AAO Foundation Award Final Report

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Award Type	Biomedical Research Award
Project Title	Mechanism by which an MSX1 mutation causes human tooth agenesis
Project Year	1998
Institution	New York University Dental Center
Summary/Abstract	Previously, we found that the cause of autosomal dominant agenesis of second premolars and third molars in one family is a missense mutation (Arg31Pro) in the homeodomain of MSX1. To distinguish between a mechanism of haploinsufficiency, a dominant negative or a novel activity of the mutant MSX1 we have performed biochemical and functional analyses of the mutant Msx1(R31P). We have showed that Msx1(R31P) has perturbed structure and reduced thermostability compared with wild-type Msx1. As a consequence, the biochemical activities of Msx1(R31P) are severely impaired, since it exhibits little or no ability to interact with DNA or other protein factors or to function in transcriptional repression. We also show that Msx1(R31P) is inactive *in vivo*, since it does not display the activities of wild-type Msx1 in assays of ectopic expression in the limb. Furthermore, Msx1(R31P) does not antagonize the activity of wild-type Msx1 in any of these assays. Based on these data, we propose that the phenotype of tooth agenesis is due to haploinsufficiency. A reduced dose of MSX1 is not tolerated in the regions of second premolars and third molars suggesting that mophogenesis of these teeth requires a greater dosage of MSX1.