



# The phenotypic characteristics of patients with athelia and tooth agenesis

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**Background:** Although athelia, which is a congenital aplastic deformity of the nipple, is seldom reported in tooth agenesis patients, we observed athelia in 2 hypodontia patients. This study aimed to summarize the phenotypic characteristics of patients with athelia and tooth agenesis.

**Methods:** A database search was conducted for publications reporting on patients with athelia and tooth agenesis, and the phenotypes of such patients were recorded. Athelia-related syndromes were identified in the Online Mendelian Inheritance in Man (OMIM) database. The common symptoms and the causative genes were documented. Potential interactions between athelia-related genes and tooth agenesis-related genes were analyzed in the Database for Annotation, Visualization, and Integrated Discovery (DAVID) Bioinformatics Resources and the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database.

**Results:** We summarized the phenotypic characteristics of 8 previously reported patients. Deformities in hair, skin, and sweat glands were common in these patients. There were 23 nipple deformity-related syndromes reported. The most common symptoms included abnormalities of the head and neck, cardiovascular, genitourinary, and skeletal systems, and the skin, nails, and hair. Hypodontia was noted in association with 10 syndromes. A total of 16 genes were related to them, including *TP63*, *KCTD1*, and *IKBK*. The interaction found in the study suggests that nipple deformity-related genes potentially interact with tooth agenesis-related genes.

**Conclusions:** These results indicated that athelia might be related to hypodontia. Additional molecular genetics research is needed to fully elucidate the underlying relationship between athelia and tooth agenesis.

**Keywords:** Athelia; tooth agenesis; hypohidrosis; phenotype; genotype

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## Introduction

Agenesis of the teeth, including the third molars, is one of the most common diseases, affecting 200 million people around the world (1,2). Based on the number of missing teeth, it includes hypodontia (<6 teeth missing), oligodontia

(≥6 teeth missing), or anodontia (all teeth missing) (3). Tooth agenesis can occur as an isolated anomaly or in association with a syndrome or a cluster of other anomalies, such as cleft palate or nail dysplasia (4). The most common syndromic tooth agenesis is ectodermal dysplasia (EDs),

which is characterized by the dysplasia of ectodermal structures (5-7). Patients present with defects relating to hair, nails, teeth, and sweat glands.

Congenital aplastic deformities of the nipple include inverted nipple, absent nipple (athelia), and can also involve the absence of breasts (amastia). The combination of nipple deformity and tooth agenesis rarely appears except in acro-dermato-ungual-lacrimal-tooth syndrome (ADULT syndrome) (8). The phenotypic features of ADULT syndrome include ectrodactyly, syndactyly, fingernail and toenail dysplasia, hypoplastic breasts and nipples, lacrimal duct atresia, and hypodontia.

In this study, we reviewed the literature in databases and summarized the features of previously reported patients who had both tooth agenesis and nipple deformity. Furthermore, we analyzed the underlying connection between athelia and tooth agenesis through predicted protein interaction.

## Methods

### *Nomenclature*

Gene symbols used in this article follow the protocol created by the Human Genome Organization (HUGO) Gene Nomenclature Committee (9).

### *Literature review*

The databases of PubMed and Institute for Scientific Information (ISI) Web of Knowledge, were searched for relevant publications. The references listed in the retrieved full articles were also included in our literature review. The keywords, (“athelia” or “tooth agenesis”), (“athelia” or “tooth missing”), (“athelia” or “hypodontia”), and (“athelia” or “oligodontia”), were used as search terms. The full texts were reviewed by 2 researchers. Only English and Chinese publications were selected. Searches for nipple deformity-related syndromes were conducted in Online Mendelian Inheritance in Man (OMIM) and PubMed. The phenotypic features and causative genes of patients were summarized.

### *Study eligibility and data collection*

The exclusion criteria were as follows: (I) patient phenotype was not reported; (II) the publication did not include original data; and (III) authors or institutes overlapped in the published literature. The reported patient phenotypes were extracted.

### *Bioinformatic analysis of nipple deformity-related genes*

The systematic and integrative analysis was conducted through the Database for Annotation, Visualization, and Integrated Discovery (DAVID) Bioinformatics Resources (<https://david-d.ncifcrf.gov>) according to the instruction of the database (10,11). The predicted protein interaction was analyzed using the (Search Tool for the Retrieval of Interacting Genes/Proteins) STRING database (Version 10.0) (<http://www.string-db.org>) under stated instructions (12).

## Results

### *Nipple deformity-related syndromes*

We had observed athelia in 2 hypodontia patients in 2017 in the dental clinic. To further analyze whether there was a correlation between hypodontia and nipple deformity, we summarized the previously reported cases involving patients with hypodontia and nipple deformity (13-20) (*Table 1*). There were 12 studies that had reported patients with athelia and tooth agenesis. After literature review, 8 studies were included in this analysis. In addition, the 2 patients with severe hypodontia, hypohidrosis, and eczema whom we had encountered in clinic were also included (*Figure 1*). Then, we listed the nipple deformity-related syndromes identified in the literature review (*Table 2*). Nipple deformity was reported to be associated with 23 syndromes. Patients with these syndromes had abnormalities of the head and neck; cardiovascular, genitourinary, and skeletal systems; and the skin, nails, and hair. Hypodontia was documented in 10 syndromes which involve 16 genes including *TP63*, *KCTD1*, and *IKBKKG*.

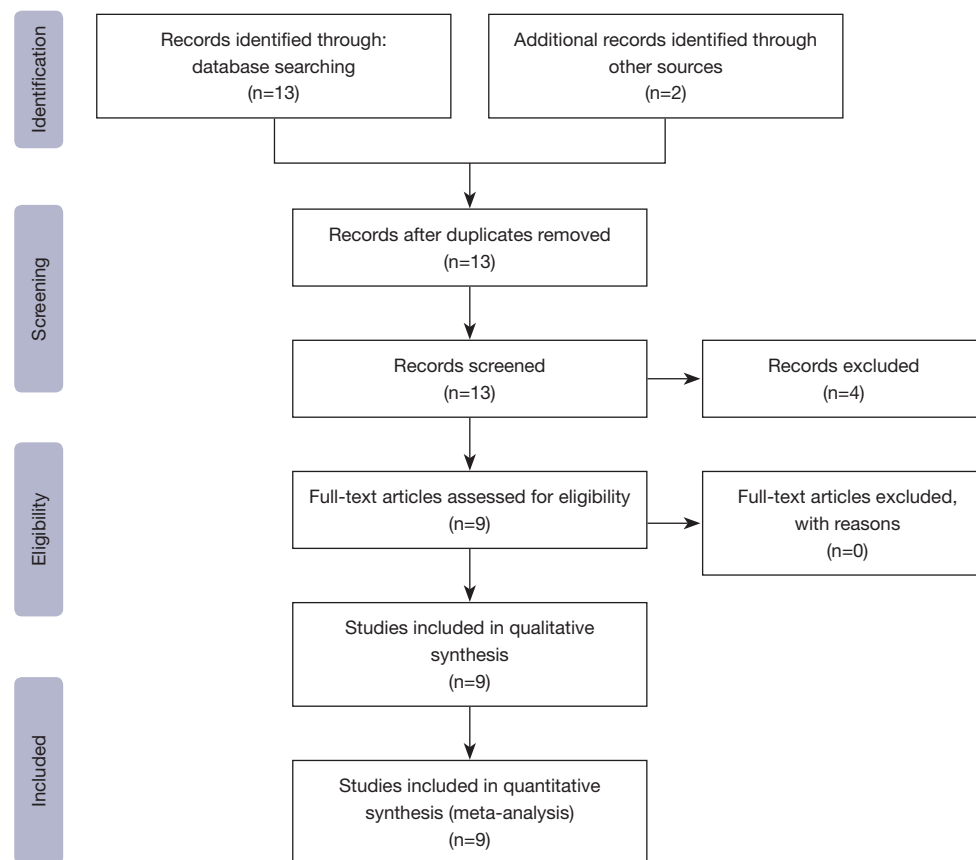
### *The gene network underlying hypodontia and nipple deformity*

After we identified the genes related to hypodontia and nipple deformity, we further analyzed the biological function of these genes. Most of them negatively regulated the “transcription”, “gene expression”, and “nucleobase, nucleoside, nucleotide, and nucleic acid metabolic process” (*Table 3*). Furthermore, we analyzed their interactions through the STRING database. Among these nipple deformity-related proteins, *KDM1A* directly interacted with *NSD1* and *ASXL1* (*Figure 2*). The interactions among them were more complicated if they were connected with other molecules (*Figure 3*). Then, we added hypodontia-related (*EDA*, *HYD2*, *LTBP3*, *MSX1*, *PAX9*, *STHAG5*, and

**Table 1** Clinical feature of reported hypodontia patients with nipple deformity

| Study             | Gender | Tooth           | Hair          | Eyebrows | Eyelash | Nipples | Nail            | Skin | Sweat gland  |
|-------------------|--------|-----------------|---------------|----------|---------|---------|-----------------|------|--------------|
| 1 (13)            | M      | Irregular shape | Total absence | NM       | NM      | Athelia | Thin, curved    | Thin | NM           |
| 2 (14)            | M      | NM              | Alopecia      | NM       | NM      | Amastia | N               | Thin | Hypohidrosis |
| 3 (15)            | M      | Oligodontia     | Alopecia      | NM       | NM      | Amastia | N               | Thin | Hypohidrosis |
| 4 (16)            | M      | Anodontia       | Alopecia      | NM       | NM      | Amastia | N               | Thin | Hypohidrosis |
| 5 (17)            | M      | Anodontia       | Alopecia      | NM       | NM      | Amastia | N               | Thin | Hypohidrosis |
| 6 (18)            | F      | Hypodontia      | Sparse        | Sparse   | Sparse  | Athelia | N               | NM   | NM           |
| 7 (19)            | M      | Hypodontia      | Aplasia cutis | NM       | NM      | Athelia | Dystrophic      | NM   | Hypohidrosis |
| 8 (20)            | F      | NM              | Sparse        | NM       | NM      | Amastia | NM              | Dry  | NM           |
| 9 (current study) | M      | Oligodontia     | Sparse        | Sparse   | Sparse  | Athelia | Onychogryphosis | Dry  | Hypohidrosis |

NM, not mentioned; N, normal.

**Figure 1** Flow diagram of the systematic review process.

*WNT10A*) and ectodermal dysplasia-related (*EDA*, *EDAR*, *EDARADD*, and *TRAF6*) genes to the analysis. More complicated interactions were observed (Figures 4,5). It is

worth mentioning that there are still many pedigrees with agenesis of the teeth in which the causative gene has not been successfully identified. The whole exome sequencing

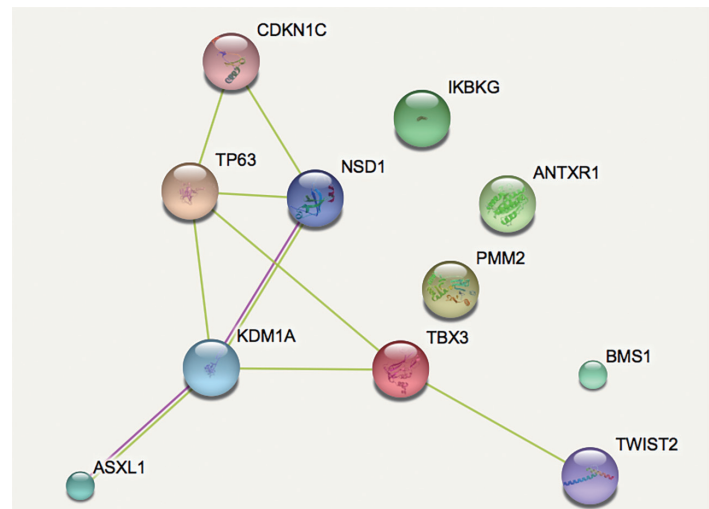
**Table 2** The phenotypic characters of nipple deformity-related syndromes

| OMIM (#) | Ears | Eyes | Nose | Teeth | Breasts (nipples) | Feet | Hands | Limbs | Hair | Nails | Skin |
|----------|------|------|------|-------|-------------------|------|-------|-------|------|-------|------|
| #604313  | +    | +    | +    |       | +                 | +    | +     |       | +    | +     | +    |
| #308300  |      | +    |      | +     | +                 |      |       |       | +    | +     | +    |
| #616728  | +    | +    | +    | +     | +                 | +    | +     |       |      |       |      |
| #181450  |      | +    |      | +     | +                 | +    | +     | +     | +    |       | +    |
| #173800  |      |      |      |       | +                 |      | +     |       |      |       |      |
| #129550  |      |      |      | +     | +                 |      |       |       |      | +     | +    |
| #107600  |      |      |      |       |                   |      |       |       |      |       | +    |
| #209885  | +    | +    | +    | +     |                   |      |       |       | +    |       | +    |
| #163700  |      |      |      |       | +                 |      |       |       |      |       |      |
| #212065  | +    | +    | +    |       | +                 |      |       | +     |      |       | +    |
| #603543  |      | +    |      | +     | +                 | +    | +     |       |      | +     | +    |
| #130650  | +    | +    |      |       |                   |      |       |       |      |       | +    |
| #613884  | +    | +    | +    |       |                   |      |       |       |      |       |      |
| #164210  | +    | +    |      |       |                   |      |       |       |      |       |      |
| #605039  | +    | +    | +    |       |                   | +    | +     | +     | +    |       | +    |
| #218649  | +    | +    | +    |       | +                 |      | +     |       |      |       | +    |
| #616001  | +    | +    | +    |       | +                 |      |       |       |      |       |      |
| #113700  |      |      | +    |       | +                 |      |       |       |      |       |      |
| #167950  |      |      |      |       |                   |      |       |       |      |       | +    |
| #181270  | +    | +    | +    | +     | +                 | +    | +     |       | +    | +     | +    |
| #305600  | +    | +    | +    | +     | +                 | +    | +     | +     | +    | +     | +    |
| #235730  | +    | +    | +    | +     | +                 |      |       |       | +    |       |      |
| #230740  | +    | +    | +    | +     | +                 |      |       |       | +    |       | +    |

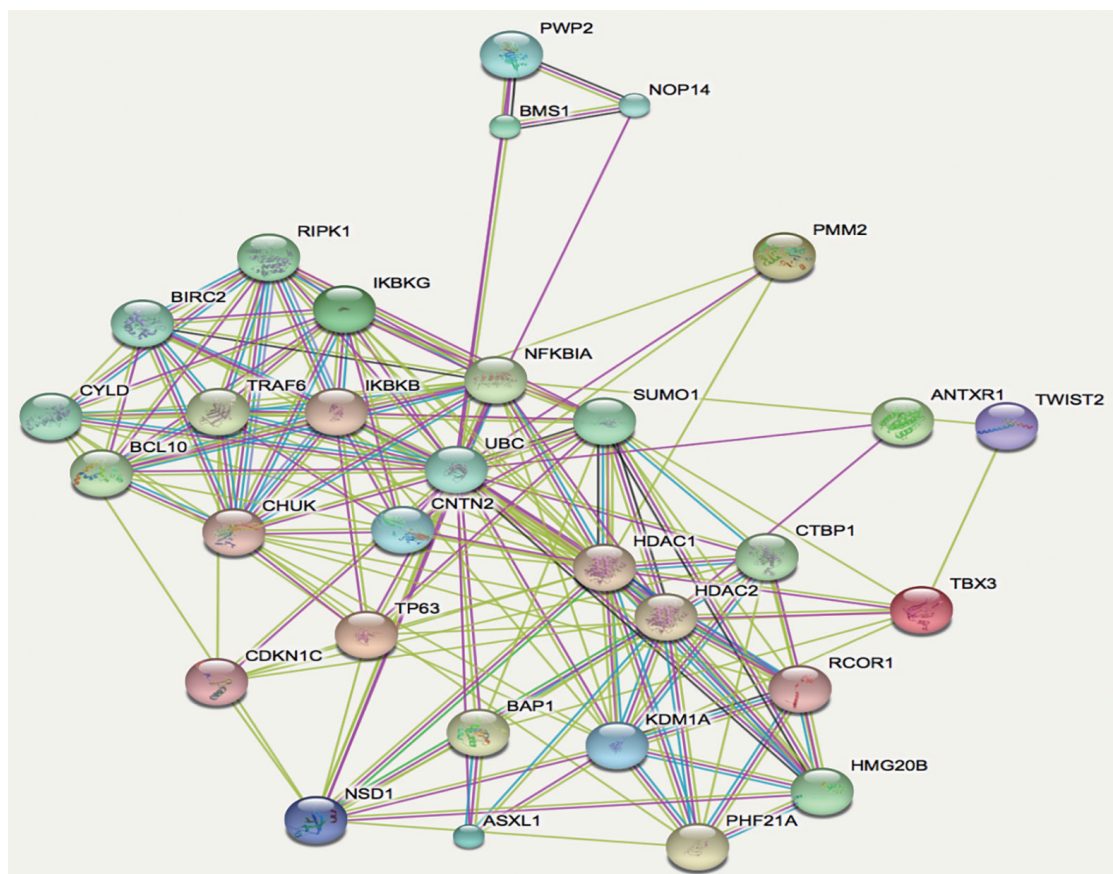
#, number of OMIM.

**Table 3** Function analysis of athelia-related genes

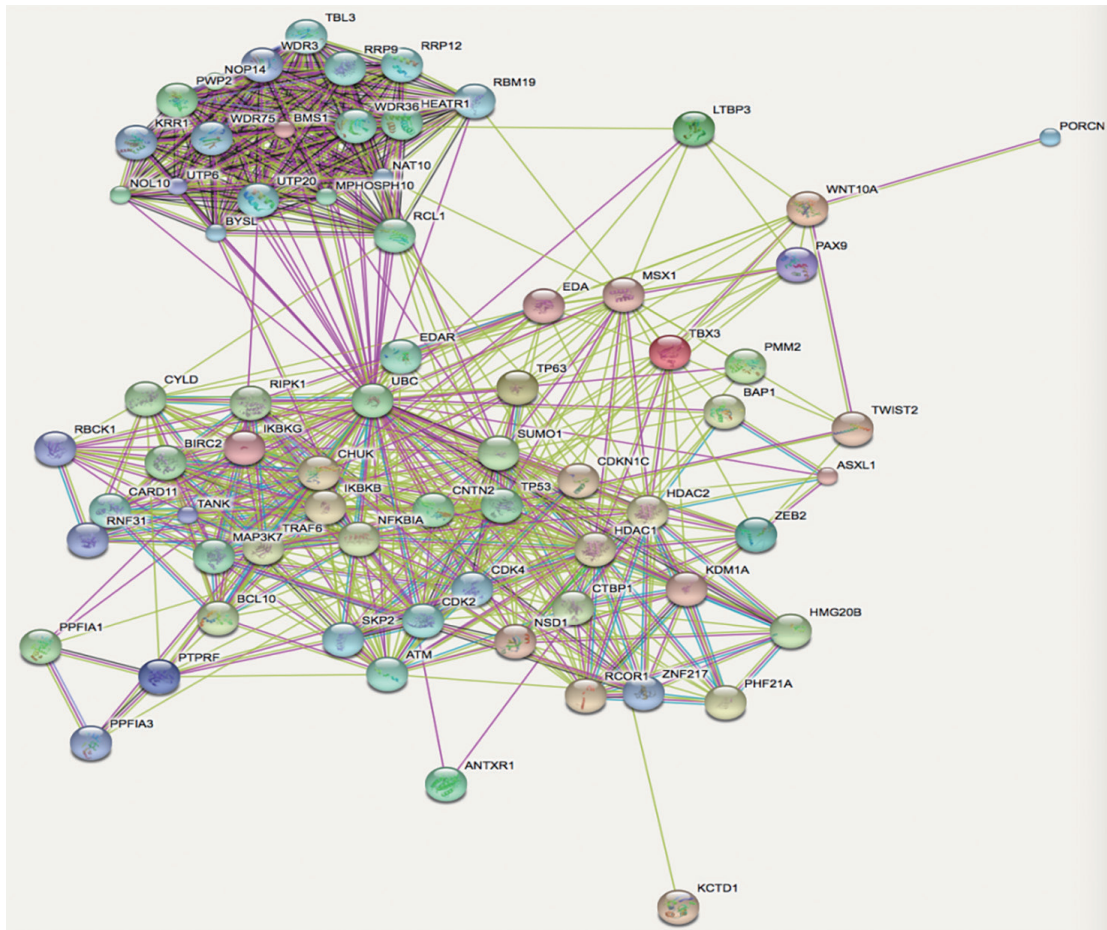
| Function  | Gene number |
|---|-------------|
| Transcriptional regulation (negative)   | 7           |
| Gene expression regulation (negative)   | 7           |
| Nucleobase, nucleoside, nucleotide and nucleic acid metabolic process regulation (negative) | 7           |
| Nitrogen compound metabolic process regulation (negative)                                   | 7           |
| Transcription repressor activity  | 6           |
| Macromolecule biosynthetic process regulation (negative)                                    | 7           |
| Repressor   | 6           |
| Cellular biosynthetic process regulation (negative)   | 7           |
| Biosynthetic process regulation (negative)  | 7           |
| Transcription, DNA-dependent regulation (negative)  | 6           |



**Figure 2** Network view of athelia-related proteins analyzed using the STRING database. The confidence level of the minimum required interaction score was set at medium. STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.



**Figure 3** Network view of athelia-related proteins analyzed using the STRING database. The confidence level of the minimum required interaction score was set at low. STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.



**Figure 4** Network view of athelia- and hypodontia-related proteins analyzed using the STRING database. The confidence level of the minimum required interaction score was set at low. STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.

provides a solution to this problem and has been used successfully in several case.

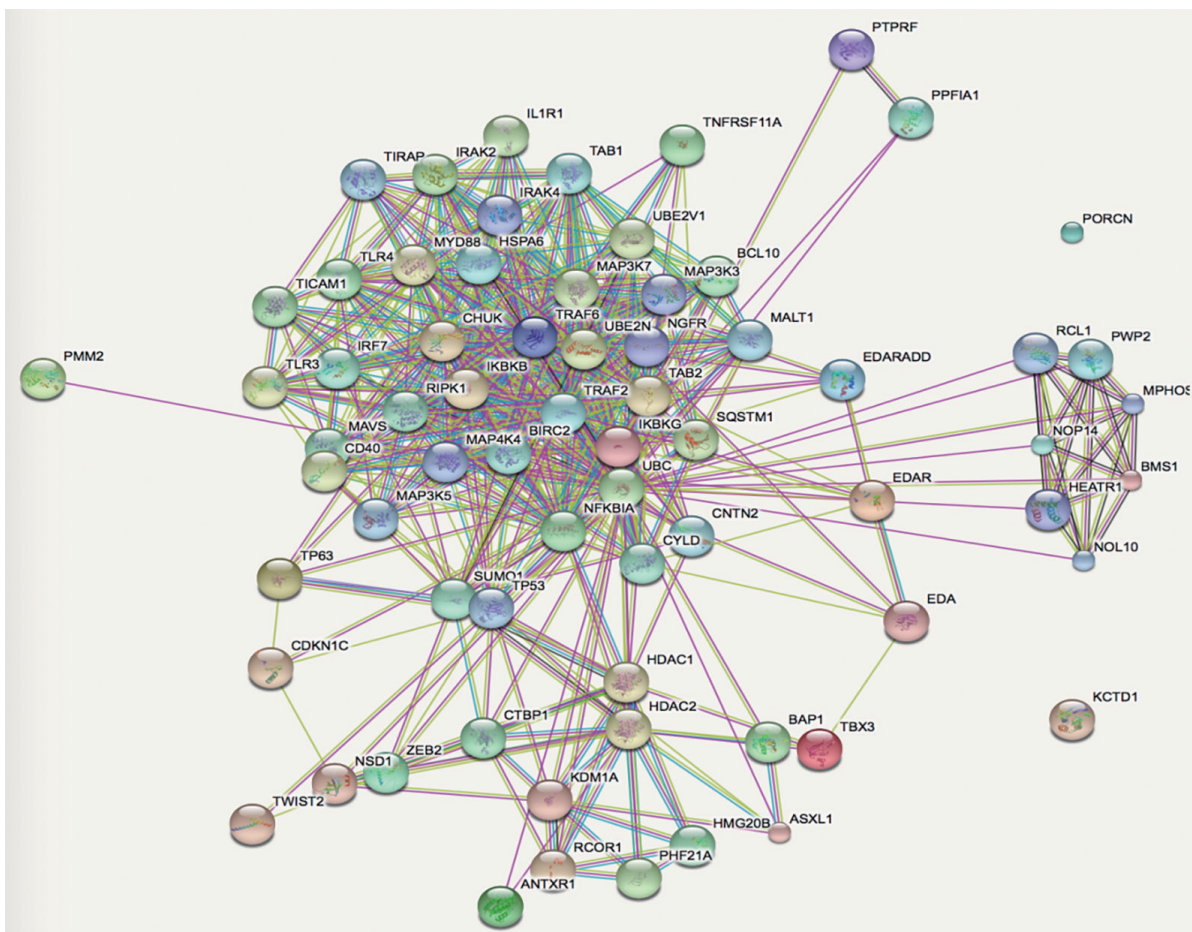
## Discussion

Congenital aplastic abnormalities of the breast and nipple were first reported in 1802 (21). Such abnormalities can be divided into 3 categories: total absence of the breasts and nipple (amastia), absence of the nipple (athelia), and absence of the mammary gland (amazia). They are predominantly isolated deformities, although approximately 15% are associated with other anomalies (22), in which the ADULT syndrome and Finlay-Marks syndrome (23) are known for nipple and tooth abnormality.

Athelia was first reported in EDs patients in 1886 (13). It has been reported in more than 10 cases since then. It is noteworthy that most athelia and tooth agenesis patients

have been males who had alopecia or aplasia cutis, whereas EDs patients usually only displayed sparse hair. The missing number of teeth was also larger than that of EDs patients. Although there reports of patients with both athelia in tooth agenesis patients have been scarce, we believe that the combination of these 2 symptoms may not be so rare as patients infrequently mention nipple dysplasia when they visit the dental clinic. In our experience, our patient was referred to the prosthodontic clinic for oligodontia treatment, with no complaints of other deformities. Athelia was observed upon physical examination, although this critical defect would have remained unnoticed if we had only focused on his dental defect.

The correlation between hypodontia and athelia seems to be reasonable. First, the development of tooth and nipple in embryo is synchronous. Both nipple and teeth originate from the ectoderm. The development of breasts and nipples



**Figure 5** Network view of athelia- and EDs-related proteins analyzed using the STRING database. The confidence level of the minimum required interaction score was set at low. STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; EDs, ectodermal dysplasia.

begins during the sixth embryonic week, while tooth development begins in the fifth week. Additionally, as shown in *Figures 2-5*, the causative genes for athelia and hypodontia are also closely connected. Molecular genetics research is needed to fully elucidate the underlying relationship between athelia and tooth agenesis in the future.

## Conclusions

In this study, we reviewed the phenotype of previously reported patients with hypodontia and nipple deformity. The phenotypic summary and gene network analysis suggested that tooth agenesis might be correlated with athelia.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-5159>). The authors declare that this work was supported by Fujian Natural Science Youth Innovation Fund Project (2020D034), Xiamen Medical and Health Guidance Project (3502Z20214ZD1275) and the Scientific and Technological Plan Projects in Xiamen (Medical and Health Program) (3502Z20199086). The authors have no other conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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