Genetic Role in Ameloblastoma: A Systematic Review

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Abstract

As one of the most prevalent benign oral tumor, genetic contribution in development of ameloblastoma was not reported as extensively as its malignant counterpart. Therefore, the aim of this study is to summarize the role of genetic in ameloblastoma. English literatures were retrieved using the following term “Ameloblastoma” and “genetic” from PubMed and Scopus (Last search was updated on February 2015). A total of 6 studies and 6 genes were included in this review.

The subjects in the study were population of Thai, Japanese, Finland, Turkey and USA. XRCC1 T allele at codon 194 and A allele at codon 399 increased the occurrence of ameloblastoma 1.62-fold and 1.83-fold respectively. P53 codon 72 contributes with its Arg Allele promoting the ameloblastoma 2.06 times higher. BRAF mutation and SMO mutation both occurred in ameloblastoma, with BRAF mainly affected mandible whereas SMO influenced maxilla. However, IL-1α-889 and PTCH1 polymorphisms were not associated with ameloblastoma. Identification of risk factor genes involving wider population are needed to confirm particular genes’ effect in the development of ameloblastoma.

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Introduction

Ameloblastoma is a locally destructive odontogenic tumor that could result in significant facial deformity and functional disturbance.[1,2] Pathogenesis of this highly recurrent neoplasm at molecular level involves complicated regulation, which also includes the role of genetic alteration of the tooth-forming apparatus.[3] Some of the important genes are bone morphogenetic proteins (BMP), fibroblast growth factor (FGF), patched (PTCH), and sonic hedgehog (SHH).[4] Not only gene mutations, transformation of a single nucleotide in a gene itself may generate different protein, and eventually aberrant clinical feature. Single nucleotide polymorphisms (SNP) have been associated with various types of malignancies, not to mention oral cancer.[5,6]

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Several studies investigated FOS, Tumor-necrosis-factor-receptor 1A (TNFR1A), and matrix metalloproteinase (MMPs) that had roles in cell proliferation, cell differentiation, apoptosis, and tumor invasion.[7] These genes’ expressions have been reported in other malignancies, such as hepatocellular carcinoma, breast, and colon carcinoma. They were also found to be highly expressed in ameloblastoma.[7]

On the contrary, CDH, TGFB1, NOTCH, and TGFB1 which involved in cell adhesion were under expressed and contribute to locally aggressive properties of ameloblastoma.[7] Moreover, ameloblastoma was reported to show similarities to basal cell carcinoma in terms of development as both of the tumors have mutations in SHH pathway.[4]

Genes that were involved in malignancies could also be related to ameloblastoma development. Nevertheless, contribution of gene polymorphism and mutation in development of ameloblastoma as one of the most prevalent benign oral tumors was not reported as extensively as its malignant counterpart. Thus, the aim of this study is to summarize the role of genetic as risk factors for ameloblastoma.

Materials and methods

English literatures were retrieved using the following term “Ameloblastoma” and “genetic” from PubMed and Scopus (Last search was updated on February 2015). Eligible articles studies that evaluate certain gene polymorphism or mutation in ameloblastoma. The selection was based on PRISMA flow diagram.[8] First author’s names, publication year, country of origin, study type, sample size, contributing gene and its specification were obtained from each study.

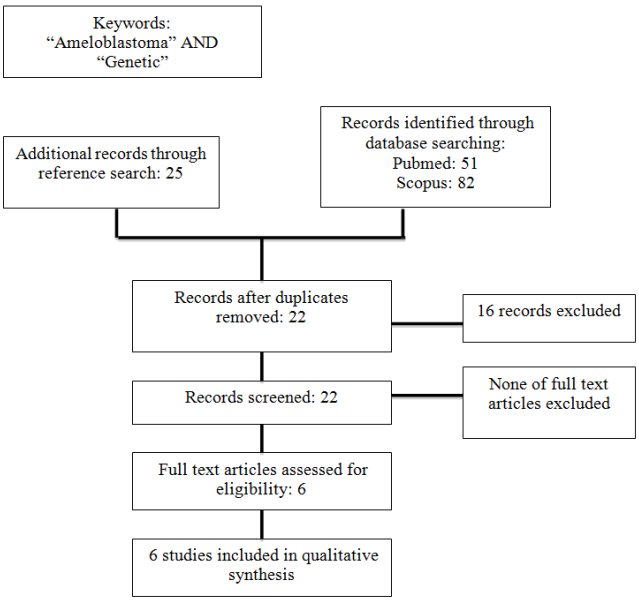

Diagram 1. Study selection process diagram.

Results

Table 1 reveals a total of six studies including six genes. Four articles were case control studies and the other two were cohort studies. Countries of origin were Thailand, Japan, Turkey, Finland and USA. Regarding the genes, XRCC1 gene polymorphism was reported to have role as risk factors for ameloblastoma. T allele at codon 194 increases the occurrence of ameloblastoma. The odds ratio or OR (95% CI) of this allele was 1.62 (1.05 – 2.48), p = 0.027. At codon 399, A was susceptibility allele with OR (95% CI) 1.83 (1.19 – 2.84), p = 0.005.[9] Other gene that possibly leads to the growth of the tumor was PTCH1, particularly CGG7/8 genotype and CGG8/8 genotype with OR (95% CI) 2.8 (0.7 – 11.4) and OR (95% CI) 7.7 (0.6 – 97.8) respectively (p=0.04).[10] Arg Allele of P53 codon 72 as a well-known tumor suppressor gene increased the risk of developing ameloblastoma with OR (95%CI) 2.06 (1.28-3.31), p = 0.002.[11] On the other hand, IL-1α polymorphism at codon 889 was not associated with ameloblastoma (p>0.05).[12]

Author (publication year)	Country of Origin	Type of study	Sample size (case/ control)	Gene	DNA Sequence variation	Specification
Yanatatsaneejit (2013)	Thailand	Case control	82/140	XRCC1	Polymorphism	194 T Allele 399 A Allele
Kawabata (2005)	Japan	Case control	14/35	PTCH1	Polymorphism	CGG7/8 genotype CGG8/8 genotype
Kitkumthorn (2010)	Thailand	Case control	78/94	P53	Polymorphism	72 Arg Allele
Senguven (2010)	Turkey	Case control	25/15	IL-1α	Polymorphism	889 T Allele
Sweeney (2014)	USA	Cohort	24/14	SMO BRAF	Mutation	L412F V600E
Kurppa (2014)	Finland	Cohort	28/-	BRAF	Mutation	V600E

Table 1. Characteristic of studies included in the review.

Furthermore, SMO mutations occurred in 39% (11/28) of the tumors while BRAF mutations were identified in 46% (13/28) cases with p = 0.02.[13] Moreover, SMO mutation was higher in maxilla (9/11) than in mandible (1/13) (p<0.0001) whereas BRAF mutation was found higher in mandible (9/13) than in maxilla (1/11). Other study also exhibited high frequency of BRAF in ameloblastoma, 63% of the tumours (15/24) harbored the BRAF V600E (1799T > A) mutation, but not related to clinical condition (p > 0.1).[14]

Discussion

After conducting the search, there were only six studies that were eligible to be included in this review. The limited amount of study and small number of population that were involved affected the probability of the gene as a risk factor. Larger population might produce a different result.

First gene was XRCC1. XRCC1 or X-ray repair complementing defective repair in Chinese hamster cells 1 gene encodes XRCC1 protein in BER pathway, which is responsible for replacing damaged bases from the genome with normal bases in order to keep the stability of the cells. XRCC1 binds as a scaffold to ligase III, DNA polymerase β, APE1, PARP1, PARP2, APE1 and other protein in repair process. Gene polymorphism was reported in codon 194, 280, and 399.[9] While codon 280’s function remains unidentified, codon 194 binds with DNA

polymerase β and codon 399 binds with APE1, PARP1 and PARP2.[9] Polymorphism at these codons might influence the stability of cell repair. However, there was only one report that we found studying the contribution of XRCC1 polymorphism to development of ameloblastoma. The authors of the report used OR and 95% CI to calculate the risk and association between ameloblastoma and SNP. According to the result, individual who had XRCC1 polymorphism at codon 194 showed 1.62-fold risk of developing ameloblastoma while the occurrence of ameloblastoma was 1.83-fold higher in those who had polymorphism at codon 399.[9] Despite the significant association, the result also demonstrated wide confidence intervals that might be caused by a small number of samples. Therefore, this result still has uncertainty and further study is needed.

Next gene was PTCH1. It encodes a protein with 1447 amino acid residues, which is believed to be a receptor for Sonic Hedgehog molecus. Nevoid basal cell carcinoma syndrome with multiple odontogenic keratocyst as one of its features is found as a consequence of PTCH1 mutation, along with sporadic odontogenic keratocysts, basal cell carcinoma, medulloblastoma, breast cancer, meningioma, and colon cancer.[15] Although CGG7/8 genotype and CGG8/8 genotype were reported to have 2.8 and 7.7 OR respectively, their confidence intervals were very wide and include 1.[10] Hence, the result in the study was not significant. Limited sample size, once again, could cause this issue.

The third gene was P53, which is one of the most extensively investigated genes. It maintains the integrity of gnome by preventing tumorigenesis. Various cancers have P53 polymorphism as its risk factor, including oral cancer.[16] The only report that we identified reviewing P53 codon 72 polymorphism in ameloblastoma suggested the odds of ameloblastoma development was 2.06-fold higher in person who had Arg allele.[11] Arg variant allele might enhance tumorigenesis and provide a selective growth advantage to tumour cells.[11] Furthermore, the result was statistically significant even though it had a wide range of CI due to the fact that less than 100 samples of Thai population were explored.[11] Even though P53 protein expressions are widely examined, its polymorphism has not been studied in a large scale.

Other gene that is also well known is Interleukin 1 (IL-1). IL-1 encodes pro inflammatory cytokine and has a pivotal role in inflammatory disease. It is also involved in hematopoiesis and proteolytically released on response to cell injury by monocytes and macrophages.[17] This inflammatory cytokine affects bone resorption by inducing degradative enzymes and activation of osteoclast-like cells.[12] Nevertheless, we obtained one study that investigated association of IL-1α -889 polymorphism with ameloblastoma in 25 samples.[12] The authors of the study concluded that despite that IL-1α -889 is not a risk factor in ameloblastoma, it could affect tumor size progression.[12] Like any other polymorphism, it needs further examination due to the complicated mechanism of tumor development.

After polymorphisms, we found articles that documented relation between gene mutation and ameloblastoma. The first one was regarding SMO mutation. SMO encodes a G-protein coupled receptor that interacts with receptor for hedgehog protein, which plays a role in cell growth, cell specialization and the normal shaping of the body.[18] Abnormal activation of hedgehog signaling (Hh) could cause various basal cell carcinoma, medullablastoma, rhadomyosarcoma, and cancers in other body part, such as glioma, breast, esophageal, gastric, pancreatic, prostate and lung.[18] SMO is activated by mutations in patched 1 (PTCH1) or excess production of sonic hedgehog homolog (SHH).[19] Several studies that were conducted to investigate SMO as a potential target for therapeutic intervention showed a promising result.[20] In the study that we retrieved, SMO mutations were documented strikingly higher in maxillary cases of ameloblastoma.[13] Early recurrence in ameloblastoma with SMO mutations was also observed in the study. In spite of statistically insignificant result, 3 of 5 ameloblastoma with SMO mutant recurred, compared to 1 to 6 cases of ameloblastoma with BRAF mutant ($p = 0.24$) three years after the treatment.[13] A cohort study with larger size is required to substantiate the result.

As previously discussed, BRAF mutation was also identified to be related with ameloblastoma. BRAF encodes a raf/mil family of serine/threonine protein kinase that involves in cell division, differentiation and secretion. Mutation in this gene has been associated with

various cancers. Mutated BRAF leads to excessive cell proliferation and survival.[21] RAS-RAF-MAPK pathway was assumed to have role in the pathogenesis of ameloblastoma due to high number of BRAF V600E mutations.[14] According to the included report in this present review, BRAF mutation mainly occurred in mandible, while SMO mutation affected ameloblastoma in maxilla ($p<0.0001$).[13] This event may reflect distinctive odontogenic pathways in the upper and lower dentition. However, there was no correlation between BRAF mutation with patients' age, gender, tumor histology and tumor recurrence. Furthermore, it also reported that tumor with BRAF mutation were given vemurafenib as a targeted therapy and may be relevant with ameblastoma positive patients that have the same mutation.[13] Moreover, other study recognized that high frequency of BRAF V600E mutation may lead to novel therapies for ameloblastoma.[14]

To sum up, six reported genes were first found to have role in malignancies, with oral cancer as one of the diseases. Each gene has role in different aspect of cancer development: PTHC1 and P53 as tumor suppressor genes, IL-1 as immune system-related gene, XRCC1 as DNA repair gene, BRAF that induces activation of catalytic activity and SMO which has responsibility for the maintenance of normal embryonic development.[20,22] Thus, there are some other genes that could be investigated in ameloblastoma, due to the same basic tumorigenesis. Some of the genes were already studied as a potential molecular targeted therapy, which could lead to new paradigm of ameloblastoma's treatment option.[13]

Conclusions

In conclusion, genetic role in ameloblastoma has not been studied extensively, compared to malignancies in oral and maxillofacial region. However, same gene families, which are involved in oral cancer development, are also reported as ameloblastoma's risk factor. The genes themselves have different role in tumorigenesis. PTHC1 and P53 as tumor suppressor genes, IL-1 as immune system-related gene, as XRCC1 as DNA repair gene, BRAF and SMO act on cell proliferation. Identification of potential genes involving wider population is needed to confirm particular genes as prognostic marker, diagnostic aid, target for therapeutic intervention and universal risk factor.

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Declaration of Interest

The authors report no conflict of interest.

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