Editorial

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FROM PHENOTYPE TO GENOTYPE: MOLECULAR PATHOLOGY OF CRANIOFACIAL DISORDERS IN PAKISTAN

The global shift toward precision medicine, driven by advances in genomic technologies such as next-generation sequencing (NGS), whole-exome sequencing (WES), and whole-genome sequencing (WGS), has transformed the diagnosis and management of rare genetic diseases. While these tools are now embedded in routine clinical care in many countries, Pakistan remains largely excluded from this genomic revolution despite bearing a disproportionately high burden of inherited disorders.

This gap is particularly troubling given Pakistan's high prevalence of consanguineous marriages, exceeding 60% in some regions, which significantly increases the incidence of autosomal recessive diseases. Yet, most rare genetic conditions remain undiagnosed or are managed symptomatically without molecular confirmation. Patients and families often endure prolonged diagnostic odysseys, receiving fragmented care that targets individual manifestations rather than the underlying genetic cause.

A substantial proportion of rare genetic disorders manifest early within the dental and craniofacial complex. Conditions such as amelogenesis imperfecta, dentinogenesis imperfecta, hypodontia, ectodermal dysplasias, cleidocranial dysplasia, and syndromic short stature commonly present with distinctive dental, facial, and skeletal anomalies. In many cases, these features are the earliest or only clinically apparent signs of an underlying multisystem disorder. Despite this, dental anomalies in Pakistan are routinely treated in isolation, with limited recognition of their syndromic or genetic significance.

Failure to utilize dental and craniofacial findings as entry points for genetic evaluation leads to missed or delayed diagnosis of associated systemic involvement, including hearing impairment, skeletal dysplasia, cardiac anomalies, and neurodevelopmental disorders. This compartmentalized approach compromises diagnostic accuracy, delays preventive care and surveillance, and deprives families of timely genetic counseling.

Limited access to genomic diagnostics remains a major barrier. While targeted gene panels, WES, WGS, chromosomal microarray analysis (CMA), and copy number variation (CNV) testing are standard internationally, availability in Pakistan is extremely restricted. Comprehensive NGS platforms, including Illumina- and Oxford Nanopore–based systems, are rarely available for routine clinical use, and molecular testing is frequently outsourced abroad, placing it beyond the financial reach of most families. The absence of national rare disease registries, biobanks, and population-specific genomic databases further hampers variant interpretation, particularly in consanguineous populations.

Compounding these limitations is a lack of awareness and a severe shortage of genetic counseling services, leaving families uninformed about recurrence risks, carrier status, and reproductive options. As precision medicine reshapes global healthcare, Pakistan remains ill-prepared to engage meaningfully. Dental and craniofacial services represent an underutilized strategic asset and could serve as frontline screening points for rare genetic diseases. Without a coordinated national genomic strategy integrating early phenotypic recognition, molecular diagnostics, and clinical genetics, Pakistan risks remaining on the periphery of the precision medicine era.

Dr. Umar Farooq
Assistant Professor
Department of Oral Pathalogy,
Khyber College of Dentistry