Angioedema-Induced by Nonsteroidal Anti-inflammatory Drugs: A Genotype-Phenotype Correlation in A Brazilian Population

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are the leading cause of hypersensitivity reactions in Latin America, both in adults and children. Among the different types of NSAID-induced hypersensitivity reactions, urticaria and angioedema are the most common [1]. These generally take the form of wheals and/or angioedema in healthy patients after at least 2 NSAIDs with a different chemical structure on separate occasions. Interestingly, some of these patients only present angioedema. The mechanism involved in these reactions is unclear, although it is likely associated with inhibition of cyclooxygenase (COX), which affects the metabolism of arachidonic acid [2]. Different gene polymorphisms have been associated with NSAID-induced hypersensitivity, including those related to prostaglandin, leukotriene, $Ca2^{+}$, cAMP, and P53 signaling pathways [3]. Therefore, in this study, we used whole-exome sequencing (WES) to detect genetic markers that determine a hypersensitivity response in patients with NSAID-induced isolated angioedema (NIA).

The local ethics committee approved the study. Four unrelated patients with NIA and their parents were selected and agreed to participate in the study. Clinical data were collected using a specific questionnaire (Supplementary Table 1) [4]. In this study, hypersensitivity to NSAIDs was characterized according to the criteria of Laidlaw and Cahill [5], and patients with a history of angioedema within 6 hours of taking 2 different NSAIDs in at least 2 different episodes were selected. Angioedema affected the eyelid in all cases, although 2 individuals also reported lip angioedema. While the location of angioedema does not seem to have a direct relationship with the mechanism of reaction, eyelid involvement in all of the cases studied indicated a homogeneous clinical profile and

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appears to be the most frequent pattern in angioedema related to NSAIDs. All the patients had positive skin test or in vitro IgE results to house dust mite.

WES was performed on the Ion ProtonTM platform according to the manufacturer's recommendations. DNA samples were extracted from collected peripheral blood using the QIAmp DNA Blood Mini Kit (Qiagen), and sequencing was performed using the Ion PITM Chip v3 at Ion ProtonTM Sequencer. Sequencing data were analyzed in Torrent Suite v5.x.x, and all sequenced reads were mapped to human genome reference (hg19/GRC37). WES was assessed in terms of its quality to ensure that the data obtained could be used for the genotype-phenotype association proposed (Supplementary Table 2). Nine genes related to the COX and 5-LO signaling pathways (*ALOX5, PTGS2, CYSLTR1, CYSLTR2, LTC4S, PTGER1, PTGER2, TBXA2R, TBXAS1*) were filtered in the VCF file according to variant segregation analysis in order to propose the genotype-phenotype association. A cohort analysis was performed in PhenoDB (https://phenodb.org), and files obtained by each approach were then filtered based on Annovar annotations and multiple computational pathogenicity predictors. Variants were analyzed on Integrative Genomics Viewer (IGV ver. 2.3.92, Broad Institute) to evaluate alignment and variant calling. Variants presenting low mapping quality and unbalanced alleles (lower than 25% for each allele) were ruled out. The remaining variants were then prioritized based on their relevance to the studied phenotype.

The cohort analysis aimed to determine a causative gene shared by at least 50% of the families studied. Each mode of inheritance was combined to generate 2 reports, one for autosomal dominance and another for autosomal recessiveness (Table). Loss of function variants found in each mode of inheritance in all 4 families are available in the supplementary material (Supplementary Tables 3-6). Both analyses return no genes mutated in at least 2 families.

Using WES, we analyzed all the genes involved in the arachidonic acid pathway. In a study comprising 15 genes related to the arachidonic acid pathway, Cornejo-Garcia et al [6] observed a positive association for the *ALOX5AP, ALOX15, PTGDR, PTGER1, PTGER2*, and *CYSLTR1* genes in the Spanish population. However, the segregation analysis in our cohort of COX/5-LO pathway genes revealed no variant of biological relevance (Supplementary Table 7).

Table. Variants Found in Each Mode of Inheritance

Family	AD	AR-H	AR-CH
		Total Variants (Final)[a]	
1	158 (33)	99 (17)	160 (10)
2	241 (64)	45 (9)	140 (23)
3	153 (37)	39 (4)	128 (28)
4	283 (55)	64 (14)	147 (24)

Abbreviations: AD, autosomal dominant; AR-H, autosomal recessive homozygous; AR-CH, autosomal recessive compound heterozygous.
[a]Total of variants found in each mode of inheritance before filtering. Final variants found before filtering are shown in parentheses.

It is still unknown why certain individuals manifest urticaria while others have angioedema or anaphylaxis, or even why the manifestations are different in each episode in the same patient. It is even more intriguing that some patients react to some NSAIDs, but not to others of similar potency [7]. It might be that COX inhibition is part of the mechanism, but not a major factor.

One of the advantages of WES is the possibility of simultaneous evaluation of different polymorphisms, such as those related to mast cell activation, histamine release, and IgE receptors. In the only genetic study performed in a Brazilian population with nonselective hypersensitivity to NSAIDs, an association with a higher risk of reaction was found for the IL10 gene, whereas an association with a protection factor was found for the DAO gene [8]. We found no relevant variant associated with these genes.

Notwithstanding, 3 different mutations in MUC5B were found in families 1, 2, and 3, namely, c.13157_13158del, c.13245_13246insC, and c.13154dupC, respectively. These 3 mutations cause a frameshift change in protein sequence and are associated with pulmonary fibrosis (OMIM # 600770). Although MUC5B is recognized as one of the most mutation-tolerant genes in the human genome, it encodes a protein member of the mucin family, which is a major gel-forming mucin in mucus, contributing to the lubrication and viscoelasticity of whole saliva, normal lung mucus, and cervical mucus. This finding suggests the possible participation of other pathways in the pathophysiology of NIA.

Taken together, our data enable us to conclude that there is probably no single genetic marker of NIA in our cohort of patients. NIA is most likely determined by a combination of genetic alterations. Following this reasoning, large WES and genome sequencing studies will certainly help to determine and establish the variants that together build this complex trait. In addition, further approaches such as transcriptomics, proteomics, and metabolomics should be addressed to better explore the genetic footprints of hypersensitivity to NSAIDs. Furthermore, a better understanding of the NSAID signaling pathway and its relationship with other systems will probably clarify the specificity of NSAIDs and NIA.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Material

Table S1 – Studied patients' clinical profiles.

Patient	Gender	Age (years)	Age at onset (years)	Nº episodes/ site	Drugs	Tolerance	Treatment	Family history	Comorbidities
1	M	23	19	>5 E 2 L	Dipyrone sodium 300 paracetamol 400 mg Ibuprofen	Paracetamol 500 mg Etoricoxib 90 mg	Antihistamines Oral corticosteroids	No	Rhinitis Aorta root dilation
2	M	13	7	4 E 4 L	Dipyrone Ibuprofen Flurbiprofen	Paracetamol 500 mg	Antihistamines Oral corticosteroids	No	Rhinitis
3	F	45	24	4 E	Topical Diclofenac Dipyrone ASA Paracetamol 750 mg	Paracetamol 500 mg Etoricoxib 90 mg	Antihistamines	No	Rhinitis Hypothyroidism Dyslipidemia
4	M	44	10	>5 E	Topical Diclofenac ASA Paracetamol 1000 mg	Paracetamol 500 mg Etoricoxib 90 mg Celecoxib 200 mg	Antihistamines	Yes	Rhinitis Nephrolithiasis

NSAIDs: nonsteroidal anti-inflamatory drugs; ASA: acetylsalicylic acid; E: eyelid; L: lips.

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Table S2. Quality parameters obtained from NGS data.

Subjects ID	Reads on target (%)	Mean base coverage	20x coverage	Aligned reads
1-P	93,47%	130,1	95,80%	8.068.458.298
1-M	93,46%	136,6	96,15%	8.457.634.816
1-F	93,40%	139,5	96,40%	8.661.388.162
2-P	95,23%	122,1	92,19%	7.455.565.365
2-F	93,97%	108,4	91,49%	6.664.218.291
2-M	93,27%	113,5	92,67%	7.010.023.254
3-P	92,84%	111,8	94,47%	6.353.454.869
3-F	94,06%	116,4	88,73%	6.042.789.030
3-M	93,10%	127,1	95,63%	7.912.164.638
4-P	95,26%	210,8	94,68%	12.174.100.407
4-F	94,48%	122,1	92,38%	7.478.588.384
4-M	93,91%	108,2	90,85%	6.654.532.405

Subject ID according to data presented on clinical profiles (Table 1).
P – proband; F – father; M – mother.

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Table S3. LOF variants found in each mode of inheritance combined for family 1.

Gene	Function	cDNA	Protein	ExAC Global	Genotype	OMIM Phenotype	MH	RVIS	ClinVar	ACMG
ACSL6	FD	c.29delG	p.G10fs	-	hom	Myelodysplastic syndrome	-	16.63	-	VUS
CBFB	FD	c.205delT	p.F69fs	6.789e-05	het	Myeloid leukemia	-	52.85	-	VUS
CHIT1	SG	c.1015_1016insAGGGACTG GGCGGGGCCATGGTCT	p.W339delinsX	-	hom	Chitotriosidase deficiency	AR	91.32	-	VUS
DGUOK	FD	c.464delT	p.L155fs	-	hom	Mitochondrial DNA depletion syndrome 3 (hepatocerebral type)	AR	35.99	-	VUS
FREM2	FI	c.6976_6977insT	p.T2326fs	-	hom	Fraser syndrome	AR	16.77	-	VUS
HTRA2	FD	c.60delG	p.L20fs	0.0005	het	3-methylglutaconic aciduria	AR	71.27	-	VUS
IL17RC	FD	c.1422delG	p.S474fs	-	het	Candidiasis	AR	97.87	-	VUS
LRP1	FD	c.9927_9928del	p.P3309fs	-	hom	Keratosis pilaris atrophicans	AR	0.02	-	VUS
MAGEL2	FD	c.563delC	p.P188fs	-	het	Schaaf-Yang syndrome	AD	68.13	-	VUS
MUC5B	FD	c.13157_13158del	p.P4386fs	-	hom	Pulmonary fibrosis	AD	99.98	-	VUS
PRX	FD	c.1482delA	p.V494fs	-	het	Charcot-Marie-Tooth disease	AD	40.17	-	VUS
RYR1	FD	c.4089delG	p.A1363fs	-	het	Central core disease	AD	0.01	-	VUS
SIK1	FD	c.1551delC	p.P517fs	-	hom	Epileptic encephalopathy	AD	34.93	-	VUS
SRCAP	FD	c.7225delG	p.A2409fs	-	het	Floating-Harbor syndrome	AD	0.15	-	VUS

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)

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Table S4. LOF Variants found in each mode of inheritance combined for family 2.

Gene	Function	cDNA	Protein	ExAC Global	Genotype	OMIM Phenotype	MH	RVIS	ClinVar	ACMG
AXIN2	FD	c.1994delG	p.G665fs	-	het	Colorectal cancer	AD	72.85	-	VUS
CACNA1D	FD	c.22delA	p.K8fs	-	hom	Primary aldosteronism	AD	0.32	-	VUS
CC2D2A	FI	c.4517dupA	p.E1506fs	1.632e-05	het	COACH syndrome	AR	9.83	-	VUS
COL9A2	FI	c.1231dupC	p.Q411fs	-	het	Stickler syndrome	AD	96.41	-	VUS
GATA1	FD	c.3delG	p.M1fs	-	hem	Anemia	XLR	17.75	-	VUS
MAD2L2	FI	c.425dupC	p.P142fs	-	het	Fanconi anemia	AR	58.26	-	VUS
MAGEL2	FD	c.563delC	p.P188fs	-	het	Schaaf-Yang syndrome	AD	68.13	-	VUS
MMP3	FI	c.132_133insG	p.K45fs	-	het	Coronary heart disease	-	15.91	-	VUS
MUC5B	FI	c.13245_13246insC	p.P4415fs	-	het	Pulmonary fibrosis	AD	99.98	-	VUS
PDP1	FD	c.27delA	p.R9fs	-	het	Pyruvate dehydrogenase phosphatase deficiency	AR	13.33	-	VUS
PLCZ1	FD	c.1589delA	p.N530fs	-	hom	Spermatogenic failure 17	AR	23.51	-	VUS
RB1	FD	c.10delA	p.K4fs	-	het	Bladder cancer	AD	15.12	-	VUS
RNF212	FD	c.713delC	p.P238fs	-	het	Recombination rate QTL 1	-	-	-	VUS
SIK1	FD	c.1551delC	p.P517fs	-	hom	Epileptic encephalopathy	AD	34.93	-	VUS
SYN1	SG	c.C1423T	p.Q475X	-	hem	Epilepsy	XLD	-	-	VUS
TCF3	FD	c.1474delG	p.A492fs	-	het	Agammaglobulinemia 8	AD	47.26	-	VUS
TMPRSS15	SG	c.1228delT	p.L410X	-	het	Enterokinase deficiency	AR	97.45	-	VUS

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)

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Table S5. LOF Variants found in each mode of inheritance combined for family 3.

Gene	Function	cDNA	Protein	ExAC Global	Genotype	OMIM Phenotype	MH	RVIS	ClinVar	ACMG
ABL2	FD	c.2445delA	p.K815fs	-	het	Leukemia	-	8.60	-	VUS
AR	FD	c.250delC	p.P84fs	-	het	Androgen insensitivity	AD	17.31	-	VUS
AVP	FI	c.120_121insC	p.C41fs	-	hom	Diabetes insipidus	AD	-	-	VUS
MUC5B	FI	c.13154dupC	p.T4385fs	-	het	Pulmonary fibrosis	AD	99.98	-	VUS
MUC7	FI	c.922_923insC	p.I308fs	-	het	Asthma	AD	98.58	-	VUS
SRCAP	FD	c.7225delG	p.A2409fs	-	hom	Floating-Harbor syndrome	AD	0.15	-	VUS
TTN	FD	c.15296delC	p.P5099fs	-	het	Cardiomyopathy	AD	98.04	-	VUS
WNK4	FD	c.3297delC	p.S1099fs	-	hom	Pseudohypoaldosteronism	AD	74.74	-	VUS
XYLT2	FD	c.608delC	p.P203fs	-	het	Spondyloocular syndrome	AR	22.80	-	VUS

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)

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Table S6. LOF Variants found in each mode of inheritance combined for family 4.

Gene	Function	cDNA	Protein	ExAC Global	Genotype	OMIM Phenotype	MH	RVIS	ClinVar	ACMG
ABL2	FD	c.2444_2445del	p.K815fs	-	het	Leukemia	-	8.60	-	VUS
ABL2	FD	c.2444delA	p.K815fs	-	het	Leukemia	-	8.60	-	VUS
ATP2B3	FD	c.1473delA	p.G491fs	-	hem	Spinocerebellar ataxia	XLR	2.68	-	VUS
ATRX	FD	c.3801delA	p.K1267fs	-	hem	Alpha-thalassemia myelodysplasia syndrome	XLD	9.75	-	VUS
ATXN7	FD	c.1898_1901del	p.G633fs	-	hom	Spinocerebellar ataxia 7	AD	67.50	-	VUS
AXIN2	FD	c.1994delG	p.G665fs	-	hom	Colorectal cancer	AD	72.85	-	VUS
CFH	FD	c.2929_2930del	p.K977fs	-	het	Basal laminar drusen	AD	80.37	-	VUS
CNTN2	FD	c.1297delG	p.G433fs	-	het	Epilepsy	AR	39.31	-	VUS
COL18A1	FD	c.3365_3366del	p.G1122fs	-	hom	Knobloch syndrome	AR	86.36	-	VUS
DDHD1	FD	c.2484delT	p.F828fs	-	het	Spastic paraplegia 28	AR	48.78	-	VUS
DST	FD	c.5609delA	p.K1870fs	-	het	Neuropathy	AR	20.71	-	VUS
FBLN1	FD	c.1839_1840del	p.P613fs	-	het	Synpolydactyly	AD	29.61	-	VUS
FRZB	FD	c.84_85del	p.P28fs	-	het	Osteoarthritis susceptibility 1	M	77.80	-	VUS
GDI1	FI	c.175_176insG	p.L59fs	-	hem	Mental retardation	XLD	25.15	-	VUS
H6PD	FD	c.1804delG	p.G602fs	-	het	Cortisone reductase deficiency 1	AR	10.19	-	VUS
INPP5E	FD	c.367delG	p.A123fs	-	hom	Joubert syndrome 1	AR	-	-	VUS
ITPR2	FD	c.5405delA	p.K1802fs	-	het	Anhidrosis	AR	2.78	-	VUS
LHCGR	FD	c.1764delT	p.F588fs	-	het	Leydig cell adenoma	AD	74.63	-	VUS
LIAS	FD	c.107delA	p.K36fs	-	het	Hyperglycinemia	AR	27.69	-	VUS
NRG1	FD	c.266delA	p.Q89fs	-	het	Schizophrenia	-	91.71	-	VUS
PALB2	SG	c.886delA	p.M296X	-	het	Fanconi anemia	AD	72.85	-	VUS
PIKFYVE	FD	c.787delA	p.K263fs	-	het	Corneal fleck dystrophy	AD	4.16	-	VUS

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RIN2	FD	c.1192delG	p.G398fs	-	hom	Macrocephaly	AR	80.40	-	VUS
RP1L1	FI	c.3955dupG	p.A1319fs	-	het	Occult macular dystrophy	AD	99.90	B	VUS
SERPINA3	FI	c.659_660insCCCCAAGATA	p.P220fs	-	het	Alpha-1-antichymotrypsin deficiency	-	25.73	-	VUS
SIK1	FD	c.1551delC	p.P517fs	-	hom	Epileptic encephalopathy	AD	34.93	-	VUS
SPRTN	FD	c.1257delT	p.N419fs	-	het	Ruijs-Aalfs syndrome	AR	18.72	-	VUS
TBCK	FD	c.1181delA	p.N394fs	-	het	Hypotonia	AR	50.50	-	VUS
TPCN2	FD	c.348delT	p.A116fs	1.649e-05	het	Skin/hair/eye pigmentation 10	-	29.62	-	VUS
UGT1A3	FD	c.511delT	p.F171fs	8.244e-06	hom	Crigler-Najjar syndrome	AR	19.73	-	VUS
WAS	FD	c.1349delC	p.A450fs	-	hem	Neutropenia	XLR	80.01	-	VUS
ZFAT	FD	c.1607delT	p.L536fs	-	het	Autoimmune thyroid disease	-	27.08	-	VUS
ZFHX3	FD	c.6847delC	p.Q2283fs	-	het	Prostate cancer	-	0.12	-	VUS
ZNF513	FD	c.867_868del	p.G289fs	-	hom	Retinitis pigmentosa 58	AR	24.53	-	VUS

Function – exonic function according to RefGene assembly; MH – mode of inheritance according to OMIM; RVIS – residual variation intolerance score; ACMG – Variant classification according to the American College of Medical Genetics and Genomics; FD – frameshift deletion; FI – frameshift insertion; SG – stop codon gain; del – deletion; ins – insertion; het – heterozygous; hom – homozygous; hem – hemizygous; AD – autosome dominant; AR – autosome recessive; XLD – X-linked dominat; XLR – X-linked recessive X; VUS – variant with uncertain significance; B – benign; fs – frame-shift; dup – duplication. ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/)

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Table S7 - Number of variants found in the 10 genes (*PTGS1, PTGS2, ALOX5AP, ALOX5, ALOX12, ALOX15, LTC4S, PTGFR, PTGDR, PTGER1, PTGER2, PTGER3, PTGER4, CYSLTR1 e CYSLTR2*) related to COX signaling pathway.

Family	Subject	Variants	Total	Real*	Rare**
			COX pathway genes variants (genes)		
1	1	52913	8 (5)	2 (1)	-
	3	53363	9 (5)	3 (3)	-
	2	52814	8 (6)	2 (2)	-
2	1	54210	8 (4)	3 (3)	1
	2	52022	11 (4)	7 (3)	1
	3	53545	9 (6)	4 (4)	2
3	3	53104	9 (5)	3 (2)	1
	1	53650	9 (6)	3 (3)	-
	2	52934	10 (6)	5 (4)	-
4	2	52730	8 (5)	2 (1)	1
	3	52500	10 (6)	4 (4)	-
	1	53173	12 (6)	3 (3)	1

*Real variants determined by analysis on IGV software (*Integrative Genomics Viewer, Broad Institute*). **Variants with frequency lower than 1% in ExAC (Exome Aggregation Consortium - http://exac.broadinstitute.org/).

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