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Original Research

Identification and Characterization of Genetic Variants in the Human ACAN Gene Using the ClinVar Database

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Abstract

The ACAN gene plays an important role in skeletal growth and development, so mutations in this gene are associated with various disorders such as short stature and skeletal dysplasia. This study aims to identify and characterize ACAN gene mutation variations using the ClinVar database at the National Center for Biotechnology Information to support the interpretation of pathogenicity and genetic diagnosis. This study was conducted in silico with a descriptive-comparative approach using ACAN gene variant data from the ClinVar database at the National Center for Biotechnology Information. Pathogenic and likely pathogenic variants were analyzed and grouped by germline classification, molecular consequence, and variant type. The results of the ClinVar database analysis at the National Center for Biotechnology Information showed that most ACAN gene variants are categorized as pathogenic, with missense, frameshift, and single-nucleotide variants being the most common mutation types. Genetic variations in the ACAN gene have a strong clinical association with skeletal growth disorders, especially short stature, so that ACAN gene variant analysis has the potential to support genetic diagnosis, prognosis, and genetic counselling in skeletal disorders. This study also shows that the use of bioinformatics databases can help understand the relationship between genetic variation and disease more systematically.

Introduction

The ACAN gene encodes the aggrecan protein, the primary proteoglycan in cartilage. Aggrecan is an essential component of the extracellular matrix of cartilage, contributing to its strength, elasticity, and resistance to pressure. Aggrecan, a product of ACAN gene expression, is crucial for chondrocyte proliferation, chondrocyte differentiation, and endochondral ossification (Kiani et al., 2002; Aspberg, 2012; Domowicz et al., 2009; Lauing et al., 2014). The ACAN gene is a key gene in polygenic inheritance closely related to height, skeletal development, and longitudinal bone growth (van der Steen et al., 2017; Hauer et al., 2017). Pathogenic mutations or variants in the ACAN gene are known to be associated with various skeletal disorders such as short stature, skeletal dysplasia, early osteoarthritis, bone growth disorders, and intervertebral disc disorders (Karatas et al., 2023; Gkourogianni et al., 2017; Gleghorn et al., 2005; Tompson et al., 2009; Stattin et al., 2010).

In NCBI, searches to identify and characterize pathogenic variants or mutations in the ACAN gene are now possible without the need for primary sequencing of individual samples. The availability of databases contributed by various researchers worldwide simplifies the search process. Further convenience allows other researchers to analyze variants, including mutation type, clinical significance,

molecular consequences, and pathogenic effects. On the other hand, much of the documentation in NCBI is presented in technical English, with unfamiliar bioinformatics terms and complex genomics terminology. While NCBI does provide data, biological interpretation still requires a sound understanding of evolution, genetics, taxonomy, and statistics, in line with current scientific developments.

Various types of analyses related to the ACAN gene can be performed using data from NCBI. Identification of SNPs, missense mutations, nonsense mutations, frameshift mutations, and pathogenicity prediction in the ACAN gene are crucial, given its role in skeletal growth and disease. For example, analysis of frameshift mutations can explain changes in the entire protein reading frame. Clinical symptoms similar to those of other diseases can also be explained by identifying mutations in the ACAN gene, thereby confirming the diagnosis and differentiating skeletal disorders. Mutation analysis can also be used to predict prognosis, severity, and disease progression. In other words, genetic analysis approaches, such as mutation analysis, support personalized medicine, which will improve disease management for patients and provide a strong basis for genetic counselling sessions for families (Ashley, 2016; Resta et al., 2006; Richards et al., 2015).

This study conducted a computational analysis of the ACAN gene. This study aimed to identify and characterize mutational variations in the ACAN gene and their potential disease pathways. This study is expected to facilitate readers, especially beginners, in determining the appropriate database, understanding relationships within the data, and providing navigation for utilizing the vast amount of data. This study demonstrated how to utilize the ClinVar database feature in NCBI to make it easier to understand, especially for new users.

Method

This study was conducted in silico using a descriptive-comparative approach, namely a study that utilizes computational analysis to identify and characterize genetic variants and clinical conditions associated with ACAN gene variants based on data obtained from the NCBI ClinVar database (Landrum et al., 2018). The genetic variants analyzed were variants with pathogenic and likely pathogenic classifications derived from the human ACAN gene based on the RefSeq NM_001369268.1 reference sequence (NCBI, 2026; Richards et al., 2015). To obtain mutation variants from the ClinVar database, the keywords "ACAN" & "pathogenic" were entered in the search field in NCBI. Variants were then grouped based on information on germline classification, molecular consequence, and variation type.

Results and Discussion

3.1 Results

Mutation analysis of the ACAN gene related to the clinical level of variants found 173 (67.8%) pathogenic variants and 82 (32.2%) likely pathogenic variants. This indicates that most variants have a strong association with disease manifestations. However, the likely pathogenic category still requires further confirmation. In the international standard guidelines developed by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (2015), genetic variants can be classified as benign, likely benign, variants of uncertain significance, likely pathogenic, and pathogenic.

Table 1. Characterization of genetic variants of the ACAN gene in relation to their clinical levels

Clinical Variants	Total	Percentage
Pathogenic	173	67.8%
Likely pathogenic	82	32.2%

The results of the characterization of mutation types in the ACAN gene resulted in four categories. Mutations that can change the structure or function of the protein (missense variants) were found most often, namely 111 of 306 variants (36.3%), followed by mutations that cause a shift in the reading frame due to the insertion or deletion of nucleotides (frameshift variants), as many as 100 of 306 variants (32.7%). Next, 76 variants (24.8%) cause the formation of premature stop codons, thus stopping protein synthesis early. In addition, 19 variants (6.2%) were found that occur in the intron-exon splicing region, which can disrupt the process of mRNA maturation and can lead to protein abnormalities.

Table 2. Characterization of the genetic variation of the ACAN gene based on its mutation type

Mutation Type	Total Variants	Percentage
Missense variant	111	36.27%
Frameshift variant	100	32.68%
Splice site	19	6.21%
Nonsense variant	76	28.84%

The characterization of genetic variation in the *ACAN* gene based on mutation type revealed five main categories. Single-nucleotide variants were the most dominant, accounting for 203 of 373 variants (54.42%). This variation occurs due to a change in a single nucleotide base within the DNA sequence, which can subsequently alter protein structure and function. Additionally, deletions comprised 94 variants (25.20%), followed by duplications at 45 variants (12.06%). Insertions and indels accounted for the remaining fractions, with 26 (6.97%) and 5 variants (1.34%), respectively. Collectively, structural variations such as deletions, duplications, insertions, and indels have the potential to disrupt nucleotide sequences, thereby affecting the stability and expression of the aggrecan protein.

Table 3. Results of the identification of genetic variations of the ACAN gene

Variation Types	Total Variants	Percentage
Deletion	94	25.20%
Duplication	45	12.06%
Indel	5	1.34%
Insertion	26	6.97%
Single nucleotide	203	54.42%

The results of characterizing the relationship between the ACAN gene and the diseases it can cause indicate seven main categories. Short stature was found to be the most dominant, with 56 of 124 variants (45.16%), indicating that variations in the ACAN gene are closely related to height growth disorders. Furthermore, inborn genetic diseases were found with 24 variants (19.35%), followed by spondyloepimetaphyseal dysplasia with 16 variants (12.90%) and ACAN-related disorders with 15 variants (12.10%). In addition, osteochondritis dissecans with 8 variants (6.45%), monogenic short stature with 3 variants (2.42%), and autosomal dominant ACAN-related disorders with 2 variants (1.61%). These results indicate that variations in the ACAN gene have a close relationship with various skeletal disorders and bone growth.

Table 4. Characterization of diseases based on genetic variations of the ACAN gene

Disease Condition	Total Variant	Percentage
Short stature	56	45.16%
Osteochondritis dissecans	8	6.45%
Spondyloepimetaphyseal dysplasia	16	12.90%
ACAN-related disorder	15	12.10%
Inborn genetic diseases	24	19.35%
Autosomal dominant ACAN-related disorder	2	1.61%
Monogenic short stature	3	2.42%

3.2 Discussion

Analysis using the NCBI ClinVar database demonstrates that genetic variation data in the ACAN gene can be used to identify mutation types, molecular characteristics, and potential associations with various skeletal disorders. The use of public databases in this study also provides a simple overview of bioinformatics data usage, particularly for novice users in understanding the relationship between genetic variation and disease and in utilizing the ClinVar database's features more systematically.

The results of this study indicate that the majority of variants in the ACAN gene are categorized as pathogenic compared to likely pathogenic. This indicates that many variations in the ACAN gene have been known to have a strong association with skeletal disorders and bone growth based on clinical and molecular evidence available in the ClinVar database. The pathogenic classification indicates that a variant has strong evidence as a cause of disease, while likely pathogenic indicates that the variant is suspected to be associated with the disease but still requires further validation. The results of this study are in line with the study conducted by Stavber et al. (2026), who reported a high frequency of pathogenic variants in the ACAN gene in individuals with familial short stature. In that study, 37.5% of the individuals studied (6 of 16 probands) were found to have pathogenic mutations in the ACAN gene, including novel variants and large intragenic deletions that contribute to the familial short stature phenotype and aggrecanopathy.

Based on the results of mutation type characterization, missense variants were the most frequently found molecular consequence in this study. Missense mutations cause a single amino acid change in the Aggrecan protein, potentially affecting its structure and function (Stattin et al., 2022). Aggrecan protein plays a crucial role in the formation and stability of cartilage, a major component of the extracellular matrix of cartilage tissue. Distortion of the protein structure can disrupt cartilage function, leading to impaired bone growth, skeletal dysplasia, and contributing to short stature.

This study also found a relatively high number of frameshift variants in the ACAN gene. Frameshift mutations can cause changes in the reading frame, resulting in abnormal or truncated proteins. These changes in the amino acid sequence resulting from frameshift mutations can affect the stability and biological function of the Aggrecan protein, thus contributing to impaired secretion and integrity of the cartilage extracellular matrix (Liang et al., 2020). A study by Huang et al. (2023) also found a relatively high number of frameshift mutations in the ACAN gene, suggesting a significant role for these types of mutations in the pathogenesis of growth disorders and clinical manifestations such as height loss and early osteoarthritis.

In addition to missense and frameshift mutations, mutations in the splice site region have also been found. Splice site mutations in the ACAN gene have the potential to disrupt mRNA splicing, resulting in abnormal transcripts and affecting Aggrecan protein synthesis. Abnormal mRNA splicing due to point mutations, such as nucleotide substitutions that alter the consensus sequence of splicing

regulators in certain genes, is known to cause specific inherited monogenic disorders (Anna & Monika, 2018).

The results of genetic variation identification indicate that single-nucleotide variants (SNVs) are the most dominant type of genetic variation found in the ACAN gene. SNVs are the most common form of genetic mutation in the human genome due to changes in a single nucleotide base. These mutations can affect protein structure and function if they occur in the coding region of a gene. The dominance of SNVs in the ACAN gene indicates that single-nucleotide changes have a significant contribution to the emergence of genetic variations associated with skeletal disorders. This is in line with the understanding that genetic variation in the form of nucleotide substitutions at specific positions is the most common type of variant found in human genome analysis and can have significant pathogenic effects on gene function and disease progression (Brookes & Robinson, 2015).

Based on the characterization of the relationship between the ACAN gene and disease, short stature is the condition most commonly associated with variants in this gene. The ACAN gene plays a crucial role in the formation of the cartilage extracellular matrix (ECM) through the production of the Aggrecan protein. Mutations or deficiencies in the ACAN gene can affect Aggrecan production and function, thereby inhibiting the organization and function of the growth plate. This condition can lead to bone growth abnormalities, such as dwarfism and linear growth retardation, due to disruption of the endochondral ossification process and bone development (Melrose et al., 2016). In addition to short stature, ACAN gene variants are also associated with several other skeletal disorders, such as spondyloepimetaphyseal dysplasia, osteochondritis, and ACAN-related disorders. Abnormalities in the ACAN gene affect the development of the spine, epiphyses, and metaphyses of long bones due to disruption of the function of the Aggrecan protein, a major component of the extracellular matrix essential for bone and cartilage morphogenesis. This disorder can cause short stature, accelerated bone maturation, and degenerative disorders of the spine, such as intervertebral disc herniation (Dateki, 2017).

Overall, the characterization results indicate that genetic variations in the ACAN gene have a strong clinical association with linear bone growth disorders. The dominance of certain types of mutations found in this study indicates the presence of a critical region in the reference sequence NM_001369268.1 that is essential for aggrecan protein function. This study successfully presents a comprehensive variant distribution map based on data from the ClinVar database. However, limitations such as bias in the representation of the global population in this database require attention. Therefore, further research is recommended to conduct functional analysis of these variants in local populations to improve the accuracy of clinical diagnosis and the effectiveness of genetic counselling for patients with skeletal disorders.

Conclusion

Identification and characterization of genetic variations in the ACAN gene can be done using data from the ClinVar database. The majority of variants found are pathogenic, indicating a strong association between ACAN gene variations and various skeletal disorders, particularly short stature. The most common mutation types are missense variants and frameshift variants. Furthermore, single-nucleotide variants (SNVs) are the most prevalent type of genetic variation, indicating the importance of single-nucleotide changes in the pathogenesis of bone growth disorders. These results strengthen the understanding that mutations in the ACAN gene contribute to bone growth disorders and various other skeletal disorders, such as spondyloepimetaphyseal dysplasia and osteochondritis dissecans. The use of the ClinVar database also demonstrates the potential use of bioinformatics data to support genetic variant analysis and aid in understanding the relationship between genetic variations and disease.

Author contribution

A.P.A. designed the research and collected the data. A.P.A. and W.C. analysed the data and wrote

the manuscript.

Conflict of Interest

All authors declare no conflict of interest.

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