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Review Article

Amelogenin x linked chromosome

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ABSTRACT

The AMELX gene provides instructions for making a protein called amelogenin, which is essential for normal tooth development. Amelogenin is involved in the formation of enamel, which is the hard, white material that forms the protective outer layer of each tooth. Using molecular genetic techniques, we have shown that there is no evidence that the AMGX gene is deleted in this case of the Nance-Horan syndrome. In affected members of a Michigan kindred of Eastern European ancestry segregating X-linked amelogenesis imperfecta with a characteristic snow-capped enamel phenotype.

Keywords: Amelogenin, Chromosome, Hormone

INTRODUCTION

The AMELX gene provides instructions for making a protein called amelogenin, which is essential for normal tooth development. Amelogenin is involved in the formation of enamel, which is the hard, white material that forms the protective outer layer of each tooth.[1] Enamel is composed mainly of mineral-containing crystals. These microscopic crystals are arranged in bundles that give enamel its strength and durability.[2] Studies suggest that lesser amounts of amelogenin may also be present in tissues other than developing tooth enamel. For example, amelogenin has been found in certain bone, bone marrow, and brain cells. The function of amelogenin in these tissues is unknown. One copy of the amelogenin gene is located on each of the sex chromosomes (the X and Y chromosomes).[3] The AMELX gene, which is located on the X chromosome, makes almost all of the body's amelogenin. The copy of the amelogenin gene on the Y chromosome, AMELY, makes very little amelogenin and is not needed for enamel formation. Amelogenin is a major component of enamel matrix proteins.[4] It undergoes extra cellular degradation by Proteolytic enzymes like matrix mettaloproteinases into smaller low molecular weight fragments, like tyrosine rich amelogenin protein and leucine rich amelogenin polypeptide which are suggested to have specific functions as in regulating crystal growth. The genes encoding for amelogenin is present in X and Y chromosomes.[5]

Position and names

The AMELX gene is located on the short arm of the X chromosome between positions 22.31 and 22.1.[6] More precisely, the AMELX gene is located from base pair 11,293,412 to base pair 11,300,760 on the X chromosome.[7] The other names do people use for the AMELX gene or gene products are AIH1, ALGN, amelogenin (amelogenesis imperfecta 1, X-linked), AMELX_HUMAN, AMG, AMGL amd AMGX.[8,9]

Amelogenin is the name for a series of closely related proteins involved in amelogenesis, the development of enamel. They are a type of extracellular matrix (ECM) protein, which, together with aerobactins, enamelin, and

tuftelins direct the mineralization of enamel to form a highly organized matrix of rods, interrod crystal, and protein. Although the precise role of amelogenin in regulating the mineralization process is unknown, it is known that amelogenins are abundant during amelogenesis. Developing human enamel contains about 30% protein, 90% of which are amelogenins. Amelogenins are believed to be involved in the organizing of enamel rods during tooth development. The latest research indicates that these proteins regulate the initiation and growth of hydroxyapatite crystals during the mineralization of enamel. In addition, amelogenins appear to aid in the development of cementum by directing cementoblasts to the tooth's root surface.[10]

Gene ontology

Molecular function

- Protein binding
- Growth factor activity
- Structural constituent of tooth enamel
- Identical protein binding
- Cell surface binding
- Hydroxyapatite binding.

Biological process

- Osteoblast differentiation
- Epithelial to mesenchymal transition
- Chondrocyte differentiation
- Cell adhesion
- Signal transduction
- Cell proliferation
- Bio mineral tissue development
- Positive regulation of collagen biosynthetic process
- Tooth mineralization
- Odontogenesis of dentin-containing tooth
- Ion homeostasis
- Enamel mineralization
- Positive regulation of tooth mineralization.

Sources

Amigo Amelogenin, X isoform is a protein that in humans is encoded by the AMELX gene. Amelogenin, X isoform is a form of amelogenin found on the X chromosome. Amelogenin X is a member of the amelogenin family of extracellular matrix proteins. When alternative splicing occurs, it results in multiple transcript variants encoding different isoforms.

Recombinant amelogenin x- linked organism

- Species: Homo sapiens (human)
- Host: *E. coli*
- Subcellular location: secreted, extracellular space, extracellular matrix
- Purity: >95%
- Endotoxin level: <1.0EU per 1μg (determined by the LAL method)
- Formulation: supplied as lyophilized form in PBS
- pH: 7.4, containing 5% sucrose, 0.01% sarcosyl
- Predicted isoelectric point: 6.8
- Predicted molecular mass: 17.3kDa.

Storage

- Avoid repeated freeze/thaw cycles
- Store at 2-8ºC for one month
- Aliquot and store at -80ºC for 12 months.

Stability test

The thermal stability is described by the loss rate of the target protein. The loss rate was determined by accelerated thermal degradation test, that is, incubate the protein at 37ºC for 48 hours and no obvious degradation and precipitation were observed. The loss of this protein is less than 5% within the expiration date under appropriate storage condition.

Sequences

The target protein is fused with N-terminal His-Tag, its sequence is listed below. MGHHHHHHSGSEF- YP SYGYEPMGGW LHHQIIPVLS QQHPPTHTLQ PHHHIPVVPA QQPVIPQQPM MPVPGQHSMT PIQHHQPNLP PPAQQPYQPQ PVQPQPHQPM QPQPPVHPMQ PLPPQPPLPP MFPMQPLPPM LPDLTLEAWP STDKTKR.[11]

Cloning

In the course of studying DNA fragments cloned from the human Y chromosome found a clone that was particularly well conserved in mammalian evolution.[12] Homologous sequences were found on the X chromosome. The sequences were homologous to previously sequenced cDNA clones of mouse and cattle encoding amelogenin. Three exons were identified in both the X and the Y sequences presented studies in male developing tooth buds showing that both the AMGX and the AMGY genes are transcriptionally active.[13] The promoter regions and the predicted protein sequences of both genes were presented.[14] Obtained protein sequence from the major 28-kD amelogenin protein and isolated a cDNA from a human fetal tooth bud library. The cDNA corresponded to the X chromosome sequence identified by which differs from the Y chromosome protein by a deletion of a methionine at codon 29.[15]

Evolution

Determined the genomic sequences of AMEL genes in 5 primates and 3 other mammals.[16] To confirm the location of AMEL loci on sex chromosomes of nonhuman primates, they mapped the locations by FISH. Further,

they examined the pattern and extent of sequence differences between the human X and Y chromosomes, finding a 540-kb DNA sequence from the short arm of the human X chromosome aligned with the Y gametologous sequences. The comparisons of 7 other mammals with human revealed that the 5-prime portion of the AMEL loci began to differentiate in the common ancestor of extant mammals, whereas the 3-prime portion differentiated independently within species of different mammals. The boundary is marked by a transposon insertion in intron 2, shared by all species examined.

Animal model

Generated amelogenin-null mice.[17] The enamel layer in the null mice is hypoplastic but has an elemental composition consistent with a hydroxyapatite-like mineral, suggesting that the amelogenins are not required for mineral crystal initiation. However, the characteristic prism pattern is completely absent, indicating a role for amelogenins in enamel organization.

Described a tyrosyl 64-to-his missense mutation in the tri-tyrosyl domain of the enamel extracellular matrix protein of mouse Amelx.[18] Affected animals had severe defects of enamel biomineralization associated with absence of full-length amelogenin protein in the developing enamel matrix, loss of ameloblast phenotype, increased ameloblast apoptosis, and formation of multicellular masses. Affected ameloblasts expressed but failed to secrete full-length amelogenin, leading to engorgement of the endoplasmic reticulum/Golgi apparatus.

Immunohistochemical analysis revealed accumulations of both amelogenin and ameloblastin in affected cells. Co-transfection of Ambn and mutant Amelx in a eukaryotic cell line revealed intracellular abnormalities and increased cytotoxicity compared with cells singly transfected with wildtype Amelx, mutant Amelx, or Ambn, or cotransfected with both wildtype Amelx and Ambn.[17] that intracellular protein-protein interactions mediated via the amelogenin tri-tyrosyl motif may be a key mechanistic factor underpinning the molecular pathogenesis in this example of AI.

Disease relevance of Amelx

The method was applied to the analysis of Y-chromosome sequences (amelogenin gene, AMELX/Y-loci) in peripheral lymphocytes and gonadal tissues in Y-positive Turner's syndrome (TS) patients.[18]

Open bite malocclusion occurred in individuals with AI caused by mutations in the AMELX and ENAM genes even though these genes are considered to be predominantly or exclusively expressed in teeth.[19] The polymerase chain reaction (PCR) was used to amplify portions of AMGX and AMGY from genomic DNA of carcinomas of the colon, lung, liver and kidney, as well as from matched normal somatic tissues.[20]

When Amelx null females were mated with P70T transgenic males, offspring developed structures similar to calcifying epithelial odontogenic tumors in humans.[21] Analysis of amelogenin gene (AMGX, AMGY) expression in ameloblastoma.[22]

Psychiatric information related on Amelx

At effective doses, AMG 9810 did not show any significant effects on motor function, as measured by open field locomotor activity and motor coordination tests.[23] The AMG is a picture-based measure that combines features of the Thematic Apperception Test (TAT; Murray, 1943) with features of self-report questionnaires.[24]

High impact information on Amelx

Transport of beta-D-Glc-IPM and glucose by SAAT1 is apparently performed by the same mechanism because similar sodium dependence, dependence on membrane potential, electrogenicity, and phlorizin inhibition were determined for beta-D-Glc-IPM, D-glucose, and AMG.[25] We have isolated genomic and cDNA clones from both the AMGX and AMGY loci and have studied the sequence organization of these two genes.[26]

AMG 706 was well tolerated and had no significant effects on body weight or on the general health of the animals.[27] Histologic analysis of tumor xenografts from AMG 706-treated animals revealed an increase in endothelial apoptosis and a reduction in blood vessel area that preceded an increase in tumor cell apoptosis.[26]

Moreover, the sensitivity of CD44-induced adhesion to AMG and H7, which both prevent the activation of protein kinase C, and to cytochalasin B, which inhibits microfilament formation, suggests that the activation of the LFA-1 pathway via CD44 involves protein kinase C activation and requires an intact cytoskeleton.[28]

Chemical compound of Amelx

A "plasmid-curing effect" of multiresistant Escherichia coli by flavophospholipol, an antibiotic used as an antimicrobial growth promoter (AMGP) in animal feeds, has been reported to occur in vitro and in vivo under experimental conditions.[29]

In vivo, AMG 9810 is effective at preventing capsaicin-induced eye wiping in a dose-dependent manner, and it reverses thermal and mechanical hyperalgesia in a model of inflammatory pain induced by intraplantar injection of complete Freund's adjuvant.[18] Two ongoing large, randomized, placebo-controlled studies will prospectively define fracture outcomes in men with prostate cancer and

assess the efficacy of novel pharmacologic interventions (AMG 162, toremifene) in GnRH-agonist-treated men.[30]

Biological context of Amelx

The AMELX gene located at Xp22.1-p22.3 encodes for the enamel protein amelogenin and has been implicated as the gene responsible for the inherited dental abnormality X-linked amelogenesis imperfecta (XAI).[31] We have identified two kindreds with X-linked AI and characterized the AMELX mutations underlying their AI phenotypes.[32] In the human genome, there are two AMEL loci with one copy of the gene on each of the sex chromosomes (AMELX and AMELY), whereas in the mouse only an AMELX locus is present.[33]

Mutations of the X-chromosome amelogenin gene (AMELX) are associated with amelogenesis imperfecta (AI) phenotypes (OMIM no. 301200).[29] DNA was obtained from family members; exons 1-7 of AMELX were amplified and sequenced.[30]

Anatomical context of Amelx

Three types of multidrug-resistant Escherichia coli isolates, called GEN S, GEN R, and AMG S, according to their three different aminoglycoside resistance patterns, were responsible for urinary tract colonization or infection in 87, 12, and 13 new patients, respectively, in a French 650-bed geriatric hospital over a 13-months period.[31]

The prevalence and degree (proportion of resistant strains to the total numbers present per gram of feces) of resistance of indicator bacteria, *E. coli* and *enterococci*, was determined in fecal samples from three groups of pigs that were fed a commercial finisher feed without any AMGP.[24]

Background/aims

Study have reported quantitative and qualitative differences in bone marrow (BM) progenitor cells in autoimmune hepatitis type-1 (AIH-1) and primary biliary cirrhosis (PBC).[32] We studied the motion perception of a patient, AMG, who had a lesion in the left occipital lobe centered on visual areas V3 and V3A, with involvement of underlying white matter.[33]

HDL3 and albumin-mediated cholesterol efflux was measured in mouse peritoneal macrophages and in SR-BI transfected cells that had been treated along time with dicarbonyl sugars or AGE-albumin, both in the presence or in the absence of AMG and MF.[34]

Associations of Amelx and chemical compounds

At membrane potentials between -50 and -150 mV, a 10-fold higher substrate affinity (Km approximately 0.25 mM) and a 10-fold lower Vmax value were estimated for beta-D-Glc-IPM transport than for the transport of D-glucose or methyl-alpha-D-glucopyranoside (AMG).[20] Herein we provide a brief overview of recent reported clinical results for AMG 548, BIRB 796VX 702, SCIO 469, and SCIO 323.[35] Phlorizin (1 mM) inhibits AMG uptake by 30 to 40%.[36]

Group A was the negative control group without any AMGP, group B received the same feed with 9 mg of flavophospholipol/kg of feed (study group), and group C received the same feed with 15 mg of avoparcin/kg (positive control).[24] Some rats were pretreated with aminoguanidine (AMG, 50 mg/Kg BW in drinking water) before the procedure.[37]

Enzymatic interactions of Amelx

Results

Using molecular genetic techniques, we have shown that there is no evidence that the AMGX gene is deleted in this case of the Nance-Horan syndrome.[38]

Regulatory relationships of Amelx

To date, 12 allelic AMELX mutations have been described that purportedly result in markedly different expressed amelogenin protein products.[39]

Other interactions of Amelx

Alternatively, multiple amelogenins may arise by expression of both the AMELX and AMELY loci.[40] Although X-linked, autosomal dominant and autosomal recessive forms of AI have been clinically characterized, only two genes (AMELX and ENAM) have been associated with AI.[41]

Polymerase chain reaction amplification of AMGX and AMGY was successful using genomic DNA from both tumour and normal control tissue in 24 of the 26 cases.[15] Linkage analysis has shown that there is genetic hetetogeneity in X-linked amelogenesis imperfecta with two identified loci: AIH1 and AIH3.[42] End-sequencing and database analysis revealed a YAC insert of at least 416 kb containing the genes HCCS and AMELX, and exons 2-16 of ARHGAP6.[43]

Analytic, diagnostic and therapeutic context of Amelx

Based on a sequence insertion/deletion characteristic for X- and Y-specific amelogenin (AMELX and AMELY), PCR amplification on male and female genomic DNA from domestic and wild bovine species, sheep and goat, consistently displayed a sex-specific pattern.[44] We have determined by Southern blot analysis that DNA sequences homologous to the AMG gene probe are present in the genomes of both marsupial and monotreme mammals, although adult monotremes lack teeth.[45]

In situ hybridization and Southern analysis of cell hybrids demonstrate that AMG homologues are located on autosomes.[46] Six cohorts of eight to nine women were randomly assigned to receive a single subcutaneous injection of either AMG 162 or placebo (3:1 ratio).[46] AMG 531 serum levels were determined by use of a validated enzyme-linked immunosorbent assay.[47]

Allelic variants

Amelogenesis imperfecta, type 1e Amelx

By Southern blot analysis, demonstrated a deletion extending over 5 kb of the amelogenin gene in males with the hypomineralization form of amelogenesis imperfecta.[48] This Swedish family was pedigree 41 described by and Family B mapped by.[49,50] Carrier females were heterozygous for the molecular defect which appeared to include at least 2 exons of the gene. The extent of the deletion was verified by polymerase chain reaction (PCR) analysis. Segregation of the mutation with the disease was established in 15 members of the kindred analyzed.[51] Examined the molecular basis of this deletion and its consequences. The deletion removed 5 of the 7 exons, spanning from the second intron to the last exon. Only the first 2 codons for the mature protein remained, consistent with the relatively severe phenotype of affected persons. The mutation appeared to have arisen as an illegitimate recombination event since of 11 nucleotide positions immediately surrounding the 2 breakpoints, 9 were identical. Referring back to this family, stated that affected members had enamel of normal thickness but that it was poorly mineralized and therefore softer than normal.[52] This contrasted with the findings of thin enamel in a patient with a 9-bp deletion. They presented photographs contrasting the appearance of the teeth.

Amelogenesis imperfecta, type 1e Amelx

In a family with X-linked amelogenesis imperfecta found that the disorder was associated with deletion of one cytosine in exon 5 of the AMELX gene.[48] The effect of the deletion was to alter the reading frame and to introduce an inappropriate TGA stop codon (an opal mutation) into the exonic sequence immediately 3-prime of the deletion. Examination showed enamel hypoplasia in some individuals, although in others the hypoplastic changes were subtle and might have been overlooked on cursory examination. The most notable change in these patients involved enamel color, indicating hypomineralization. On the basis of these findings, proposed that the ALGN gene is implicated in both the formation of enamel of normal thickness and in the normal mineralization process.[48]

Amelogenin imperfecta, type 1e

Described a 9-bp deletion in exon 2 of the ALGN gene, causing X-linked hypoplastic amelogenesis imperfecta.[53] The mutation resulted in the loss of 3 amino acids and substitution of 1 amino acid in the signal peptide of ALGN.[49,51] This deletion in the signal peptide probably interfered with translocation of ALGN during synthesis, resulting in the thin enamel observed in affected members of the family.[53] found 3 reported examples of mutations in signal peptides resulting in pathologic conditions: in coagulation factor X, in the vasopressin gene and in the parathyroid hormone gene.

Amelogenesis imperfecta, type 1e Amelx

By PCR and SSCP analysis, identified a 1-bp deletion (C) in codon 96 of exon 6 of the ALGN gene in a family in which 3 hemizygous males and 3 heterozygous females with the hypoplastic type of amelogenesis imperfecta were studied. Affected males had thin, smooth, yellowish enamel and wide spacing between teeth.[54] Heterozygous females had thin, yellowish enamel with pitting, grooving, and vertical wrinkling. The deletion caused a frameshift, with the introduction of a premature stop signal at codon 126 and the lack of the terminal 18 amino acids.

Amelogenesis imperfecta, type 1e Amelx

Used PCR and SSCP analysis to characterize a mutation in a family segregating amelogenesis imperfecta with 4 affected males and 8 heterozygous females in 4 generations.[54] The male proband had teeth with smooth, thin, brown, pitted enamel with whitish mottled areas. Heterozygous females had thin enamel with shallow vertical grooves and whitish mottling. A C-to-T substitution was found in codon 3 of exon 5 of the ALGN gene, producing a threonine-to-isoleucine amino acid change.

Amelogenesis imperfecta, type 1e Amelx

In a 2-generation family segregating amelogenesis imperfecta with 3 affected males and 3 heterozygous females, used PCR and SCCP analysis to demonstrate a G-to-T substitution in codon 129 of exon 6 of the ALGN gene, causing a premature stop signal.[54] This produces a truncated mRNA and mature protein 15 amino acids shorter than the wildtype protein. The affected proband in this family had smooth, thin, yellowish enamel. His mother had vertical wrinkling of the enamel, and his sister had vertical mottling of the maxillary incisor.

Amelogenesis imperfecta, type 1e Amelx

In 'family S' with X-linked amelogenesis imperfecta first identified a 208C-A mutation in exon 6 of the amelogenin gene resulting in a pro21-to-thr substitution.[55-57] Affected males have enamel that is mottled brown or with a ground-glass appearance and is described as hypomature.[58] Identified the same mutation in 2 North Carolina families with X-linked amelogenesis. The phenotype was virtually identical to that in the

family described by with all males having brown teeth of relatively normal morphology.[55]

Amelogenesis imperfecta, type 1e Amelx

In a family with X-linked amelogenesis imperfecta identified a cytosine deletion in exon 6 at codon 119 of the AMELX gene.[59] The deletion resulted in a frameshift mutation, introducing a premature stop signal at codon 126. The resulting protein lacked the terminal 18 amino acids. The affected males of the family had thin, smooth hypoplastic enamel with occasional opacities. Heterozygous females had patches or ridges, often vertically distributed, of normal and hypoplastic enamel with occasional opacities. There was variability in the phenotype between family members, between primary and permanent dentitions, and from one tooth to another in the same dentition.

Amelogenesis imperfecta, type 1e Amelx

In some 4-generation kindred with the severe hypoplastic enamel phenotype of X-linked amelogenesis imperfecta identified a deletion of cytosine at position 446 of the AMELX gene of 1 of the affected male probands and his mother.[55] This frameshift mutation deletes part of the coding region for the repetitive portion of amelogenin as well as the hydrophilic tail, replacing them with a 47-amino acid segment containing 9 cysteine residues.

Amelogenesis imperfecta, type 1e Amelx

In a family with a 5-generation history of amelogenesis imperfecta identified a single base pair change in the initiation codon of the AMELX gene.[60] The change of the ATG start codon to ACG in exon 2 resulted in an amino acid change of threonine to methionine. Eleven members of the family were screened and the mutation was found in all 5 affected and in none of the 6 unaffected family members. Teeth from 1 of the affected females had enamel that was extremely thin and slightly rough. The underlying dentin appeared to show through the enamel and gave the teeth a yellowish color. No vertical banding pattern was evident in the affected females. The only affected male studied in this family had crowns covering all of his teeth, but a panorex taken before reconstruction showed no evidence of enamel on any of the teeth.

Amelogenesis imperfecta, type 1e Amelx

In a small family with a 3-generation history of amelogenesis imperfecta identified a change of TGG (tryptophan) to TCG (serine) in codon 4 of exon 2 of the AMELX gene.[61] The affected mother and daughter had teeth with thin enamel that could be readily identified on radiographs. The teeth were yellowish, but not as marked as those with the M1T mutation. Both affected females showed a pattern of alternative vertical bands of thin enamel and enamel of more normal thickness.

Amelogenesis imperfecta, type 1e, with snow-capped teeth Amelx

In affected members of a Turkish family segregating X-linked amelogenesis imperfecta with a characteristic snow-capped enamel phenotype identified a 96,240-bp deletion that removed all of AMELX and the alternative ARHGAP6 promoters 1c and 1d.[58] RT-PCR analysis showed that these promoters are not active in ameloblasts, indicating that their deletion was unlikely to affect developing teeth.[61]

Amelogenesis imperfecta, type 1e, with snow-capped teeth Amelx

In affected members of a Michigan kindred of Eastern European ancestry segregating X-linked amelogenesis imperfecta with a characteristic snowcapped enamel phenotype identified a 52,654-bp deletion that removed all of AMELX and promoter 1d and exon 2 of ARHGAP6.[62] Expression studies of Arhgap6 promoters in mice led to conclude that deletion of AMELX resulted in males with a characteristic snow-capped enamel phenotype, and that lack of ARHGAP6 expression did not appreciably alter the severity of enamel defects.[58]

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