investigation involving almost 6000 individuals that included maternal reports of periconceptional alcohol consumption and clefting, four subgroups were analyzed, formed by cases with cleft lip, cleft palate, cleft lip and palate, and unaffected controls. The study found an association between alcohol consumption and cleft lip, that might be most influenced by the type of beverage consumed and folic acid intake. However, the results were not significant and might not reflect causal associations [102] Thus, studies with larger cohorts are required.

Another population-based study examined maternal alcohol consumption and the risk of clefts among >4600 infants with cleft lip only, cleft lip with cleft palate, or cleft palate only, along with >10,000 unaffected controls [103]. Logistic regression analysis showed that mothers who drank an average of at least 5 drinks/sitting were more likely to deliver an infant with cleft lip only, and the estimate was higher among women who drank at least 3 times. It was also found that repeated heavy maternal alcohol consumption was associated with an increased risk of cleft lip only in offspring [103].

Another study found that cleft risk associated with maternal smoking generally declines with higher body mass index. This negative interaction was also observed for isolated clefts and across cleft types. They also found that the risk of clefts associated with maternal smoking is largest among underweight mothers [45].

Beyond smoking and drinking, several other environmental factors have also been reported to be potentially involved with cleft lip occurrence. Factors such as genetic, environmental, geographic and even race are important, but it is still inconclusive which ones can, together or in an isolated manner, define the phenotype for cleft lip [104]. Furthermore, increased population exposure to toxins may also have a negative impact by influencing CL/P formation, however novel investigations are required on this topic.

3.6. Important genes associated with cleft/lip palate

Studies have associated CL/P phenotypes and maternal polymorphisms in CYP1A1, RARA (Retinoic Acid Receptor Alpha), and NAT2 (N-Acetyltransferase 2), when passed to their offspring. These genes are considered the best candidate genes in terms of conferring a genetic predisposition to NSCLP, because they encode molecules responsible for the biotransformation of a great number of toxins and carcinogens present in diet, cigarette smoke, and environment [105–108].

Genetic variants in *CYP1A1* were investigated in a Japanese population of non-syndromic oral clefts using a transmission disequilibrium test (TDT) and case-control study, but none was found to be significant. Only mutations in the gene ARNT were significantly associated with the condition [109].

Another study of the *CYP1A1* gene investigated two large populations from Denmark and Iowa, one formed by 1244 subjects with facial clefting and the second formed by 4183 individuals corresponding to their parents, siblings, or unrelated population controls [106]. They found that mutations in the fetal NAT2 and CYP1A1 genes were observed in individuals with facial clefting. Additionally, mutations in NAT2 also showed significant over transmission of a mutated allele to the fetus.

Another study of patients with NSCLP analyzed eight and five SNPs in the genes *NAT1 (N-Acetyltransferase 1) and NAT2,* respectively, in a population of 204 probands and 226 controls [110]. Strong evidence of an association between NSCLP and mutations in the genes *NAT1* (SNP rs4921580) and *NAT2* (rs1041983) was found, and a combination of these mutations were found to increase the risk of NSCLP, suggesting that interactions between the *NAT1* and *NAT2* genes may be important in susceptibility to NSCLP [110]

SNPs in *NAT2* gene were also found in a study of 97 Argentinian progenitor-case trios of NSCLP [105]. After applying a transmission disequilibrium analysis, a mutated allele (481C > T, rs1799929) was found to be significantly higher in those cases with congenital NSCLP. Another study checked a single genetic variant in the gene *NAT2* (rs1799929) in a group of 285 NSCLP patients and in 315 controls, but did not found any significant association with the condition [111].

For the RARA gene, several other studies investigated its connection with NSCLP occurrence. In a study involving 36 multiplex families [310 individuals, 23 families whose probands had CL/P, 13 with cleft lip alone (CL), with probands from hospitals in Shanghai, China], loci on chromosome 17, including the RARA gene, was investigated for the occurrence of genetic variants [107]. A significant association between the RARA locus and the pathogenesis of non-syndromic oral clefts was found. Further, the formation of CL and CLP was due to either differing alleles at the same genetic locus or different but related (and/or linked) genes that modify the severity and expression of oral clefting [107].

Another investigation of the association between the RARA gene locus and NSCLP in 48 Japanese parent-offspring trios, involved exon-by-exon sequencing and a transmission disequilibrium test (TDT) [112]. The investigation did not find any variant associated with NSCLP, suggesting that variations in RARA gene do not contribute to the development of the condition, at least with respect to the tested variants [112]. However, a positive correlation between the RARA gene alleles and NSCLP was found by an independent study [108]. The study investigated 140 Hunan Hans with NSCLP. It was found that two alleles of the RARA gene presented at significantly higher frequency in affected individuals compared to healthy individuals, suggesting that these alleles may be correlated with the development of NSCLP [108].

Based on these studies, it has become evident that additional research is required to better establish how mutations in all CLP-candidate genes can determine the phenotypes of this birth condition.

In conclusion, *AHRR* has an important role in the response to exogenous toxins, figures in gene-environment interaction leading to several multifactorial diseases, and, therefore, could also be influencing the occurrence of NSCLP. Although additional data and investigations are required to conclude that *AHRR* has a pathogenic effect on this disease, several analyses could be proposed to support the genotype-phenotype connection. The inclusion of this gene in GWAS investigations, as well as performing novel studies with CL/P multiplex families can improve the power of the correlation between genetic variants in this gene and specific types of the condition. Additionally, current genetic variants described within the *AHRR* gene could be subjected to functional studies to verify the potential contribution to the CL/P phenotype. Using in vitro and animal models, this gene can be modulated,

overexpressed, knock-down or inactivated using CRISPR/cas9-based technology to verify the molecular, cellular and morphological impact in animal offspring carrying mutations in this gene. Such studies are needed to develop a more precise genotype-phenotype understanding for *AHRR* and guide future studies.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.] We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email.

Acknowledgements

RHH is supported by the Fundação Araucária (FA, Brazil) (grant #FA 09/2016). BDWL was financed by the Institutional Master Fellowship Program (PIBIC-Master) of Pontifícia Universidade Católica do Paraná (PUCPR, Brazil).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mrrev.2020.108319.

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