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Deciphering the Genomic Complexity of Acromesomelic Dysplasia Type Maroteaux: Insights from a Consanguineous Pakistani Family

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ABSTRACT

Purpose: This study delves into the genetic basis of Acromesomelic Dysplasia (AMD), a rare skeletal disorder, particularly focusing on the Maroteaux type within a consanguineous Pakistani family. The purpose is to explore the genetic landscape beyond known mutations and understand the underlying causes of AMD.

Methodology: A comprehensive approach was adopted, combining detailed clinical examinations with advanced genomic methodologies. Ethical clearance was obtained, and pedigree design facilitated the identification of affected individuals. Molecular techniques including DNA extraction and linkage analysis were conducted to investigate known AMD-related genes such as NPR2, BMPR1B, GDF5, GALNS, GLB1, and GHR. Whole-genome sequencing was emphasized despite financial constraints to uncover potential novel genetic loci associated with AMD.

Findings: Despite exhaustive analysis, no mutations in known AMD-related genes were identified within the studied family. Linkage analysis did not correlate with any known genetic loci, suggesting the presence of unidentified genetic elements contributing to AMD. Autosomal recessive inheritance was confirmed through pedigree and molecular scrutiny, highlighting the complexity of AMD genetics.

Unique Contribution to Theory, Policy and Practice: This research underscores the importance of employing advanced genomic strategies, such as whole-genome sequencing, in decoding rare genetic disorders like AMD. By revealing the limitations of current diagnostic approaches and advocating for collaborative efforts and resource pooling, this study contributes to the advancement of genetic counseling, therapeutic interventions, and precision medicine in rare genetic disorders.

Keywords: *Acromesomelic Dysplasia Type Maroteaux, AMDM, Skeletal Abnormalities, Autosomal Recessive Inheritance, Diagnostic Challenges AMDM, Linkage Analysis AMDM*

INTRODUCTION:

Congenital skeletal abnormalities represent a diverse group of disorders characterized by irregular bone formation, stemming from intrinsic defects in the growth, development, and differentiation of specialized skeletal cells. With an estimated prevalence of one in 1,000 individuals globally, these conditions hold paramount clinical significance, necessitating advancements in prenatal diagnosis, targeted therapeutic interventions, and preventive strategies for subsequent pregnancies (Spurna *et al*., 2024). Diagnosis, however, poses a formidable challenge due to the multitude of factors influencing these disorders, including facial and cranial defects, disproportionate stature, delayed bone maturation, shortened or curved fingers, and abnormalities in joint and spine development, among other phenotypic manifestations (Lee *et al*., 2022; Litrenta *et al*., 2021; Cavallo *et al*., 2021; Stolerman *et al*., 2019).

One subset of congenital skeletal abnormalities is Acromesomelic Dysplasia (AMD), an autosomal recessively inherited skeletal disorder with distinctive features leading to a specific form of short stature. These deviations primarily manifest in the middle and distal segments of the extremities, resulting in dwarfism (Haliloglu *et al*., 1999; Demirhan *et al*., 2005). The disorder presents in both syndromic and non-syndromic forms, with syndromic cases often associated with genital, cardiac, respiratory, and neurological abnormalities (Khan *et al*., 2016).

Within the spectrum of AMD, the Maroteaux type has been extensively studied. This form of AMD is associated with compound heterozygous or homozygous mutations in the NPR2 gene, located on chromosome 9p13. NPR2 encodes natriuretic peptide receptor B, a protein crucial for skeletal growth regulation. The clinical presentation includes severe dwarfism, with affected individuals exhibiting serious limb abnormalities, including short broad fingers, square flat feet, and curvature of the radius (Faivre *et al*., 2000). Diagnosis becomes more apparent in the early years of life, marked by abnormal growth plates and misshapen bones in the limbs and spine. Notably, adults with AMDM Maroteaux type present with heights more than 5 standard deviations below the mean, indicative of a significantly reduced stature. While the genetic underpinnings of AMDM have been linked to mutations in NPR2, there is a growing need to explore potential novel genetic elements, particularly in cases where reported gene mutations are not detected.

In this study, our primary objective is to unravel the intricate genetic factors specific to the AMDM-affected family. The absence of detected mutations in the known AMDM-related genes prompts a critical reevaluation of the genetic landscape. This exploration aims to redefine our understanding of the genetic basis of AMDM, providing insights that could contribute to more targeted diagnostic and therapeutic approaches for affected individuals.

Material and Methods:

This study delves into the clinical and molecular characterization of Acromesomelic Dysplasia Maroteaux Type (AMDM) within a consanguineous family residing in a remote region of Pakistan. The family's geographic isolation, coupled with prevalent consanguineous marriages, provides a unique backdrop for exploring the genetic underpinnings of AMDM. The research focuses on a specific family member showcasing the AMDM phenotype in Khyber Pakhtunkhwa (KPK). Extensive clinical examinations involve a comprehensive assessment of age, height, weight, gender, intelligence level, and morphological traits. Noteworthy details such as head circumference and other abnormal features observed in the affected individual are meticulously documented.

The study strategically utilizes graphical pedigree representations, meticulously crafted in accordance with (Bennet *et al*., 1995). Guidelines, employing symbols denoting gender, consanguineous unions, carriers, and affected individuals.

In the pedigree design, hollow circles and squares symbolize normal family members, with circles representing females and squares males. Consanguineous marriages are denoted by crossed lines, carriers by dots, and affected individuals by filled (black) symbols. Roman numerals signify generations in descending order, while Arabic numerals indicate individual order from left to right. This visual narrative enhances the understanding of familial relationships and genetic inheritance patterns.

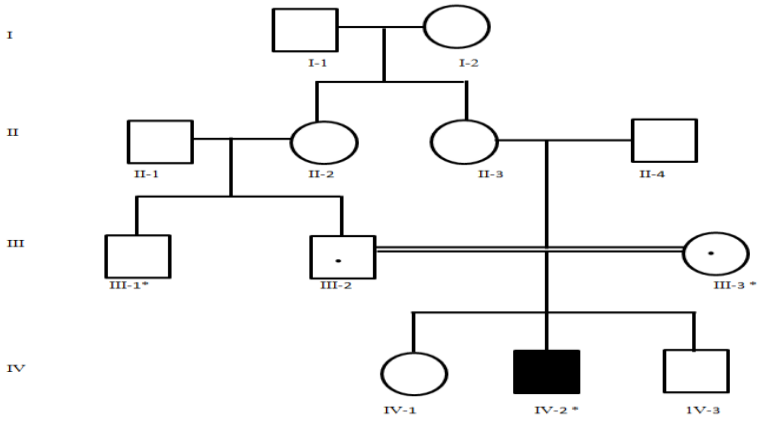


Figure 1: Pedigree of family a representing autosomal recessive Acromesomalic Dysplasia Type Maroteaux.

Squares and circles represent males and females respectively. Double line is representing consanguineous marriage. A filled symbol represents an affected individual and unfilled symbol represents the normal Individuals. The roman numerals indicate the generation of family within a pedigree while Arabic numeral indicates individual positions within a generation. The individual numbers labeled with asterisks indicate the samples available for this study.

Venous blood samples from affected and unaffected family members are procured for genomic DNA extraction using the Phenol-Chloroform Method as outlined by (Sambrook *et al*., 1989). The ensuing purification steps, including centrifugation and agarose gel electrophoresis, ensure high-quality DNA. Microsatellite markers facilitate linkage analysis and genetic mapping, guided by the UCSC Genome browser and Rutgers's Combined Linkage-Physical Map (Matise et al., 2007). Polymerase Chain Reaction (PCR) amplifies target DNA sequences, while Polyacrylamide Gel Electrophoresis (PAGE) visually separates and verifies the amplified fragments.

RESULT:

The investigation centered on a familial cohort hailing from District Lakki Marwat, Khyber Pakhtunkhwa, Pakistan, with a specific focus on unraveling the clinical and molecular dimensions of Acromesomelic Dysplasia Maroteaux Type (AMDM). Notably, an in-depth phenotypic analysis of the identified affected individual, IV-2, revealed distinctive AMDM characteristics, including a diminished stature of 120 cm, anomalous limb segments, facial dysmorphisms, and joint swellings. A meticulous pedigree was systematically crafted, encapsulating the familial genetic architecture and pertinent health histories. DNA specimens were judiciously procured from both the affected proband (IV-2) and unaffected family members (III-1, III-3) via the established Phenol-Chloroform methodology.

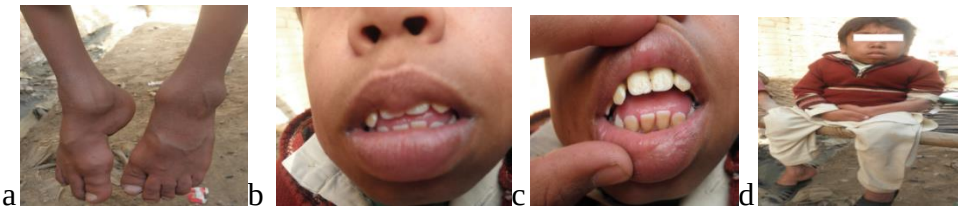


Figure 2: Affected individual (III-2) in family

A with autosomal recessive Acromesomalic dysplasia type Maroteaux. Clinical finding revealed that the affected individual (IV-A) knew/joint swollen, broad short feet, the greater toe is relatively larger than other, the feet appeared abnormally flat (a), slightly flattened midface, an abnormally small, pug nose (b) Teeth abnormality (c), having short stature 120cm associated with deviation of middle and distal segments, pigeon shape chest, the hands, feet, toe nail often seem unusually broad, square, short, enlarged head frontal bossing, occipital prominence and facial abnormality (d).

The genetic cartography endeavor sought to pinpoint candidate genes associated with hereditary skeletal dysplasia. However, the outcome of the linkage analysis involving NPR2, BMPR1B, GDF5, GALNS, GLB1, and GHR delineated an absence of correlation, suggestive of the

potential implication of an enigmatic gene in driving the manifestation of hereditary AMDM within this particular familial milieu.

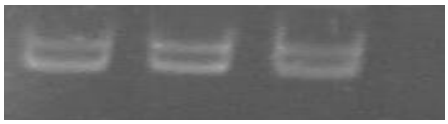
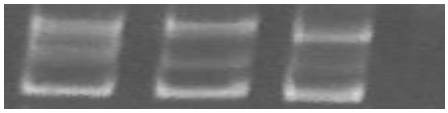
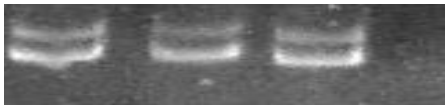
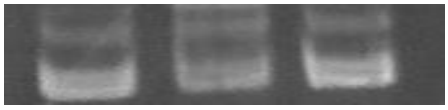
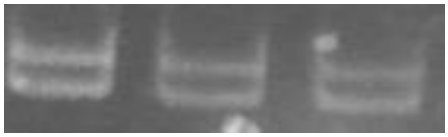
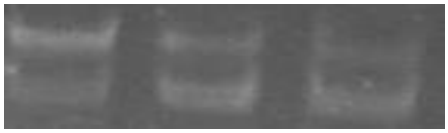
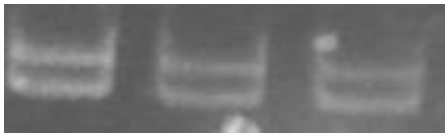
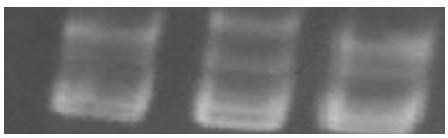
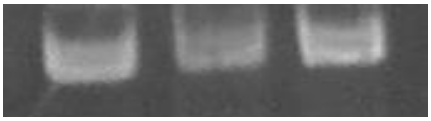
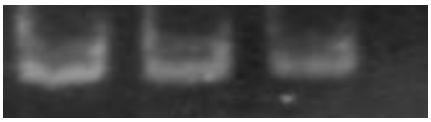
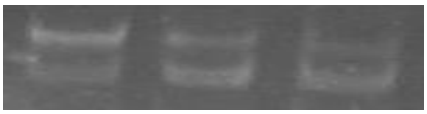
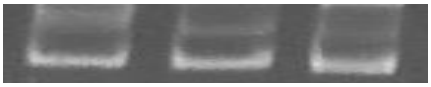
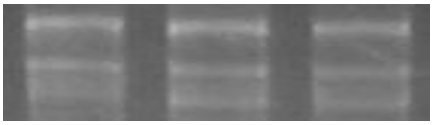
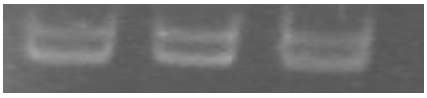
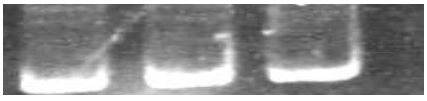
Sr- no	Marker name	Map unit cM	Results		
			1N	2 N	3A
1	D20S432	47.48			
2	D20S54	50.36			
3	D20S477	51.14			
4	D20S865	55.42			
5	D20S34	56.41			
6	D20S478	58.9			
7	D20S881	58.9			
8	D20S107	60			
9	D20S108	61.97			

Figure 3: The image of polyacrylamide gel (Electropherogram)

The figure showed allel pattern with particular markers of *GDF5* candidate gene, cytogenetic location of gene is 20q11.22 were taken after staining the gel with ethidium bromide. Homozygous banding patterns shows that the individual is affected whereas heterozygous pattern of bands shows that individual is normal, the symbol N is indicating that individual is normal while A is indicated the affected individual. The Arabic numerals are representing number of family member.

Sr-no	Marker name	Map unit Cm	Results		
			1 N	2 N	3A
1	D4S1534	98.67			
2	D4S2284	100.28			
3	D4S423	105.65			
4	D4S433	107.3			
5	D4S2909	107.35			
6	D4S1560	108.56			
7	D4S2986	109.89			
8	D4S2634	110.05			

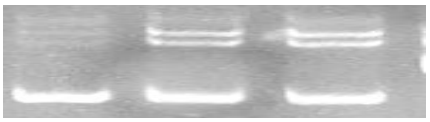
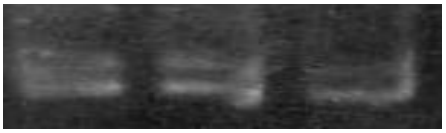
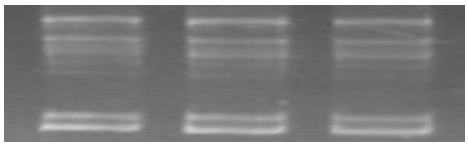
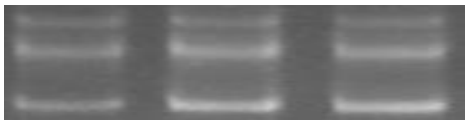
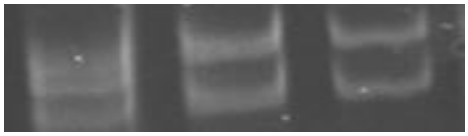
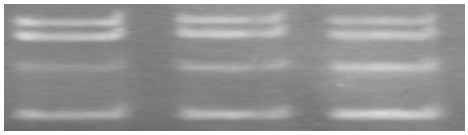
9	D4S1572	113.05	
10	D4S1570	114.16	

Figure 4: The image of polyacrylamide gel (Electropherogram)

The figure showed allel pattern with particular markers of *BMPR1B* candidate gene, cytogenetic location of gene is 4q22.3 was taken after staining the gel with ethidium bromide. Homozygous banding patterns shows that the individual is affected whereas heterozygous pattern of bands shows that individual is normal, the symbol N is indicating that individual is normal while A is indicated the affected individual. The Arabic numerals are representing number of family member.

sr –no	Marker name	Map unit cM	Results		
			1 N	2 N	3A
1	D9S169	51.71			
2	D9S1678	54.78			
3	D9S319	55.51			
4	D9S1118	57.01			

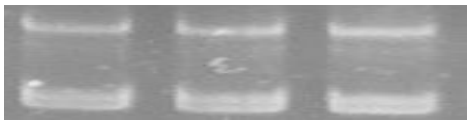
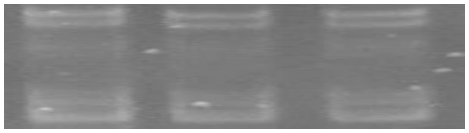
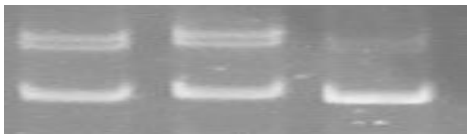
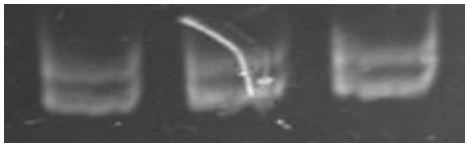
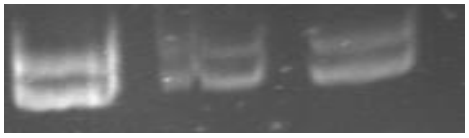
5	D9S1817	59	
6	D9S200	61.8	
7	D9S229	62.66	
8	D9S55	62.66	
9	D91862	66.55	

Figure 5: The image of polyacrylamide gel (Electropherogram)

The figure showed allel pattern with particular markers of *NPR2* candidate gene, cytogenetic location of gene is 9p13.3 was taken after staining the gel with ethidium bromide. Homozygous banding patterns shows that the individual is affected whereas heterozygous pattern of bands shows that individual is normal, the symbol N is indicating that individual is normal while A is indicated the affected individual. The Arabic numerals are representing number of family member

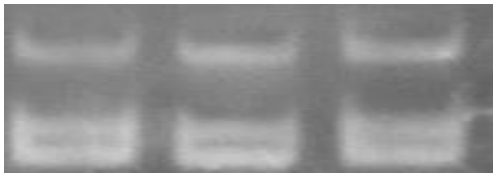
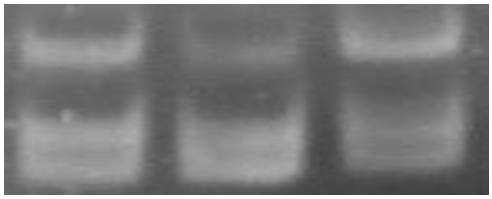
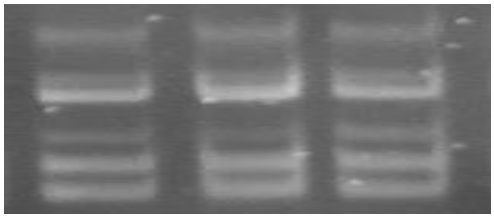
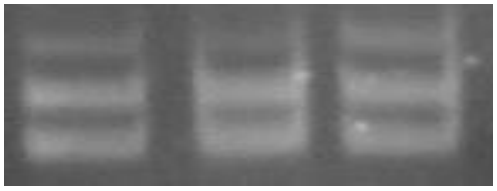
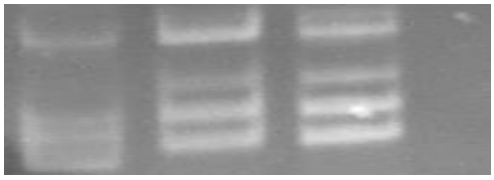
Sr-no	Markers name	Map unit cM	Results		
			1N	2N	3A
1	D3S2432	57.43			
2	D3S3623	62.36			
3	D3S1260	63.37			
4	D3S3527	64.17			
5	D3S3521	64.17			

Figure 6: The image of polyacrylamide gel (Electropherogram)

The figure showed allel pattern with particular markers of *GLB1* candidate gene, cytogenetic location of gene is 3p22.3 was taken after staining the gel with ethidium bromide. Homozygous banding patterns shows that the individual is affected whereas heterozygous pattern of bands shows that individual is normal, the symbol N is indicating that individual is normal while A is indicated the affected individual. The Arabic numerals are representing number of family member.

Sr –no	Marker name	Map unit cM	Results		
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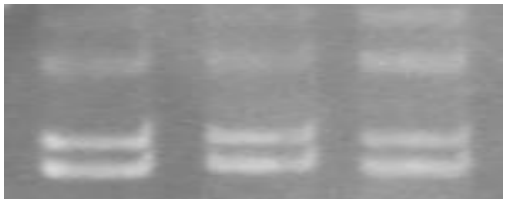
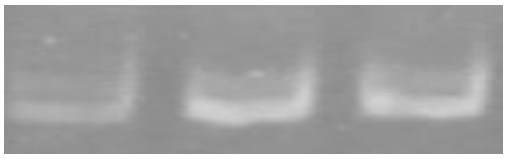
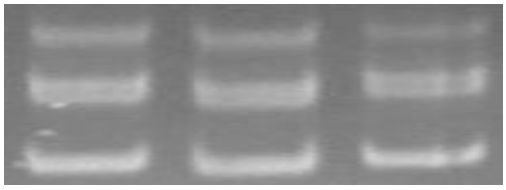
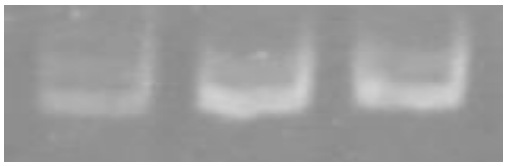
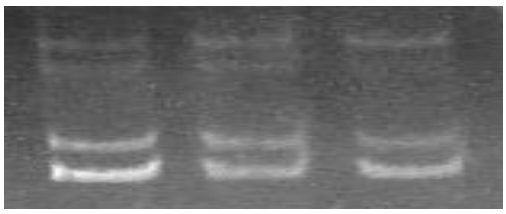
1	D16S486	126.17			
2	D16S3077	128.98			
3	D16S3063	129.12			
4	D16S3123	129.12			
5	D16S3026	132.03			

Figure 7: The image of polyacrylamide gel (Electropherogram)

The figure showed allel pattern with particular markers of *GALNS* candidate gene, cytogenetic location of gene is 16q24.3 was taken after staining the gel with ethidium bromide. Homozygous banding patterns shows that the individual is affected whereas heterozygous pattern of bands shows that individual is normal, the symbol N is indicating that individual is normal while A is indicated the affected individual. The Arabic numerals are representing number of family member

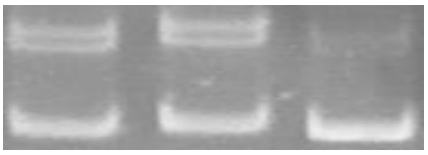
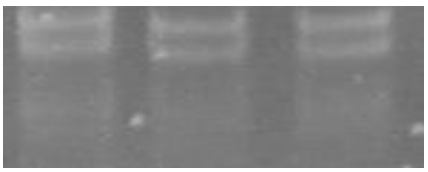
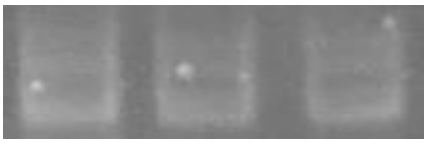
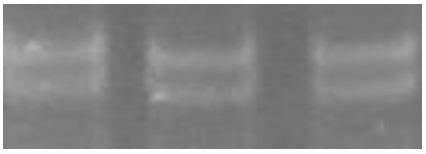
Sr-no	Markers	Map unit cM	Results		
			1N	2 N	3N
1	D5S577	64.49			
2	D5S418	64.56			
3	D5S856	65.07			
4	D5S430	65.19			
5	D5S660	66.83			

Figure 8: The image of polyacrylamide gel (Electropherogram)

The figure showed allel pattern with particular markers of *GHR* candidate gene, cytogenetic location of gene is 5p12-13 was taken after staining the gel with ethidium bromide. Homozygous banding patterns shows that the individual is affected whereas heterozygous pattern of bands shows that individual is normal, the symbol N is indicating that individual is normal while A is indicated the affected individual. The Arabic numerals are representing number of family member.

The autosomal recessive inheritance pattern of AMDM within the familial enclave was substantiated through a meticulous fusion of pedigree scrutiny and molecular scrutiny. The conspicuous non-linkage to established genes underscores the plausible involvement of an as-yet-unidentified genetic locus in steering the pathogenesis of AMDM within this familial

panorama. The illustrative depictions of gel electrophoresis figure 2- 7 provide a visual rendition of homozygous banding patterns in affected individuals and heterozygous configurations in their unaffected counterparts, accentuating the imperative for an expanded exploration into the intricate genetic determinants underpinning AMDM in this distinctive familial context

DISCUSSION:

The quest to decipher the intricate genetic landscape underlying Acromesomelic Dysplasia Maroteaux Type (AMDM) within a consanguineous family has unraveled both challenges and prospects. Despite a thorough analysis of reported candidate genes associated with skeletal dysplasias, the elusive genetic culprit remained unidentified. The increasing mutation rate, propelled by various environmental factors, further complicates the genetic puzzle. This underscores the need for advanced genomic methodologies to transcend the limitations of conventional genetic mapping.

Our exhaustive examination of established candidate genes such as NPR2, BMPR1B, GDF5, GALNS, GLB1, and GHR did not yield the anticipated breakthrough in understanding Acromesomelic Dysplasia, Maroteaux Type (AMDM) within a consanguineous family. However, a separate study identified pathogenic variants in the FGFR3, GHR, COL2A1, and SHOX genes among a small group of patients with similar skeletal abnormalities (Spurná et al., 2024).

While many studies have consistently reported Acromesomelic dysplasia, type Maroteaux, as an autosomal recessive skeletal dysplasia resulting from biallelic loss-of-function variations in NPR2, which encodes the cartilage regulator C-type natriuretic peptide receptor B (Kılıç et al., 2021) . AMDM results from loss-of-function NPR2 mutations affecting the C-type natriuretic peptide receptor (Arya et al., 2020), mutations in the gene NPR2 in five families (Khan et al., 2012), Mutations in the Transmembrane Natriuretic Peptide Receptor NPR-B Impair Skeletal Growth and Cause Acromesomelic Dysplasia, Type Maroteaux (Bartels et al., 2004), Exclusion of chromosome 9 helps to identify mild variants of acromesomelic dysplasia Maroteaux type (Faivre et al., 2000).

This scenario hints at the potential existence of a novel mutation or undiscovered genetic locus governing AMDM in this consanguineous family. To unravel this complexity, a paradigm shift to whole-genome sequencing emerges as the most compelling strategy. While acknowledging the financial constraints associated with this approach, its efficiency in uncovering rare mutations and expediting diagnostic timelines cannot be overstated.

The inability to identify a specific genetic culprit within the currently known loci necessitates a broader perspective. Recognizing the escalating mutation rates and the multifactorial nature of genetic anomalies, our findings advocate for a comprehensive genomic approach, particularly in consanguineous populations. The implications extend beyond diagnostics, influencing genetic

counseling practices and potentially informing therapeutic interventions in the evolving landscape of precision medicine.

In light of these findings, the study urges collaborative efforts and the pooling of genomic resources across populations. The exploration of the entire genome is not merely a scientific luxury but an imperative to unearth the complexities of rare genetic disorders like AMDM. While the financial considerations are undeniable, the investment in whole-genome sequencing promises dividends in terms of diagnostic accuracy and, perhaps more importantly, in the elucidation of novel genetic paradigms.

CONCLUSION:

In conclusion, the study underscores the challenges inherent in unraveling the genetic basis of rare skeletal dysplasias. The surge in mutation rates and the limited yield from traditional genetic mapping necessitate a shift towards comprehensive genomic strategies. The call for whole-genome sequencing, albeit resource-intensive, aligns with the imperative to decode the complexities of novel mutations in AMDM and paves the way for a more precise understanding of the genetic underpinnings of rare disorders

RECOMMENDATION

Genomic Strategies Adoption: Encourage the wider adoption of advanced genomic methodologies, particularly whole-genome sequencing, in diagnosing rare genetic disorders like AMD. Institutions and healthcare providers should invest in these technologies despite financial constraints, as they offer greater diagnostic accuracy and potential for uncovering novel genetic elements contributing to the disorder.

Collaborative Research: Advocate for collaborative efforts among researchers, clinicians, and geneticists from diverse populations to pool resources and data. Collaboration can facilitate the sharing of knowledge, samples, and technologies, ultimately advancing our understanding of rare genetic disorders and improving diagnostic and therapeutic approaches.

Genetic Counseling Enhancement: Enhance genetic counseling services for families affected by rare genetic disorders like AMD. Genetic counselors should provide comprehensive information about the genetic basis of the disorder, potential inheritance patterns, available diagnostic tests, and therapeutic options. Moreover, they should offer support and guidance to families navigating the complexities of genetic testing and treatment decisions.

Precision Medicine Implementation: Promote the integration of precision medicine approaches in the management of rare genetic disorders. Tailoring therapeutic interventions based on the specific genetic mutations or underlying mechanisms identified through advanced genomic analyses can optimize treatment outcomes and improve patient care.

Longitudinal Studies: Conduct longitudinal studies to monitor the natural history and clinical outcomes of individuals with AMD and other rare genetic disorders. Long-term follow-up can provide insights into disease progression, treatment responses, and potential complications, guiding the development of personalized care plans and therapeutic strategies.

Public Health Awareness: Increase public awareness and education about rare genetic disorders, including their symptoms, diagnostic approaches, and available resources for affected individuals and families. By raising awareness, reducing stigma, and promoting early detection and intervention, public health initiatives can improve outcomes and quality of life for individuals living with rare genetic disorders like AMD.

Statements and Declarations:

Data Transparency: The authors are committed to ensuring transparency in the presentation of data throughout this research endeavor.

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Data Availability: All datasets generated or analyzed during this study are comprehensively documented and available within the published article.

Declarations:

Conflict of Interest: The authors affirm that they have no pertinent financial or non-financial interests to disclose that could influence the integrity or interpretation of the research findings.

Ethical Approval: Ethical clearance was obtained from the Institutional Review Board (IRB) at Quaid-i-Azam University, Islamabad, adhering strictly to established ethical protocols.

Consent to Publication: Publication consent is not applicable to this research project.

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