

Minireview Article

Dental Fluorosis: Dilemma of Genetic Susceptibility

Abstract

Excessive exposure to fluoride during formation of teeth may lead to a severe hypomineralization condition, called dental fluorosis. Genes such as Collagen type 1 alpha 2 (COL1A2), Estrogen receptor (ESR), Prolactin (PRL), Catechol-o-methyltransferase (COMT), matrix metalloproteinase 20 (MMP20) and many others have been implicated in the incidence of dental fluorosis. This mini-review is an insight into the fact that fluorosis incidence and intensity are significantly related to individual's genetic background.

Key words: Fluorosis; fluoride; COL1A2, gene.

INTRODUCTION

Tooth formation process may encounter several factors which could disturb the amelogenesis, dentinogenesis and cementogenesis; resulting in developmental tooth defects. The excessive intake of fluoride during tooth formation leads to dental fluorosis (1, 2). The fluorotic tooth is characterized by insufficient mineralisation of enamel, dentin, and cementum. In enamel, the subsurface area all along the crown becomes increasingly porous. This is due to amelogenin retention as fluoride induces endoplasmic reticulum stress and suppresses proteinase secretion by ameloblasts in dose-dependent manner (3-8). In dentine, there is increased interglobular dentin and increased secondary curvatures. In cementum, the cementodentinal junction is diffuse and Tomes' granular layer thickness is increased (9).

Fluoride is an inorganic anion of fluorine, commonly found in our environment. Once ingested, it is absorbed into the blood through the digestive tract and tend to collect in the bones and teeth as it has a high affinity to mineralised tissues (10).

The risk of developing fluorosis is increased when the ingestion of fluoride occurs during secretory and maturation stages of tooth matrix formation (11-14).

It has been reported that when fluoride is incorporated during crystals formation, it results in greater release of protons into the forming enamel matrix and more proteins bind to the forming mineral, at the same time; there is a suppression in the proteolysis of these proteins by proteases, due to the fact that fluoride acts as an enzyme inhibitor (5, 15, 16). However, other reports showed contradicting results in the case of both MMP20 and KLK4 as well as pooled enamel organ protein extracts; these reports concluded that fluoride does not directly inhibit enamel proteolytic activity of these two enzymes (17, 18).

Amelogenins play an important role in buffering the generated protons and regulating the pH during the secretory stage of amelogenesis (19, 20). Fluoride accelerates the process of minerals deposition, which in turn, leads to generation of large number of protons that exceeds the buffering capacity of amelogenins. This results in an acidification of the enamel matrix, disaggregation and detachment of amelogenin nanospheres from the crystal surface (5, 6). Consequently, abnormal mineralization occurs, leading to dental fluorosis (21).

The fundamental composition of the teeth enamel and bones is hydroxyapatite, and the fluoride displaces the hydroxide for the formation of fluoroapatite (22, 23). Properties of the fluoroapatite include low solubility and are closely packed, giving it a slower ability to rebuild bones, as compared to hydroxyapatite (24, 25). Affinity of fluoride has been proven to be relatively high for mineralized tissues, and raised concentrations could lead to several disturbances of the teeth and bones mineralization process (4, 5, 26). The correlation between the severity of fluorosis and the proportion of fluoride intake must be considered with several others factors such as the genetic factors (27-31).

Previous studies on the genetic components of dental fluorosis have highlighted the genetic influence and susceptibility to dental fluorosis, both in humans and in experimental animal models (29, 32-37).

INFLUENCE OF GENETIC FACTOR IN DENTAL FLUOROSIS

The severity of fluorosis does not always depend on the amount of fluoride consumed (29). It was reported that the prevalence of dental fluorosis was higher and more severe among African American children as compared to the white

Comment [JFGC1]: proteolysis

Comment [JFGC2]: It is desirable that you explain the role of MMP20 and KLK4 in amelogenesis in order to understand the effect of F-

Comment [JFGC3]: Reference17 says: Our results show that fluoride does not directly inhibit enamel proteolytic activity. Reference 18 says: The proposition that fluoride could directly inhibit enzymes was not confirmed in this study.

Comment [LY4]: Both references are telling the same conclusion

Comment [JFGC5]: Check the grammar and the meaning of the sentence.

Comment [JFGC6]: I think it would be convenient to analyze the role of genetic variations related to fluoride metabolism, especially renal elimination. Carvalho JG, Leite AL, Yan D, Everett ET, Whitford GM, Buzalaf MA. Influence of genetic background on fluoride metabolism in mice. J Dent Res. 2009 Nov;88(11):1054-8. doi: 10.1177/0022034509347249.

Carvalho JG, Leite Ade L, Peres-Buzalaf C, Salvato F, Labate CA, Everett ET, Whitford GM, Buzalaf MA. Renal proteome in mice with different susceptibilities to fluorosis. PLoS One. 2013;8(1):e53261. doi: 10.1371/journal.pone.0053261. Epub 2013 Jan 4.

Comment [LY7]: It was already mentioned earlier in reference number 41. Thank you

Comment [JFGC8]: In strains of mice

children; where some ethnic groups are more prone to dental fluorosis than other groups, in both fluoridated and non-fluoridated living area (38-40). The findings suggest that fluorosis could have great involvement with the biological susceptibility or higher fluoride intake. Previous animal studies found that different strains of the genetic determinants influence the susceptibility of mice to have different degrees of fluorosis (35). This was probably attributed to the influence of genetic background on fluoride metabolism which consequently resulted in different forms of fluorosis (41).

Comment [JFGC9]: Fluoride concentration of water and saliva was not different for the two groups; however, the fluoride content in urine was significantly higher in African Americans than in Whites [P < 0.05; 1.40 +/- standard deviation (SD) 0.65 ppm versus 1.08 +/- SD 0.28 ppm]. (Martínez- Mier y Soto, 2010)

Comment [JFGC10]: Ok, Here you should talk about renal elimination

GENES EXPRESSED IN DENTAL FLUOROSIS

Recent studies revealed that there is considerable inter-individual variation in predisposition to fluorosis (42-44). Fluorosis may result from a complex reaction between the implicated genes involved in fluorosis and the ingested fluoride (32, 45, 46). Genes such as Collagen type 1 alpha 2 (COL1A2), Calcitonin receptor gene (CTR), Estrogen receptor (ESR), Catechol-o-methyltransferase (COMT), Glutathione S-transferase pi 1 (GSTP1), Prolactin (PRL), Vitamin D receptor (VDR) Myeloperoxidase (MPO), Matrix metalloproteinase 2 (MMP-2) (42) or MMP20 (43) could act negatively to increase the risk of individuals to endemic fluorosis (47, 48). Studies conducted on the COL1A2 PvuII revealed that the genetic polymorphism in this gene was highly associated with increasing the risk of dental fluorosis; and the genetic variants in COL1A2 represent a relevant risk factor to develop dental fluorosis (44, 49). This could happen concurrently with existence of other environmental factors (50).

Comment [JFGC11]: I suggest you say: Gene polymorphisms associated with fluorosis

Comment [LY12]: I think the topic is also on the gene associated with fluorosis.

Comment [JFGC13]: It is a conceptual error, there are no genes associated with fluorosis

Previous researches reported that fluoride has different levels of effects on different ethnic groups. Cases from various ethnic groups were exposed to similar doses of fluoride. The results revealed that different ethnic groups developed different intensities of skeletal fluorosis; which could be correlated to the role of human genes and specificity of genetic background in the pathogenesis of fluorosis (42, 47, 51, 52). However, other studies on water fluoridation concluded that enamel fluorosis was not associated with race/ethnicity. In addition, the results of these studies were not significant to place certain race/ethnic groups at a higher risk for developing enamel fluorosis (53).

Comment [JFGC14]: These studies have pointed out that genetic variants in some candidate genes like COL1A2 (Collagen type 1 alpha 2), CTR (Calcitonin receptor gene), ESR (Estrogen receptor), COMT (Catechol-o-methyltransferase), GSTP1 (Glutathione S-transferase pi 1), MMP-2 (Matrix metalloproteinase 2), PRL (Prolactin), VDR (Vitamin D receptor) and MPO (Myeloperoxidase) could increase or decrease the risk of fluorosis among the exposed individuals in endemic areas. Pramanik S, Saha D. The genetic influence in fluorosis. *Environ Toxicol Pharmacol.* 2017;56:157-62.

Comment [JFGC15]: What is it that a gene acts negatively to increase the risk of dental fluorosis?

Comment [JFGC16]: The presence of polymorphism in the COL1A2 gene was not associated with the severity of dental fluorosis. Escobar-García D, Mejía-Saavedra J, Jarquín-Yáñez L, Molina-Frechero N3, Pozos-Guillén A. Collagenase 1A2 (COL1A2) gene A/C polymorphism in relation to severity of dental fluorosis. *Community Dent Oral Epidemiol.* 2016 Apr;44(2):162-8. doi: 10.1111/cdoe.12201. Epub 2015 Nov 12.

Comment [JFGC17]: 52. Our results provided evidence that polymorphisms in TIMP1, DLX1 and DLX2 genes may be associated with DF phenotypes.

Fluoride causes disruption of protein synthesis by inducing endoplasmic reticulum (ER) stress response genes in ameloblasts (54, 55). The induced ER stress response involves caspase and increased level expression level of Binding immunoglobulin protein (Bip), X-box binding protein 1 (Xbp-1), growth arrest and DNA damage 153 (GADD153), growth arrest and DNA-damage-inducible alpha (GADD45 α), IRN1, and the non-secreted form of carbonic anhydrase VI (CA-VI). Previous reports found that fluoride may upregulate glucose-regulated protein78 in ameloblasts, and activate inositol-requiring kinase 1 α and transcription factor 6 pathway; that ultimately result in unfolded protein response (3, 54), and premature cellular senescence (56). Consequently, these cellular disturbances would negatively affect the secretory function of ameloblasts and end up in laying down a defective enamel matrix. In cases where ER stress cannot be reversed, cellular functions deteriorate, often leading to cell death (57).

CONCLUSION

Apart from environmental factor, genetic polymorphism / genetic variant also enhances the susceptibility to dental fluorosis. Hence, it would be possible to identify that a subset of the population as a high-risk group for developing dental fluorosis.

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