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A Call to Study Orphan Diseases

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EDITORIAL

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The National Institutes of Health and the National Human Genome Research Institute jointly fund the Genetic and Rare Diseases (GARD) Information Center, a program of the National Center for Advancing Translational Sciences.[1] GARD is a publicly accessible, curated database that provides patients, health care professionals, scientists, and educators with an array of informational resources regarding rare diseases, including "orphan" diseases. Orphanet is a similar resource initially established in 1997 and currently supported by a consortium of 38 countries throughout Europe, Asia, and Africa, in addition to Argentina and Canada.[2]

Orphan diseases include a collection of over 7000 developmental, acquired, neoplastic, and genetic disorders that, individually, afflict fewer than 200,000 people in the United States, less than 250,000 people in the European Union, and under 50,000 patients in Japan.[1] A cursory search of the GARD database yielded information on orphan diseases, including ameloblastoma, McCune-Albright syndrome, adenoid cystic carcinoma, pemphigus vulgaris, oral submucous fibrosis, and Gorham disease, among many others, which may be of particular importance to the readership of *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*. However, the database can only be as complete and accurate as the information from its curated sources. For example, a search for "segmental odontomaxillary dysplasia" failed to yield any information, and "adenomatoid odontogenic tumor" was incorrectly described as a synonym of ameloblastoma. A concerted effort geared toward the study of orphan diseases could help fill in potential gaps in the literature and promote public understanding. However, for this to happen, there must be interest and motivation in investigators; scientifically sound and, when appropriate, clinically relevant questions asked; and commitment from funding organizations to provide the necessary resources.

Two examples of orphan genetic diseases that I have personally encountered in clinical practice and been called upon to aid in diagnosis are dyskeratosis congenita (DC; estimated prevalence 1:1,000,000) and Schimmelpenning syndrome (SS; estimated prevalence unknown). DC is a genetically heterogeneous, chromosomal instability disorder that is characterized by early-onset skin pigmentation, dystrophic nails, and oral leukoplakia.[3] Variably severe systemic manifestations, not limited to aplastic anemia, pulmonary fibrosis, osteoporosis, and cancer susceptibility, including oral squamous cell carcinoma, further complicate the disease and quality of life of affected individuals. SS is a noninherited disorder characterized by cutaneous nevus sebaceous and an array of ocular, skeletal, and neurologic abnormalities.[4] Oral manifestations may include hypoplastic, malformed teeth; central giant cell granulomas; odontogenic tumors; odontomas; and mucosal papillomatosis.[5]

To date, DC is known to be associated with loss-of-function mutations in at least 11 different genes; likely more genes remain to be identified.[3] Each of the respective gene products, including several distinct telomerase ribonucleoprotein subunits, contributes to telomere homeostasis. This has led to characterization of DC as a disease of defective telomere maintenance or as a telomeropathy.[3] How does telomere dysfunction contribute to oral carcinogenesis? Intriguingly, why is oral squamous cell carcinoma the most commonly reported cancer in patients with DC?[3] Could local factors, including regional chronic inflammation, oral microbial flora, salivary proteins, or the regional presence of viruses, such herpesviridae or human papillomavirus, contribute to tumorigenesis? Oral lichenoid lesions, hypodontia, hypoplastic teeth, caries, periodontal disease, and premature tooth exfoliation may also be observed in DC.[3] How does telomere dysfunction impair tooth development or increase the risk for periodontal disease? These are just a few of the potentially fascinating questions for which the answers currently remain mostly unknown. Thus, novel insight into oral keratinocyte homeostasis, tooth development, and pathogenesis of periodontal disease could be gained by detailed investigation of the proteins implicated in the orphan disease DC. In the interest of full disclosure, an encounter with a young patient with DC prompted my own professional interest in studying this orphan disease in a laboratory setting. In contrast, participation in the diagnosis of a patient with SS prompted my interest in this unique orphan disease from a purely didactic standpoint.

In 2007, we reported a patient with SS who manifested recurrent, multifocal central giant cell granulomas, adenomatoid odontogenic tumor, multiple complex odontomas, bilateral maxillary fibro-osseous lesions, and numerous misshapen teeth lacking roots.[5] At that time, the pathogenesis of this orphan disease was unknown. However, we speculated that the development and homeostasis of the maxillomandibular complex, including tooth development, were clearly disrupted by whatever genetic change we presumed our patient had. Five years later, Groesser et al.[4] reported that SS was associated

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with postzygotic, gain-of-function mutations in *HRAS* or *KRAS*.

HRAS, KRAS, and NRAS are plasma membrane guanosine triphosphatases that help promote cell proliferation; enhance metabolism; suppress apoptosis; modulate the cellular microenvironment, in part, through stimulating angiogenesis; and contribute to immune evasion.[6] Although *RAS* genes have long been recognized as proto-oncogenes, they have recently gained importance for investigators interested in the pathogenesis of odontogenic neoplasia. In particular, sporadic *RAS* mutations have been identified in a subset of ameloblastoma, which is recognized as an orphan tumor.[7] In addition, a sporadically occurring, but recurrent, KRAS G12V mutation was reported in adenomatoid odontogenic tumors—another orphan tumor, and one of the lesions identified in our patient with SS.[8] What are the mechanisms by which *RAS* mutations drive odontogenic neoplasia? How do RAS proteins regulate tooth development? These are lines of investigation currently being pursued by various investigators and reinforce the notion that studying orphan diseases could provide critical insight into the pathogeneses of not only oral and maxillofacial disorders but also the physiologic development of the regional structures.

RASopathies, including SS, represent a group of diseases caused by either *RAS* gene mutations or disruption of the RAS signaling pathways.[6] Germline RAS mutations have been identified in a subset of patients with Noonan syndrome, which, like SS, may also be associated with multifocal giant cell lesions of the jaws.[9] Do *RAS* oncogenic mutations contribute to the pathogenesis of syndrome-associated and sporadic central giant cell granulomas? Intriguingly, a recent report does suggest that mutations in *KRAS* and other RAS signaling proteins may be observed in a subset of sporadic central giant cell lesions.[10] Thus, if an oncoprotein can drive the development of central giant cell granuloma, should these lesions, which historically have been regarded as non-neoplastic, be considered true benign neoplasms? Hereditary gingival fibromatosis type 1 is another known RASopathy.[6] How does RAS signaling regulate gingival homeostasis?

It is not surprising that lack of understanding of etiologies and pathogeneses remain major obstacles in the development of novel therapies and potential cures for most orphan diseases. Moreover, the significant costs associated with research and development are unlikely to motivate corporate science to expend years of effort and resources on orphan diseases, especially when the returns are unlikely to match their investments. The persistent efforts of patient advocacy groups, such as the National Organization for Rare Disorders and the Orphan Disease Pathway Project, have led to some measurable progress. One successful example of patient advocacy effort is the Orphan Drug Act, which was signed into United States law in 1983, with similar landmark legislation adopted in Japan in 1993 and European Union in 2000.[11] Nonetheless, the vast majority of orphan diseases remain understudied. This relative vacuum in interest has led to recent partnerships among private foundations, governmental bodies, and scientific and academic research institutions to bring awareness to these diseases, develop patient and family support and advocacy networks, and help provide a clarion call for more research and more research funding.

As the new Oral Pathology Section Editor, I have been afforded a unique opportunity to use this "bully pulpit" to draw attention to scientific questions and topics focused on the study, diagnosis, and treatment of oral and maxillofacial diseases, including an array of orphan diseases that may be encountered in clinical practice. The study of orphan diseases may provide critical understanding of homeostatic principles governing the development of the oral and maxillofacial complex, and equally critical insight into what happens when these mechanisms are perturbed. Scientific study of orphan diseases has helped yield and will continue to yield a wealth of critical insight and a multitude of fascinating questions about fundamental biologic processes that may be common to eukaryotes and prokaryotes. Let us increase the focus on orphan oral diseases and study of oral phenotypes associated with orphan diseases to help drive some of this valuable research. As scientists, clinicians, educators, readers of *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, and our respective academies, we are well-positioned to lead this effort.

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