Case Report

Indian Journal of Genetics and Molecular Research
Volume 9 Number 1, January–June 2020
DOI: http://dx.doi.org/10.21088/ijgmr.2319.4782.8219.4

Novel SERPING1 Small Deletion Mutation in an Indian Family with Autosomal Dominant Hereditary Angioedema-TypeI

Bhawna Dubey[1], Chaitanya Vegi[2], Anuradha Udumudi[3]

How to cite this article:

Bhawna Dubey[1], Chaitanya Vegi[2], Anuradha Udumudi[3] Novel SERPING1 Small Deletion Mutation in an Indian Family with Autosomal Dominant Hereditary Angioedema-TypeI Indian J Genet Mol Res. 2020;9(1):29–33

Abstract

Hereditary Angioedema (HAE) is characterized by recurrent attacks of submucosal or subcutaneous edema and is caused by mutations in gene SERPING1. We identified a novel heterozygous small deletion in SERPING1 using targeted exome sequencing in an HAE patient from an Indian family. The mutation c.491_502delAGACCAACATGG,p. Glu164_ Met167del, in exon 3 of SERPING1 gene is reported in the proband and her father but was not found in proband's unaffected sibling and control samples. The mutation was classified as 'Likely Pathogenic' according to ACMG guidelines for interpretation of sequence variants. To the best of our knowledge, this is the first documented report for SERPING1 mutation in HAE type1 patients from India.

Keywords: Hereditary Angioedema; SERPING1; C1-INH; Exome Sequencing;Small Deletion Mutation.

Introduction

Angioedema (AE) is an autosomal dominant disease that affects 1 in 10,000–1 in 150,000 individuals worldwide,[1] although; incidence in India has not been established yet. Clinical symptoms of AE include recurrent attacks of submucosal or subcutaneous edema which lasts 2–5 days, commonly involving skin, lips, intestines, upper respiratory tract, and oropharynx. The condition can be life–threatening in cases where breathing is restricted due to swelling of the airways of respiratory system. The genetic form of the disease is due to mutations in SERPING1 gene, leading to reduced C1 esterase inhibitor (C1-INH) levels in plasma and is known as Hereditary Angioedema (HAE). Mutations related to type I HAE occur randomly in the gene resulting in truncated or misfolded proteins that are not secreted efficiently[2] and the mutated allele and C1-INH deficiency segregate into HAE families according to Mendelian law in an autosomal dominant mode.

Case Report

Clinical Features

Patient1 (P1), the female patient is 22 years old, born to non consanguineous parents and is clinically diagnosed with HAE type1. Age of onset was around 22 yrs with symptoms including abdomen swelling, face edema, swelling in hands, and back pain. Abnormally low levels of functional C1 Esterase Inhibitor Serum (C1-INH) = 1.7% and low levels of complement C4 (6.8 mg/ dl).

Patient2 (P2), 59 years old male and is father of P1; affected with the same condition. Age of onset was around 30 years with symptoms of bowel, hands, lips and testicles. Abnormally low levels of functional C1 Esterase Inhibitor Serum (C1-INH) = 2% and low levels of complement C4 (7 mg/ dl). Additional clinical details are given in Table 1

Genetic Studies

The genetic analyzes was requested by the

Author's Affiliation: [1,3]Chief Scientific Officer, [2]Department of Molecular Genetics, Institution, ATS GeneTech, 8-2-293/174/A25, Road number 14, Banjara Hills Hyderabad, Telangana 500034, India.

Corresponding Author: Anuradha Udumudi, Chief Scientific Officer, ATS GeneTech, 8-2-293/174/A25, Road number 14, Banjara Hills Hyderabad, Telangana 500034, India.

E-mail: deepakoushik305@gmail.com

patient's unaffected sibling who was planning a pregnancy with consanguineous partner. Family history of proband shows, father, paternal uncles and paternal first cousins affected with similar condition (Fig 1.). The family has seven members affected with HAE of which 3 are deceased. Two affected members and the unaffected sibling are studied here as other two members did not consent to the study. In all the cases age of onset was around 20-30 yrs. Samples from several HAE unaffected people were tested as normal controls. Mutation in proband P1 was identified through targeted exome sequencing on Ion S 5 Gene Studio sequencing instrument (Thermofisher Scientific, USA) followed by bioinformatics analysis using Torrent Suite and Ion Reporter Software (Thermofisher Scientific, USA).

Table 1: Clinical features of patients used in the study

Feature	P1	P2
Age	23	59
Gender	Female	Male
Age of HAE onset	22	30
Triggering Factors	Stress, heat, allergy to nuts	Stress, heat, spices
Location of edemas	Bowels, stomach lining, face	Bowels, stomach lining, hands, lips, testicles
Frequency	Once a month	Once in 10 days
Prodomal symptoms	Fever, skin rashes	Body pains
C1 levels %	1.7	2
C4 levels (mg/dl)	6.8	7
Duration of attack	36-48 hrs	24-36 hrs
Management	Hydrocortisone	Danazol

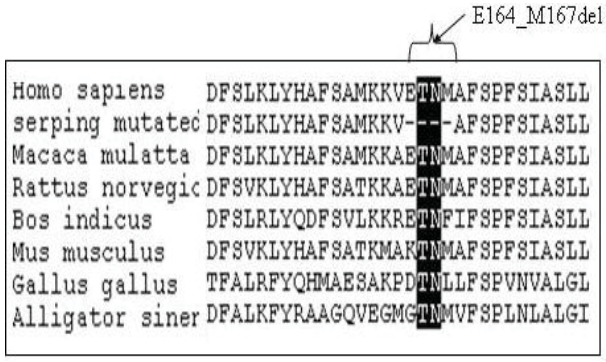

Fig. 1: Sequence alignment among species around the E164_M167del mutation site.

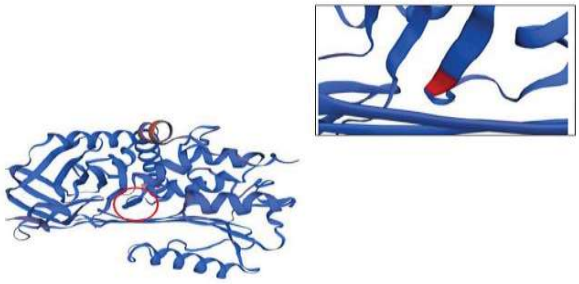

Fig. 2: Structure of Crystal structure of human Plasma protease C1 inhibitor (PDB id 5DU.3.1.A) is shown as ribbon model with a close–up view in the square region. The mutation region is colored red.

Targeted exome sequencing data (supplementary table 1) analyzes revealed a heterozygous 12 bp inframe deletion (NM_000062.2: c.491_502delAGACCAACATGG), p.Glu164_Met 167 del in exon 3 of SERPING1 gene, in the proband (P1). The indel causes deletion of 2 amino acids (Glu, Thr, Asn and Met) impacting protein features and was predicted to be pathogenic by insilico tools (supplementary table 2). Amino acid sequence alignment shows the wild type residues are conserved across species (supplementary Fig. 1). The position of deleted amino acids was mapped onto the crystal structure of human Plasma protease C1 inhibitor (PDB id 5DU.3.1.A) using molecular modeling (supplementary Fig. 2). The mutation with above interpretation has been submitted to ClinVar (Accession id: SCV000920778). The variant was confirmed by Sanger sequencing in proband and her father and was not detected in the unaffected sibling (Fig. 2) and among other controls. In the follow up counseling the unaffected sibling who requested genetic analysis was informed about no risk for inheritance of the condition since she did not carry the disease–causing mutation detected in her sibling and father.

Supplementary **Table 1**: Targetted Exome sequencing data output for patient 1.

Sequencing Platform	**Ion Torrent**
Number of Reads	16,138,760
Number of aligned reads	16,037,644
Mean Read Length	109 bp
Target regions coverage >2x	99.9%
Target regions coverage >20x	97.8%
Average depth on target	80.49
Number of Variants (passed quality filters)	14,877

Supplementary **Table 2**: Prediction Scores

Amino acid Change	E164_M167del
PROVEAN Score	-16.67
PROVEAN Prediction (cut off= -2.5)	Deleterious

Supplementary **Table 3**: List of filtered variants (Filters: Variants of the disease research area-HAE, not a UCSC common SNP, non-synonymous variants, coverage >20X)

Gene	Variant	HGVS	Mutation taster prediction
SERPING1	chr11:57367787: GTGGAGACCAACA>G	NM_000062.2: c.491_502delAGACCAACATGG p.Glu164_Met167del	Disease Causing
IFT43	chr14:76488691:C>T	NM_001102564.1:c.169C>T p.Arg57Cys	Polymorphism
HLA-DRB1	chr6:32546843:T>C	NM_001243965.1:c.799A>G	Polymorphism
HLA-DRB1	chr6:32551831:C>A	NM_001243965.1: c.343+55G>T	Polymorphism
HLA-DRB1	chr6:32628602:G>GC	NM_002123.4:c.772+522C>GC	Polymorphism

Mutation Taster Prediction	Disease Causing
SIFT-Indel	Damaging
Basewise conservation (PhastCons scores)	0.8
	0.81
	0.93
	0.99
	1
	1
	1
	0.99
	0.99
	0.99
	0.99
	0.99

Supplementary Table 3. List of filtered variants (Filters: Variants of the disease research area-HAE, not a UCSC common SNP, non-synonymous variants, coverage >20X)

Discussion

Here we describe an Indian family which had seven members affected with HAE, characterized by recurring attacks of edema involving skin, gastrointestinal and respiratory tract. Two affected members were included in this study; an unaffected sibling of the proband was also included to understand the variant segregation in the family. We identified a heterozygous variant, c.491_502delAGACCAACATGG in exon 3 of SERPING1 gene in the proband (P1) and her father (P2). This variant is novel and is classified as likely pathogenic according to ACMG criteria[3] because: (1) The indel variant was absent in population databases (ExAC, 1000 Genomes Project, gnomAD, dbSNP); (2) the variant is located in protein domain with well classified pathogenic variants and lacks benign variants; (3) the indel mutation leads to deletion of amino acids (Glu, Thr, Asn and Met), and was deemed deleterious/damaging by various insilico variant effect predictors[4,5]; (4) the variant was detected in two of the affected family members (proband and father) but was absent in the unaffected member (sibling) and other normal controls, providing an evidence of segregation of genotype with HAE phenotype; (5) patient's phenotype is highly specific for the SERPING1 gene whose role is well established in HAE etiology. Multiple studies on HAE patients from different populations have identified that the mutational spectrum of SERPING1 gene ranges from missense, nonsense and intronic mutations to small and large deletions.[6,7,8,9] Similar to our case, a Brazilian study documented small deletions in SERPING1 (c.97_115del19; c.776_782del7; c.1075_1089del15) among 16 HAE subjects with 19, 7 and 15 bp deletions in the gene.[8] Larger gene rearrangements or copy number variants (CNVs) in SERPING1 gene causing HAE type I or II are also reported.[10]

In summary, we have identified a distinct, novel deletion variant in SERPING 1 related to HAE I. To the best of our knowledge this is first documented report describing HAE causative SERPING1 mutation in an Indian family. Given that clinical genetics data from Indian patients is lacking in many cases, this report is expected to add to our knowledge on pathogenic mutations and disease etiology from this subcontinent. HAE is a rare but important disease for clinicians in terms of diagnosis and management due to life threatening nature of the disease. Our study indicates, exome sequencing can thus be considered as an effective tool for molecular diagnosis, prevention and adequate treatment of acute and life-threatening oedema. Molecular diagnosis in HAE patients become more relevant as researchers work towards the development of gene therapy for HAE, which would be aimed to provide a correct copy of the human C1-INH cDNA and hence restore functional C1-INH levels in plasma. Lastly, genetic analysis of SERPING1 gene for HAE patients may be especially imperative for familial cases for pre-symptomatic understanding and identifying the carriers early on before any clinical manifestation.

Patient Consent

Written informed consent was obtained from the participating family members. The study protocol was approved by IRB.

Acknowledgements

The authors are thankful to the patients and their family members who participated in this study.

Conflict of Interest

The authors declare no conflict of interest

References

1. Lumry W R. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. Am J Manag Care 2013; 19(7 Suppl):S103–S110.
2. Cugno M, Zanichelli A, Foieni F, et. al. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. Trends Mol Med 2009; 15(2): 69–78.
3. Richards S, Aziz N, Bale S, et. al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17(5):405–24.
4. SIFT web server: predicting effects of amino acid substitutions on proteins. Nucleic Acids Res 2012; 40 (Web Server Issue): W542–7
5. Schwarz JM, Cooper DN, Schuelke M, Seelow D. Mutation Taster 2: mutation prediction for the deep-sequencing age. Nature Methods 2014; 11(4), 361–362.
6. Jaradat S A, Caccia S, Rawashdeh R, Melhem M, et. al. Hereditary angioedema in a Jordanian family with a novel missense mutation in the C1-inhibitor N-terminal domain. Mol Immunol 2016; 71: 123–130.
7. Cagini N, Veronez CL, Constantino-Silva RN, et. al. New mutations in SERPING1 gene of Brazilian patients with hereditary angioedema. Biol. chem 2016; 397: 337–344.
8. Veronez CL, Moreno AS, Constantino-Silva RN, et. al. Hereditary Angioedema with Normal C1-inhibitor and F12 Mutations in 42 Brazilian Families. J Allergy Clin Immunol Pract. 2017.
9. Steiner U C, Keller M, Schmid P, et. al. Mutational spectrum of the SERPING1 gene in Swiss patients with hereditary angioedema. Clin. xp. Immunol 2017; 188: 430–436.
10. Alberto L L, Sofía G, Olga R, Margarita LT. SERPING1 mutations in 59 families with hereditary angioedema. Molecular Immunology 2011; 49(1–2):18–27.