Published in final edited form as:

Oral Dis. 2018 March ; 24(1-2): 277–279. doi:10.1111/odi.12750.

The importance of studying oral and craniofacial manifestations of Mendelian phenotypes

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One of the main goals of the Human Genome Project (HGP), completed in April of 2003 (All About the Human Genome Project, 2015), was to improve understanding of human disease. This wonderful roadmap accelerated the discovery of genes that increased risk for more common, complex diseases such as diabetes, but also hereditary disorders that are found in families and passed from parents to children (Mendelian phenotypes) (Chong *et al*, 2015). The value of studying Mendelian phenotypes is that the identification of the germline mutation (single-nucleotide variant) or copy-number variants that are responsible for the phenotype expands our understanding of the protein that is encoded by the gene, its function, how it is expressed, and how altered forms of the protein may contribute to more common, similar diseases in the general population.

Below are examples of Mendelian phenotypes with distinct oral and craniofacial manifestations that the research community has identified, demonstrating how this area of research is growing exponentially. Through continued investigations of Mendelian phenotypes, the future holds great promise for discoveries that establish how diseases of the oral cavity and other craniofacial diseases develop, as well as processes responsible for maintenance of oral health.

Initial observations of Mendelian phenotypes - Primary immunodeficiencies

For several decades, Prof. Scully and others recognized that distinct oral manifestations occurred in individuals with primary immunodeficiencies and other inborn errors of the immune system (Porter and Scully, 1994). Early descriptions of the classical diseases focused on the systemic and oral clinical presentations of the unique phenotypes, their clinical laboratory findings and the clinical courses primarily of children (Porter and Scully, 1993a, 1993b, 1993c). Before hematopoietic stem cell transplantation, many affected individuals with the most severe forms of immunodeficiencies did not survive adolescence.

These studies, conducted in the middle 1990s, were important because they occurred after the discovery of lymphocyte subsets and their unique functions. Tertiary care centers that cared for these patients could carefully phenotype affected individuals and sometimes their families and create a road map that characterized those cells most involved in maintaining

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oral homeostasis and mounting defenses against certain pathogens. The role that different classes of immunoglobulins played in oral health was established through studies of individuals lacking selected classes such as IgG. These studies added to the knowledge base that helped clinicians care for others with secondary or acquired immunodeficiencies, that result either from decreased production or increased destruction of immune cells or loss of components of humoral immunity (Atkinson *et al*, 2015). For example, the recognition that individuals lacking CD4+ lymphocytes were highly susceptible to infections with *Candida albicans*, other non-*albicans* species and viral infections of the *Herpes* family accelerated our understanding of why those with HIV infection were susceptible to these intraoral infections. Guidelines for care of cancer patients whose immune systems are suppressed secondary to cancer therapy are based in part from knowledge gained by careful observations of individuals with inherited immunodeficiencies.

The importance of genotype/phenotype correlations

Discoveries of genetic mutations and subsequent biochemical deficiencies underlying Mendelian phenotypes have resulted in a better understanding of the complex network of processes that influence oral health. These findings have helped clarify why individuals with deficiencies in a common cell type such as neutrophils do not always present with similar oral complications such as aggressive periodontitis (Porter and Scully, 1993a), and why there is variability in the clinical presentation of disease within a disease group such as severe congenital neutropenia (Ye *et al*, 2011). For example, individuals with Chronic Granulomatous Disease (CGD) have defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway that results in a failure of their neutrophils to kill phagocytized organisms. CGD patients do not typically have aggressive periodontitis. In contrast, patients with mutations in cathepsin C that results in Papillon-Lefèvre syndrome and associated defective neutrophil chemotaxis do develop aggressive periodontitis (Atkinson *et al*, 2015; Moutsopoulos *et al*, 2015). These discoveries not only help define why the clinical presentations of the diseases differ, but also establishes the roles of these pathways in maintaining periodontal health.

In the last 15 years, many genetic defects underlying classic Mendelian phenotypes have been identified (Chong *et al*, 2015), though many are yet to be identified. Many of those identified are inborn errors in immunity that are associated with distinct oral phenotypes, such as chronic mucocutaneous candidiasis and aggressive periodontitis (Moutsopoulos *et al*, 2015). Recent research has helped explain that the variability in clinical presentation within groups of individuals with a defined immunodeficiency can be explained by different gene mutations. A study of periodontal disease in fourteen patients with severe congenital neutropenia and different genetic backgrounds found that those with mutations in the neutrophil elastase gene, *ELANE*, had the most severe forms of periodontitis despite regular dental care (Ye *et al*, 2011). Future studies may examine the role that genes and gene products identified in Mendelian phenotypes with aggressive periodontitis may play in chronic periodontitis in the other populations.

Current and future directions

Recently, the establishment of large registries of individuals and families with known rare diseases have allowed the study of the full, highly variable spectrum of clinical consequences associated many Mendelian phenotypes. This has led to the observation that not all individuals with a mutation underlying the monogenic disease will demonstrate the classic hereditary disease. A good example is osteogenesis imperfecta (OI), a congenital connective tissue disorder characterized by bones that break easily with little cause. Most affected individuals have a dominant mutation in one of the two genes that produce type 1 collagen (*COL1A1* or *COL1A2*, Miko, 2008), and certain mutations are found more frequently in those with associated dentinogenesis imperfecta (Andersson *et al*, 2017). However, there are individuals with collagen mutations known to cause OI that do not express the disease in their bones or teeth. This has led to many studies trying to explain factors controlling the penetrance of a gene and gene expression. It has also emphasized the need to study large numbers of patients and their families to fully understand the pathways from genetic mutations to clinical presentation.

Other investigators have studied mediators responsible for the oral presentations of classic neutrophil deficiencies, and the role they may play in the presentation of periodontitis. Recent work of Moutsopoulos and colleagues (Moutsopoulos *et al*, 2017) first demonstrated that excessive levels of interleukin-17 were present in inflamed periodontal tissues of individuals with Leukocyte-Adhesion Deficiency-1 (LAD-1), a classic immunodeficiency with associated aggressive periodontitis that presents in childhood. Administration of ustekinumab, a monoclonal antibody that inhibits interleukin-12 and interleukin-23 signaling and reduces the interleukin-17 response, to an individual with LAD-1 who had an intractable, deep, nonhealing sacral wound, severe periodontitis that did not respond to conventional therapy and oral ulcerations, resulted in resolution of the sacral wound, a decrease in the oral ulcerations, and a reduction in the severity of the periodontitis (Moutsopoulos *et al*, 2017). This study complements the work of others studying the role of IL-17 in inflammatory-mediated periodontal disease in the general population (Liao *et al*, 2017) and its role in maintenance of oral health.

Investigators characterizing neutrophil function in Papillon-Lefevre syndrome recently found elevated levels of neutrophil chemoattractants MIP-1 α and CXCL8 were present in neutrophils from these patients, suggesting continuous recruitment of neutrophils in addition to the reduced antimicrobial capacity secondary to mutations in the cathepsin C gene create a chronic inflammation that results in destruction of alveolar bone (Roberts *et al*, 2016).

Conclusions

While the mechanisms underlying the development of classical findings associated with Mendelian phenotypes such as aggressive periodontitis are being elucidated, further research is needed to understand the expression of many other oral manifestations that have been long recognized. Prof. Scully understood the importance of continuing studying genetic diseases and the need for the oral health research community to stay integrated with the broader research community defining the role of genes in overall health.

Acknowledgments

This work was funded in by the extramural program of NIDCR, NIH.

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