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Commentary

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Investigating the genetic causes of rare diseases in siblings from a Pakistani family

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DESCRIPTION

We conducted an in-depth genetic analysis on five siblings with a unique set of symptoms, born to consanguineous Pakistani parents. Utilizing SNP-based linkage mapping and exome sequencing, we sought to identify the underlying genetic cause. The three most severely affected siblings presented with primordial dwarfism, microcephaly, failure to thrive, delayed developmental milestones, and characteristic skeletal and craniofacial anomalies. Initially, we hypothesized that the disorder might represent a novel syndrome and focused on identifying a single causative gene. However, exome data analysis revealed a complex genetic landscape, with six rare homozygous mutations identified in five genes (CENPE, POC1A, PCNT, TMEM38B, and TMEM43) associated with recessive or dominant diseases. Notably, each sibling harbored a distinct combination of these variants, highlighting the challenges of genetic diagnosis in cases with similar phenotypes. Furthermore, one sibling with severe scoliosis had mutations in POC5 and ESR1, known to predispose to idiopathic scoliosis, as well as a mutation in the HOOK2 gene, an interaction partner of POC5. Our findings underscore the importance of considering genetic heterogeneity and the potential for multiple genetic contributors to complex phenotypes, cautioning against assumptions of a single underlying genetic cause in seemingly "novel syndromes" within sibling groups. This comprehensive genetic investigation into a consanguineous Pakistani family with multiple affected siblings reveals a complex interplay of genetic factors contributing to overlapping clinical features. While initial observations suggested a potentially novel, single-gene syndrome, exome sequencing and SNP-based mapping uncovered multiple rare homozygous mutations across several known disease-associated genes. The distinct combination of these variants in each sibling, despite shared symptoms, highlights the intricate nature of genetic inheritance in consanguineous families and emphasizes the potential for multilocus pathogenicity. Additionally, the presence of scoliosis-linked mutations in one sibling further illustrates the possibility of phenotype-modifying or disease-enhancing genetic variants. These findings reinforce the necessity of broad, unbiased genetic analyses and caution against oversimplifying genotype-phenotype correlations, especially in cases with consanguinity and phenotypic overlap.

CONCLUSION

This study demonstrates the genetic complexity underlying shared clinical features in siblings from a consanguineous family. Though the presentation initially pointed toward a single-gene disorder, detailed genomic analysis uncovered multiple rare homozygous mutations in genes previously linked to distinct syndromes. Each sibling carried a unique combination of these variants, indicating that similar phenotypes can arise from different genetic backgrounds even within the same family. Moreover, the presence of additional mutations related to scoliosis in one sibling suggests that secondary genetic factors may influence or modify the severity and presentation of symptoms. These insights highlight the importance of considering multilocus contributions and genetic heterogeneity in diagnosing rare and complex conditions. Ultimately, this case reinforces the value of comprehensive genomic approaches in uncovering the full spectrum of genetic influences in familial disorders, particularly in populations with high levels of consanguinity.