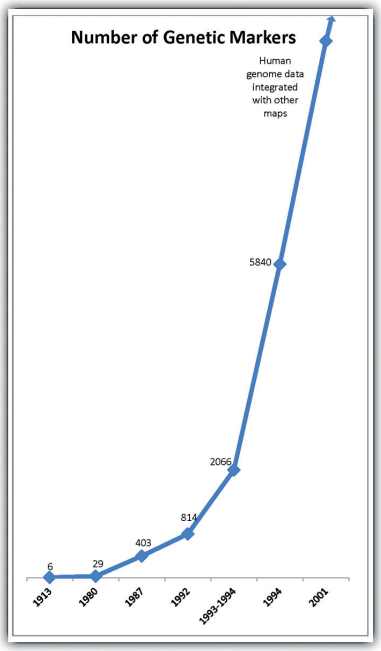
HUMAN MOLECULAR GENETICS AND ITS IMPACT ON DENTISTRY

The genetics field came a long way in regards to utilizing genetic variation to identify linkage between specific loci and phenotypes. From the first suggestion that linkage could be used to physically locate genes in chromosomes in 1911 to genome wide genotyping scans utilizing array-base devices with more than one million single nucleotide polymorphisms (Figure 1),[1-5] fulfilling the promise to utilize genomic approaches to clinically manage patients is upon us.



The first concrete step in dentistry has been the ability of predicting treatment responses for head and neck squamous cell carcinomas. Cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), was approved in the United States in 2006 as the first molecular targeted therapy for head and neck squamous cell carcinoma. Cetuximab in conjunction with radiotherapy significantly improved survival in 5 years by 9% (from 36.4% to 45.6%).[6,7] EGFR is bound by mainly EGR or transforming growth factor alpha (TGFA), which promotes dimerization with other molecules, which will activate an intracellular signaling pathway that leads to apoptosis, activation of cell proliferation and angiogenesis, and increased metastatic spread potential.[8]

There have been signs that genomic information may be helpful for other areas of dentistry as well. Of the interest of the orthodontist, the genetic variant rs10850110 in the myosin 1H gene is a potential marker for the genetic susceptibility to class III malocclusion with mandibular prognathism.[9,10]

For the general dentist, the genetic variant rs1784418 in *MMP20* (metalloproteinase 20) appears to be a protecting factor against dental caries.[11] Another promising genetic variant regarding individual risk for higher caries experience is the *ESRRB* (estrogen related receptor beta) rs1676303. Interestingly, *ESRRB* recessive mutations cause a form of hearing imparment.[12] Another interesting finding for the general dentist and potentially the endodontist is that the assessment of the *MMP2* rs9923304 genetic variant may be useful to predict the more likely need for endodontic treatment and formation of periapical lesions when individuals have untreated deep lesions in dentin or the more likely loss of an extensive dental composite resin restoration.[13,14]

Finally, insurance claims data regarding individual preventive visits and their tooth losses (the ultimate consequence of dental caries and/or periodontal diseases) showed that individuals classified as low risk based on smoking, diabetes, and interleukin 1 genotype statuses did not benefit from additional preventive dental visits when tooth loss was measured.[15] We performed a similar experiment adding high blood pressure as an additional risk factor for tooth loss, and showed that a portion of the population that "tests" positive for a higher risk for tooth loss based on smoking and diabetes statuses, blood pressure levels, and interleukin 1 genotypes should visit the dentist more often, potentially as much as four to six times per year.[16]

These developments call for a better preparation of the dental professional to a dentistry that incorporates molecular approaches to diagnose and treat oral and dental disease. It is coming the time when gene therapy for radiation-induced hyposalivation will be a reality. Patients that survived head and neck cancer radiation therapy and lost their salivary gland functionality showed signs of salivation after adenoviral-mediated transfer of the aquaporin 1 gene.[17] Remarkable is that this effect appears to last for a few years.[18] Similarly, after more than a decade of animal studies, patients born with the X-linked form of hypohidrotic ectodermal dysplasia may benefit from a single course of an ectodysplasin protein replacement to rescue and permanently correct the ectodermal defects (tooth agenesis, abnormally conical teeth, dysplastic nails, sparse hair, lack of sweat glands) present in this syndrome.[19]

There has been the suggestion that dentists and dental hygienists need to learn human molecular genetics and clinical research in general.[20] How the professionals in the future can quickly translate the growing knowledge of genomics and translational research into their practices? Although the answer for this question may not be obvious, if the dentist does not proactively embrace the era in which decisions are based on genomic information and therapies include gene and protein replacement, some other professional (likely a physician) will be performing these procedures.

REFERENCES

1. Botstein D, White RL, Skolnick M, Favis RW. Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet 1980; 32:314-331.
2. Donis-Keller H, Green P, Helms C, Cartinhour S, Weiffenbach B, Stephens K, Keith TP, Bowden DW, Smith DR, Lander ES, Botstein D, Akots G, Rediker KS, Gravius T, Brown VA, Rising MB, Parker C, Powers JA, Watt DE, Kauffman ER, Bricker A, Phipps P, Muller-Kahle H, Fulton TR, Ng S, Schumm JW, Braman JC, Knowlton RG, Barker DF, Crooks SM, Lincoln SE, Daly MJ, Abrahamson J. A genetic linkage map of the human genome. Cell 1987; 51:319-337.
3. Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau, Marc S, Bernardi G, Lathrop M, Weissenbach J. The 1993-94 Généthon human genetic linkage map. Nat Genet 1994; 7:246-339.
4. Murray JC, Buetow KH, Weber JL, Ludwigsen S, Scherpbier-Heddema T, Manion F, Quillen J, Sheffield VC, Sunden S, Duyk GM; Généthon: Weissenbach J, Gyapay G, Dib C, Morrissette J, Lathrop GM, Vignal A; University of Utah: White R, Matsunami N, Gerken S, Melis R, Albertsen H, Plaetke R, Odelberg S; Yale University: Ward D; Centre d'Etude du Polymorphisme Humain (CEPH): Dausset J, Cohen D, Cann H. A comprehensive human linkage map with centimorgan density. Cooperative Human Linkage Center (CHLC). Science 1994; 265:2049-2054.
5. The International Human Genome Mapping Consortium. A physical map of the human genome. Nature 2001; 409:934-941.
6. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354(6):567–78.
7. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11(1):21–8.
8. Roskoski R Jr. The ErbB/HER receptor protein-tyrosine kinases and cancer. Biochem Biophys Res Commun 2004;319:1–11.
9. Tassopoulou-Fishell M, Deeley K, Harvey EM, Sciote J, Vieira AR. Genetic variation in Myosin 1H contributes to mandibular prognathism. Am J Orthod Dentofac Orthop 2012; 141:51-59.
10. Cruz CV, Mattos CT, Maia JC, Granjeiro JM, Reis MF, Mucha JN, Vilella B, Ruella AC, Luiz RR, Costa MC, Vieira AR. Genetic polymorphisms underlying the skeletal class III phenotype. Am J Orthod Dentofacial Orthop 2017;151(4):700-707.
11. Filho AVA, Calixto MS, Deeley K, Santos N, Rosenblatt, Vieira AR. MMP20 rs1784418 protects certain populations against caries. Caries Res 2016;51(1):46-51.
12. Weber ML, Hsin H-Y, Kalay E, Bro•ková DS, Shimizu T, Bayram M, Deeley K, Küchler EC, Forella J, Ruff TD, Trombetta VM, Sencak RC, Hummel M, Briseño-Ruiz J, Revu SK, Granjeiro JM, Antunes LS, Abreu FV, Costa MC, Tannure PN, Koruyucu M, Patir A, Poletta FA, Mereb JC, Castilla EE, Orioli IM, Marazita ML, Ouyang H, Jayaraman T, Seymen F, Vieira AR. Role of estrogen related receptor beta (ESRRB) in DFN35B hearing impairment and dental decay. BMC Medical Genetics 2014; 15:81.
13. Menezes-Silva R, Khaliq S, Deeley K, Letra A, Vieira AR. Genetic susceptibility to periapical disease: Conditional contribution of MMP2 and MMP3 genes to the development of periapical lesions and healing response. J Endod 2012; 38: 604-607.
14. Vieira AR, Silva MB, Souza KA, Filho AVA, Rosenblatt A, Modesto A. A pragmatic study shows failure of dental composite fillings is genetically determined: A contribution to the discussion on dental amalgams. Front Med 2017;4:186.
15. Giannobile WV, Braun TM, Caplis AK, Doucette-Stamm L, Duff GW, Kornman KS. Patient stratification for preventive care in dentistry. J Dent Res 2013;92(8):694-701.
16. Vieira AR, Hilands KM, Braun TW. Saving more teeth – a case for personalized care. J Pers Med 2015; 5(1):30-35.
17. Baum BJ, Alevizos I, Zheng C, Cotrim AP, Liu S, McCullagh L, Goldsmith CM, Burbelo PD, Citrin DE, Mitchell JB, Nottingham LK, Rudy SF, Van Waes C, Whatley MA, Brahim JS, Chiorini JA, Danielides S, Turner RJ, Patronas JJ, Chen CC, Nikolov NP, Ilei GG. Early responses to adenoviral-mediated transfer of the aquaporin-1 cDNA for radiation-induced salivary hypofunction. Proc Natl Acad Sci U.S.A. 2012;109(47):19403-19407.
18. Alevizos I, Zheng C, Cotrim AP, McCullagh L, Billings ME, Goldsmith CM, Tandon M, Helmerhost EJ, Catalán MA, Danielides SJ, Perez P, Nikolov NP, Chiorini JA, Melvin JE, Oppenheim FG, Illei GG, Baum BJ. Late response to adenoviral-mediated transfer of the aquaporin-1 gene for radiation-induced salivary hypofunction. Gene Ther 2017;24(3):176-186.
19. Hutker K. Future developments in XLHED treatment approaches. Am J Med Genet A 2014;164(10):2433-2436.
20. Slavkin HC. The impact of research on the future of dental education: How research and innovation shape dental education and the dental profession. J Dent Educ 2017;81(9):eS108-eS127.

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