Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

Research Article

# GENE NOMENCLATURE OF DIFFERENT TYPES OF SPINOCEREBELLAR ATAXIA (SCA) AND THE IN SILICO STUDY OF NON-SYNONYMOUS SINGLE-NUCLEOTIDE POLYMORPHISMS (NSSNP) OF ATXN1 GENE ASSOCIATED WITH SPINOCEREBELLAR ATAXIA TYPE 1 (SCA1)

**M. MADHUMATHI* AND PRITI TALWAR**

**Division of Biomedical Sciences, School of Bio Sciences and Technology, VIT University, Vellore, Tamil Nadu-632014, India.**
**Email: mmmbioinfo@gmail.com**

*Received: 09 July 2013, Revised and Accepted: 11 Aug 2013*

**ABSTRACT**

Objective: The objective is to distinguish the gene nomenclature of 36 types of spinocerebellar ataxia (SCA) and to find the non-synonymous single-nucleotide polymorphism (nsSNP) which is main target for spinocerebellar ataxia type 1 (SCA1).

Method: The gene nomenclatures of spinocerebellar ataxias (SCAs) were collected from Entrez gene on NCBI website. SCA1 gene single nucleotide polymorphisms (SNPs) are retrieved from single nucleotide polymorphism database (dbSNP) and the insilico study was done for SCA1 by using SIFT and polyphen server.

Results: Gene information's like gene ID, gene name, gene full name, other aliases, other designations, location of gene, gene length, gene type and protein length are collected and briefly tabulated in this study. Among 24,000 SNP, 13 are nsSNP and among these 13 nsSNPs 5 were found to be deleterious and it was found by SIFT program. Among the same 13 nsSNPs 7 were found to be damaged and it was done by polyphen server. 4 nsSNPs (rs116599639, rs2175378, rs75068405 and rs62387706) are found to be common in both SIFT and polyphen.

Conclusion: The nomenclature of genes and its information's are briefly explained and it is used for further research. Among 24,000 SNPs 4 nsSNPs (rs116599639, rs2175378, rs75068405 and rs62387706) are found to be common in both SIFT and polyphen server. So the conclusion is that, the 4 nsSNPs are the main target mutation for SCA type 1.

**Keywords:** Spinocerebellar ataxia, Spinocerebellar ataxia type1, ATXN1, SIFT, Polyphen, nsSNPs, Gene Nomenclature.

## INTRODUCTION

Spinocerebellar ataxia (SCA) is an inherited disease, nearly 36 distinct genetic causes of SCA are known and each of which could be considered a disease in its own right. The nomenclature of 36 types of Spinocerebellar ataxia and a computational work on Spinocerebellar ataxia type 1 (SCA1) are done in this study. SCA1 is a progressive, degenerative and often fatal neurodegenerative disorders. There is no known effective treatment or cure. It is caused by either a recessive or dominant gene. Many times people are not aware that they carry the ataxia gene until they have children who begin to show signs of having the disorder [1]. Symptoms manifest between third and fourth decade with death resulting from bulbar dysfunction after 10-20 years. Juvenile onset has been seen in some kindred's [2]. The prevalence is approximately three cases per 100,000 people, because SCAs are highly heterogeneous, the prevalence of a specific subtype varies significantly among different ethnic groups and geographically separated populations [3].

SCA1 is mostly dominantly-inherited ataxia for which the locus and gene defect were identified [4]. SCA1 begins as a gait disorder, evolving to severe four limb ataxia with dysarthria and leaving most patients wheelchair-bound with 15-20 years. SCA1 is caused by polyQ-encoding CAG repeat expansions. As a result of this expansion, the SCA1 disease protein, ataxin-1, has an abnormally long stretch of the amino acid glutamine [5]. The causative gene for SCA1 is ATXN1 which maps to the short arm of chromosome 6 and has been isolated using a positional cloning approach. The SCA1 transcript is 10660 bases and encodes a novel protein, ataxin-1, with a molecular weight of 87 KDa [6]. The single nucleotide variations in the genome that occur at a frequency of more than 1% are referred to as single nucleotide polymorphisms (SNPs). In the human genome SNPs occur in just about every 3000 base pairs and the frequency of occurrence of the different alleles differs in different populations [7]. The harmful SNPs for the ATXN1 gene have not been predictable to date insilico. Therefore, to explore possible genetic mutations, different algorithms like Sorting Intolerant From Tolerant (SIFT) and Phenotyping Polymorphism (polyphen) were used for prioritization of high-risk nonsynonymous single nucleotide polymorphisms (nsSNPs) in coding regions that are likely to have an effect on the function and structure of the protein, and the classification of distinct 36 genes of SCA are also done in this work.

## MATERIALS AND METHODS

### Gene Nomenclature and Dataset

The Nomenclature of SCA and its 36 types was collected from Entrez Gene on NCBI website (http://www.ncbi.nlm.nih.gov/sites/enterz). SNPs associated with ATXN1 gene was retrieved from the single nucleotide polymorphism database (dbSNP), these are commonly referred to be their reference sequence IDs (rsID) [8].

### Prediction of tolerated and deleterious SNPs using SIFT

The Identified ATXN1 gene, nonsynonymous Single Nucleotide Polymorphism (nsSNP) and prediction effect of the variant amino acid substitution on protein function was performed using SIFT (http://blocks.fhcrc.org/sift/SIFT.html), the substitution of SNPs has the potential to affect protein function. SIFT is a program that predicts the amino acid substitution affects protein function so that we can prioritize substitutions for the study. We have shown that SIFT can distinguish between functionally neutral and deleterious amino acid changes in mutagenesis studies and on human polymorphisms. SIFT also searches for similar protein sequences from different species in the database, obtains the multiple alignments of these sequences, and then calculates from the alignment the tolerance index (from 0 to 1) for all possible substitutions at each position. The higher a tolerance index, the less functional impact a particular amino acid substitution is likely to have [9-14].

### Prediction of functional modification of coding nsSNPs

Polyphen version 2.1.0 (http://genetics.bwh.harvard.edu/pph2/) uses empirically derived rules based on previous research in protein structure, interaction, and evolution that automatically predict whether a replacement is likely to be deleterious for the protein on the basis of three-dimensional structure and multiple alignments of homologous sequences [15, 16]. Polyphen input is a protein amino acid sequence or accession number, together with sequence position

and two amino acid variants characterizing the polymorphism [15]. Prediction rules: Polyphen uses empirically derived rules to predict that an nsSNP is damaging, i.e. is supposed to affect protein function, or benign, i.e. most likely lacking any phenotypic effect. The rule is based on the analysis of the ability of various structural parameters and profile scores to discriminate between disease mutations and substitutions between human proteins and closely related mammalian orthologues [17]. Another two categories of prediction is nsSNPs possibly damaging protein function/structure and nsSNPs probably damaging protein function/structure [12-14, 18].

## RESULTS

### Gene Nomenclature and Dataset

The different types of SCA diseases are collected and their Gene Information's like gene ID, gene name, Gene full name, other aliases, other designations, location of gene, gene length, gene type and protein length are also collected and listed in Table 1. A total of 24,000 SNPs associated with ATXN1 gene was collected and are subjected to SIFT and polyphen server to detect the deleterious coding nsSNPs and to see the functional change in coding nsSNPs.

**Table 1: Gene nomenclature of different types of spinocerebellar ataxia**

| Disease | Gene ID | Gene name | Full name | Other aliases | Other designations | Location | Gene length | Gene type | Protein length |
|---|---|---|---|---|---|---|---|---|---|
| SCA1 | ID: 6310 | ATXN1 | Ataxin 1 | ATX1, SCA1, D6S504E | Ataxin-1, spinocerebellar ataxia type 1 protein | 6p23 | 462.38 kb (base start from 16299343 to 16761721) | Protein coding | 815 amino acid |
| SCA2 | ID: 6311 | ATXN2 | ataxin 2 | ASL13, ATX2, SCA2, TNRC13 | Ataxin2; spinocerebellar ataxia type 2 protein; trinucleotide repeat containing 13; trinucleotide repeat-containing gene 13 protein | 12q24.1 | 147.46kb region from base 111890018 to 112037480. | Protein coding | 1313 amino acid |
| SCA3 | ID: 4287 | ATXN3 | Ataxin3 | AT3, ATX3, JOS, MJD, MJD1, SCA3 | Machado-joseph disease (spinocerebellar ataxia 3, olivopontocerbellar ataxia 3, autosomal dominant, ataxin3), Machado-joseph disease protein1, ataxin3 variant h, ataxin3 variant m, ataxin 3 variant ref, ataxin 3,josephin, olivopontocerebellar ataxia 3, spinocerebellar ataxia type 3 protein | 14q21 | 48.07kb region from base 92524896 to 92572965. | Protein coding | 370 amino acid |
| SCA4 | ID:25894 | PLEKHG4 | Pleckstrin homology domain containing, family G (with RhoGef domain) member 4 | SCA4, PRTPHN1, ARHGEF44 | - | 16q22.1 | 11.99kb region from base 67311413 to 67323403. | Protein coding | 1191 amino acid |
| SCA5 | ID:6712 | SPTBN2 | Spectrin, beta, non-erythrocytic 2 | SCA5, GTRAP41 | Beta-III spectrin, glutamate transporter EAAT4-associated protein 41; spectrin beta chain, brain 2; spectrin beta chain, non-erythrocytic 2; spectrin, non-erythroid beta chain2, spinocerebellar ataxia 5 protein | 11q13 | 36.15kb region from base 66452720 to 66488870. | Protein coding | 934 amino acid |
| SCA6 | ID:773 | CACNA1A | Calcium channel, voltage-dependent, P/Q | APCA, BI, CACNL1A4, CAV2.1, EA2, | Brain calcium channel 1; brain calcium channel l; | 19p13 | 300.02kb region from base | Protein coding | 2512 amino acid |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | type, alpha 1A subunit | FHM, HPCA, MHP, MHP1, SCA6 | calcium channel, L type, alpha-1 polypeptide; voltage-dependent P/Q-type calcium channel subunit alpha-1A; voltage-gated calcium channel subunit alpha Cav2.1 | | 13317256 to 13617274. | | |
| SCA7 | ID:6314 | ATXN7 | Ataxin7 | SCA7, OPCA3, ADCAII | Ataxin-7,spinocerebellar ataxia type 7 protein | 3p21.1-p12 | 138.91kb region from base 63850233 to 63989138. | Protein coding | 945 amino acid |
| SCA8 | ID:724066 | ATXN8 | Ataxin8 | ATXN3 | Ataxin-8; protein 1C2 | 13q21 | 43M-90M bp | Protein coding | 684 amino acid |
| SCA9 | ID:140451 | SCA9 | Spinocerebellar ataxia 9 | - | - | - | - | Unknown | - |
| SCA10 | ID:25814 | ATXN10 | Ataxin10 | E46L, SCA10, HUMEEP | Ataxin10, brain protein E46 homolog, spinocerebellar ataxia type 10 protein | 22q13.31 | 173.51kb region from base 46067678 to 46241187. | Protein coding | 475 amino acid |
| SCA11 | ID:146057 | TTBK2 | Tau tubulin kinase 2 | SCA11, TTBK | Tau-tubulin kinase 2 | 15q15.2 | 176.47kb region from base 43036536 to 43213007. | Protein coding | 1244 amino acid |
| SCA12 | ID:5521 | PPP2R2B | Protein phosphatase 2, regulatory subunit B, beta | B55BETA, PP2AB55BETA, PP2ABBETA, PP2APR55B, PP2APR55BETA, PR2AB55BETA, PR2ABBETA, PR2APR55BETA, PR52B, PR55-BETA, PR55BETA, SCA12 | PP2A subunit B isoform B55-beta; PP2A subunit B isoform PR55-beta; PP2A subunit B isoform R2-beta; PP2A, subunit B, B-beta isoform; protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), beta isoform; protein phosphatase 2 (formerly 2A), regulatory subunit B, beta isoform; serine/threonine protein phosphatase 2A, 55 kDa regulatory subunit B, beta isoform; serine/threonine protein phosphatase 2A, neuronal isoform; serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B beta isoform | 5q32 | 491.97kb region from base 145969067 to 146461033. | Protein coding | 549 amino acid |
| SCA13 | ID:3748 | KCNC3 | Potassium voltage-gated channel, shaw-related subfamily, member 3 | KSHIIID, KV3.3, SCA13 | Shaw-related voltage-gated potassium channel protein 3; potassium voltage-gated channel subfamily C member 3; voltage-gated potassium channel protein KV3.3; voltage- | 19q13.33 | 13.87kb region from base 50818765 to 50832634. | Protein coding | 757 amino acid |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | gated potassium channel subunit Kv3.3 | | | | |
| SCA14 | ID:5582 | PRKCG | Protein kinase C, gamma | PKC-gamma, PKCC, PKCG, SCA14 | Protein kinase C gamma type | 19q13.4 | 25.43kb region from base 54385467 to 54410901. | Protein coding | 697 amino acid |
| SCA15 | ID:3708 | ITPR1 | Inositol 1,4,5-trisphosphate receptor, type 1 | INSP3R1, IP3R, IP3R1, SCA15, SCA16 | IP3 receptor; IP3R 1; inositol 1,4,5-triphosphate receptor, type 1; inositol 1,4,5-trisphosphate receptor type 1; type 1 InsP3 receptor; type 1 inositol 1,4,5-trisphosphate receptor | 3p26.1 | 354.49kb region from base 4535032 to 4889524. | Protein coding | 721 amino acid |
| SCA16 | ID:3708 | ITPR1 | Inositol 1,4,5-trisphosphate receptor, type 1 | INSP3R1, IP3R, IP3R1, SCA15, SCA16 | IP3 receptor; IP3R1; inositol 1,4,5-triphosphate receptor,type 1;inositol 1,4,5-triphosphate receptor type 1;type 1 InsP3 receptor; type 1 inositol 1,4,5-triphosphate receptor | 3p26.1 | 354.49kb region from base 4535032 to 4889524. | Protein coding | 721 amino acid |
| SCA17 | ID:6908 | TBP | TATA box binding protein | RP1-191N21.3, GTF2D, GTF2D1, HDL4, SCA17, TFIID | TATA sequence-binding protein; TATA-box binding protein N-terminal domain; TATA-box factor; TATA-box-binding protein; transcription initiation factor TFIID TBP subunit. | 6q27 | 18.54kb region from base 17086342 1 to 17088195 8. | Protein coding | 339 amino acid |
| SCA18 | ID:94008 | SCA18 | Spinocerebellar ataxia 18 (sensory with neurogenic muscular atrophy) | SMNA | - | 7q22-q32 | - | Unknown | - |
| SCA19 | ID:140452 | SCA19 | Spinocerebellar ataxia 19 | - | - | 1p21-q21 | - | Unknown | - |
| SCA20 | ID:407973 | SCA20 | Spinocerebellar ataxia 20 | DUP11q12; C11DUPq12 | - | 11p11.2-q13.3 | - | unknown | - |
| SCA21 | ID:170545 | SCA21 | Spinocerebellar ataxia 21 | - | - | 7p21.3-p15.1 | - | Unknown | - |
| SCA22 | ID:140575 | SCA22 | Spinocerebellar ataxia 22 | - | - | 1p21-q23 | - | Unknown | - |
| SCA23 | ID:5173 | PDYN | Prodynorphin | ADCA, PENKB, SCA23 | Beta-neoendorphin-dynorphin; leu-enkephalin; leumorphin; neoendorphin-dynorphin-enkephalin prepropeptide; preprodynorphin; preproenkephalin B; proenkephalin-B; rimorphin | 20p13 | 15.53kb region from base 1959402 to 1974931. | Protein coding | 254 amino acid |
| SCA24 | ID:260415 | SCASI | Spinocerebellar ataxia with saccadic intrusions | SCA24, SCAR4 | - | 1p36 | - | Unknown | - |
| SCA25 | ID:338435 | SCA25 | Spinocerebellar ataxia 25 | - | - | 2p21-p15 | - | Unknown | - |
| SCA26 | ID:408221 | SCA26 | Spinocerebellar ataxia 26 | - | - | 19p13.3 | - | Unknown | - |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SCA27 | ID:2259 | FGF14 | Fibroblast growth factor 14 | RP11-39708.6, FGF-14, FHF-4, FHF4, SCA27 | bA39708.2; fibroblast growth factor homologous factor 4 | 13q34 | 680.92kb region from base 102373205 to 103054124. | Protein coding | 252 amino acid |
| SCA28 | ID:10939 | AFG3L2 | AFG3 ATPase family member 3-like 2 (S.cerevisiae) | SCA28, SPAX5 | AFG3 ATPase family gene 3-like 2; AFG3-like protein 2; ATPase family gene 3, yeast; paraplegin-like protein | 18p11 | 48.33kb region from base 12328943 to 12377275. | Protein coding | 797 amino acid |
| SCA29 | ID:100038747 | SCA29 | Spinocerebellar ataxia 29 | ACV, CLA4 | - | 3p26 | - | Unknown | - |
| SCA30 | ID:100359393 | SCA30 | Spinocerebellar ataxia 30 | - | - | 4q34.3-q35.1 | - | unknown | - |
| SCA31 | ID:100312950 | SCA31 | Spinocerebellar ataxia 31 | BEAN, BEAN1 | Brain-expressed protein associating with Nedd4 homolog; protein BEAN1 | 16q21 | 66.23kb region from base 66461200 to 66527432. | Protein coding | 259 amino acid |
| SCA32 | ID:100653368 | SCA32 | Spinocerebellar ataxia 32 | - | - | 7q32-q33 | - | Unknown | - |
| SCA33 | - | - | - | - | - | - | - | - | - |
| SCA34 | ID:100750330 | SCA34 | Spinocerebellar ataxia 34 | - | - | 6q12.3-q16.2 | - | Unknown | - |
| SCA35 | ID:343641 | TGM6 | Transglutaminase 6 | TG6, TGY, SCA35, TGM3L, dJ734P14.3 | - | 20p13 | 51.85kb region from base 2361554 to 2413399. | Protein coding | 706 amino acid |
| SCA36 | ID:10528 | NOP56 | NOP56 ribonucleoprotein | NOL5A, SCA36 | - | 20p13 | 5.86kb region from base 2633178 to 2639039. | Protein coding | 594 amino acid |

**Table 2: Showing prediction results of tolerated and deleterious SNPs of Human ATXN1 gene**

| S. No. | SNP rsIDs | Amino acid change | Amino acid position | SIFT prediction | SIFT Score |
|---|---|---|---|---|---|
| 1 | rs4229722 | G to S | 57 | Tolerated | 0.96 |
| 2 | rs116599639 | R to C | 403 | Damaging | 0.03 |
| 3 | rs112951110 | Q to R | 399 | Tolerated | 0.74 |
| 4 | rs112175378 | S to C | 186 | Damaging | 0.04 |
| 5 | rs75068405 | I to T | 19 | Damaging | 0.00 |
| 6 | rs62387706 | S to I | 613 | Damaging | 0.00 |
| 7 | rs59310777 | H to Q | 211 | Tolerated | 0.37 |
| 8 | rs41267702 | A to V | 717 | Tolerated | 0.41 |
| 9 | rs34265178 | G to S | 467 | Tolerated | 0.94 |
| 10 | rs28555263 | Q to H | 208 | Tolerated | 0.24 |
| 11 | rs11969612 | H to Q | 209 | Tolerated | 0.30 |
| 12 | rs3817753 | Q to H | 213 | Tolerated | 0.20 |
| 13 | rs16885 | P to S | 753 | Damaging | 0.02 |

**Prediction of tolerated and deleterious SNPs using SIFT**

The SIFT program evaluates the significance of an amino acid substitution influencing protein function design on sequence homology and the physical properties of amino acids and in combination with naturally occurring nonsynonymous polymorphisms altering phenotype by aligning orthologous protein sequences. SIFT program was used to examine the tolerance and intolerance of a substitution among the SNPs [9, 19]. 13 amino acid substitution variants were identified in the systemic screening of human ATXN1 gene. Among 13 nsSNPs, 5 were found to be deleterious, i.e. intolerance and having a score of ≤ 0.05 and 8 substitutions are tolerance, and the results are shown in Table 2. Among 5 deleterious nsSNPs, 2 showed a highly deleterious tolerance index score of 0.00 (rs75068405, rs62387706) and 3 showed the score of 0.03, 0.04 and 0.02 (rs116599639, rs112175378 and rs16885) respectively.

**Prediction of functional modification of coding nsSNPs**

Polyphen was used to determine the protein structural modifications exhibiting potential impact of amino acid substitution on the structure and function of the protein. Among 13 nsSNPs 4 (rs4229722, rs41267702, rs34265178 and rs16885) are predicted to be benign, 3 SNPs (rs112951110, rs28555263 and rs11969612) are predicted as possibly damaging, 4 (rs116599639, rs112175378, rs75068405 and rs62387706) predicted as probably damaging and 2 (rs59310777 and rs3817753) are predicted as unknown and this results are shown in Table 3.

**Table 3: Showing prediction of functional effect of nsSNPs of Human ATXN1 gene**

| S. No. | SNP rsIDs | Amino acid change | Amino acid position | Polyphen prediction |
|---|---|---|---|---|
| 1 | rs4229722 | G to S | 57 | Benign |
| 2 | rs116599639 | R to C | 403 | Probably damaging |
| 3 | rs112951110 | Q to R | 399 | Possibly damaging |
| 4 | rs112175378 | S to C | 186 | Probably damaging |
| 5 | rs75068405 | I to T | 19 | Probably damaging |
| 6 | rs62387706 | S to I | 613 | Probably damaging |
| 7 | rs59310777 | H to Q | 211 | Unknown |
| 8 | rs41267702 | A to V | 717 | Benign |
| 9 | rs34265178 | G to S | 467 | Benign |
| 10 | rs28555263 | Q to H | 208 | Possibly damaging |
| 11 | rs11969612 | H to Q | 209 | Possibly damaging |
| 12 | rs3817753 | Q to H | 213 | Unknown |
| 13 | rs16885 | P to S | 753 | Benign |

## CONCLUSION

The different types of SCA diseases were obtained from NCBI and the Nomenclature of the genes and its information including Gene ID are briefly explained in Table 1 and it is used for the further research. Insilico study was done for SCA type 1 and the associated gene is ATXN1 to predict the deleterious and damaged nsSNPs by using SIFT and Polyphen. Of the total 24,000 SNPs, 13 are nsSNPs, among these 13 nsSNPs 5 (rs116599639, rs112175378, rs75068405, rs62387706 and rs16885) are found to be deleterious by SIFT and 7 (rs116599639, rs112951110, rs112175378, rs75068405, rs62387706, rs28555263 and rs11969612) were damaged as by polyphen program. 4 nsSNPs (rs116599639, rs112175378, rs75068405 and rs62387706) are found to be common in both SIFT and polyphen. So these 4 nsSNPs are the main target mutation for the Spinocerebellar ataxia type 1 caused by ATXN1 gene. The identification of these nsSNPs using bioinformatics tools such as SIFT and polyphen narrows down study fields and is the first step of the progress to evaluate their possible phenotypic importance in costly clinical studies.

## REFERENCES

1. Henry Paulson L, The spinocerebellar Ataxias. J Neuroophthalmol 2009; 29: 227-237
2. Franklin Q, Joanne J and Bradley W. Popovich, A novel CAG repeat configuration in the SCA1 gene: implications for the molecular diagnostics of spinocerebellar ataxia type 1. Hum Mol Gent 1995; 12: 2411-2413
3. Schols L, Bauer P, Schmidt T, Schulte T, Riess O, Autosomal dominant cerebellar ataxias: Clinical features, genetics, and pathogenesis. Lancet Neurol 2004; 3: 291-304
4. Orr HT, Zoghbi HY, Trinucleotide repeat disorders. Annual review of neuroscience. 2007; 30:575-621
5. Zoghbi HY, Orr HT, Pathogenic mechanisms of a polyglutamine-mediated neurodegenerative disease, spinocerebellar ataxia type 1. J Biol Chem 2009; 12: 7425-7429
6. Huda Y. Zoghbi HY, Orr HT, Spinocerebellar ataxia type 1. J Cell Biol 1995; 6: 29-35
7. Cargill M, Altshuler D, Ireland J, Sklar P, et al, Characterization of single nucleotide polymorphisms in coding regions of human genes. Nat Genet 1999; 22: 231-238
8. Wheeler DL, Barrett T, Benson DA, Database resources of the National Center for Biotechnology information. Nucleic Acids Res 2008; 36: 13-21
9. Ng PC, Henikoff S, Predicting deleterious amino acid substitutions. Genome Res 2001; 11: 863-874
10. Ng CP, Henikoff S, SIFT: Predicting amino acid changes that affect protein function. Nucleic Acids Res 2003; 31: 3812-3814
11. Shen J, Deininger PL, Zhao H, Applications of computational algorithm tools to identify functional SNPs in cytokine genes. Cytokine 2006; 35: 62-66
12. Anand A, Arpita K, Influence of SMAD1 gene in osteoporosis: A bioinformatics approach. Bioinformatics 2010; 2: 79-87
13. Arpita K, Parvathy R, Ambika R, Nivedita VD, Anand A, Analysis of non-synonymous single-nucleotide polymorphisms and population variability of PLD2 gene associated with hypertension. Int J Bioinform Res Appl 2013; 9: 227-241
14. Anand A, Arpita K, Analysis of Non Synonymous Single-Nucleotide Polymorphisms of Collagen Type 1 Alpha 1 Gene Associated with Osteoporosis: An In-silico Study. OMICS Res 2011; 1(1): 32-40
15. Ramensky V, Bork P, Sunyaev S, Human non-synonymous SNPs: server and survey. Nucleic Acids Res 2002; 30: 3894-3900
16. Sunyaev S, Ramensky V, Koch I, Lathe W, Kondrshov AS, Prediction of deleterious human alleles. Hum Mol Genet 2001; 10: 591-7
17. Sunyaev S, Ramensky V, Koch I, Lathe W III Kondrashov AS, Bork P, Prediction of deleterious human alleles. Hum Mol Genet 2001; 10: 591-597
18. Vasily R, Peer B, Shamil S, Human non-synonymous SNPs: server and survey. Nucleic Acids Res 2002; 30: 3894-3900
19. Xi T, Jones IM, Mohrenweiser HW, Many amino acid substitution variants identified in DNA repair genes during human population screenings are predicted to impact protein function. Genomics 2004; 83: 970-979.