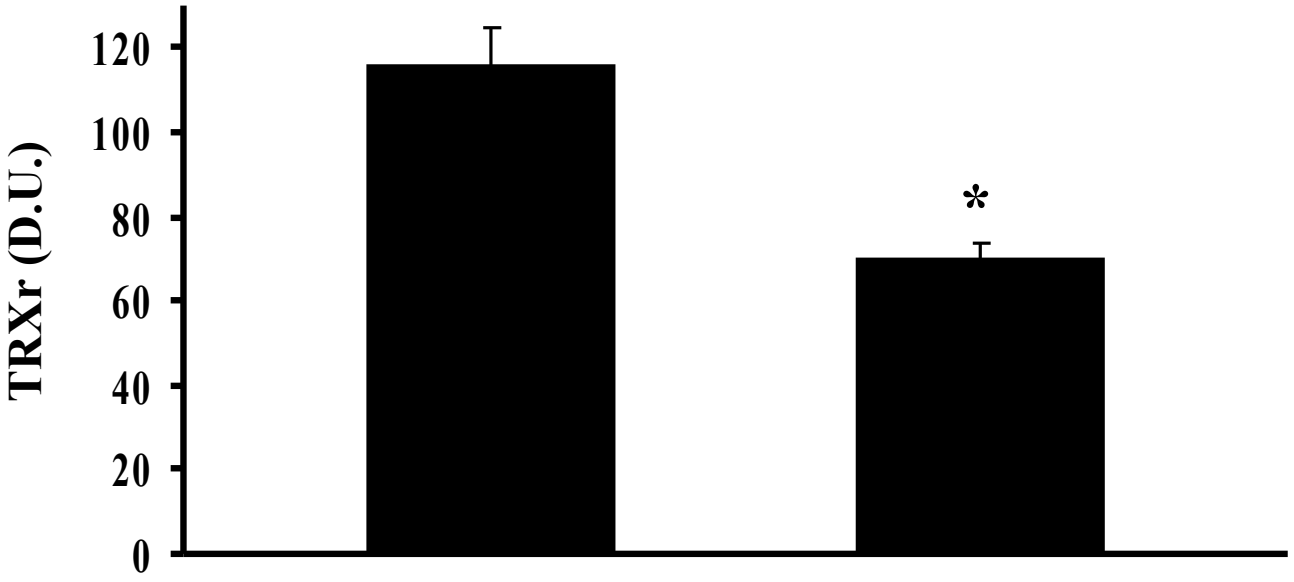
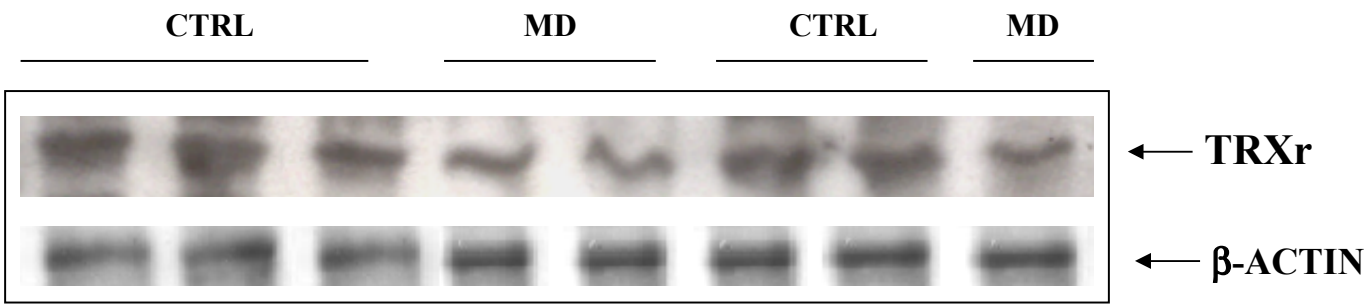
Fig 1

THIOREDOXIN REDUCTASE (TRXr) EXPRESSION LEVELS IN LYMPHOCYTES OF CONTROL HEALTHY VOLUNTEERS (CTRL) AND MENIERE' DISEASED PATIENTS (MD)

A)



B)

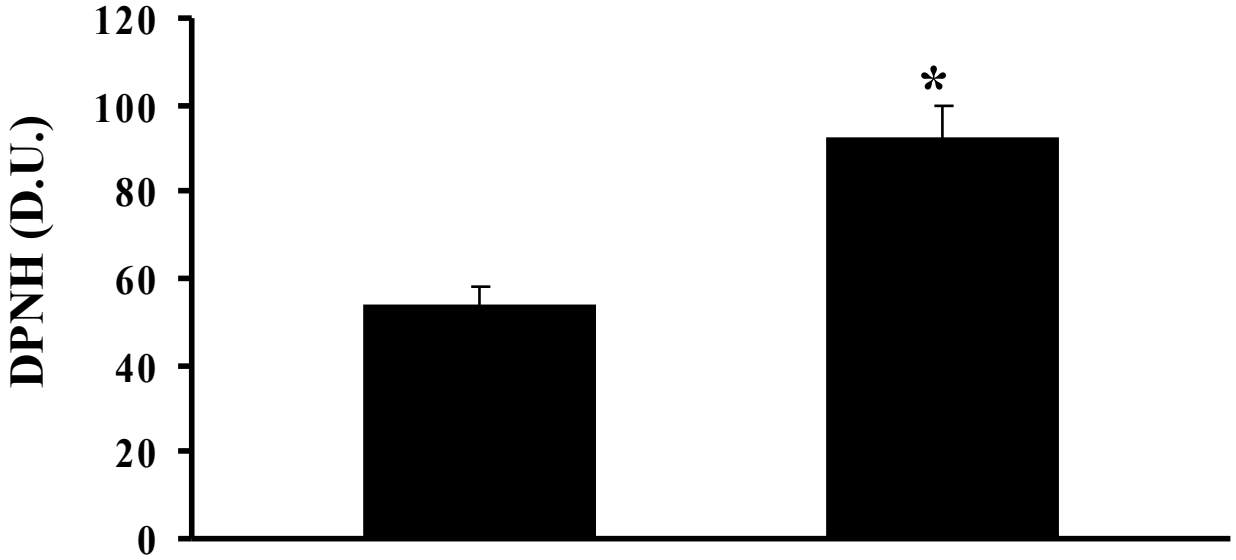


* p<0.01 vs ctrl

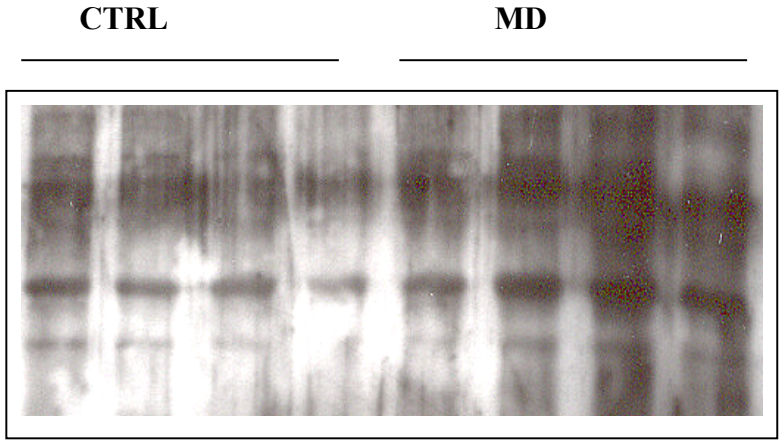
Fig 2

PROTEIN CARBONYLS (DPNH) IN LYMPHOCYTES OF CONTROL HEALTHY VOLUNTEERS (CTRL) AND MENIERE' DISEASED PATIENTS (MD)

A)



B)

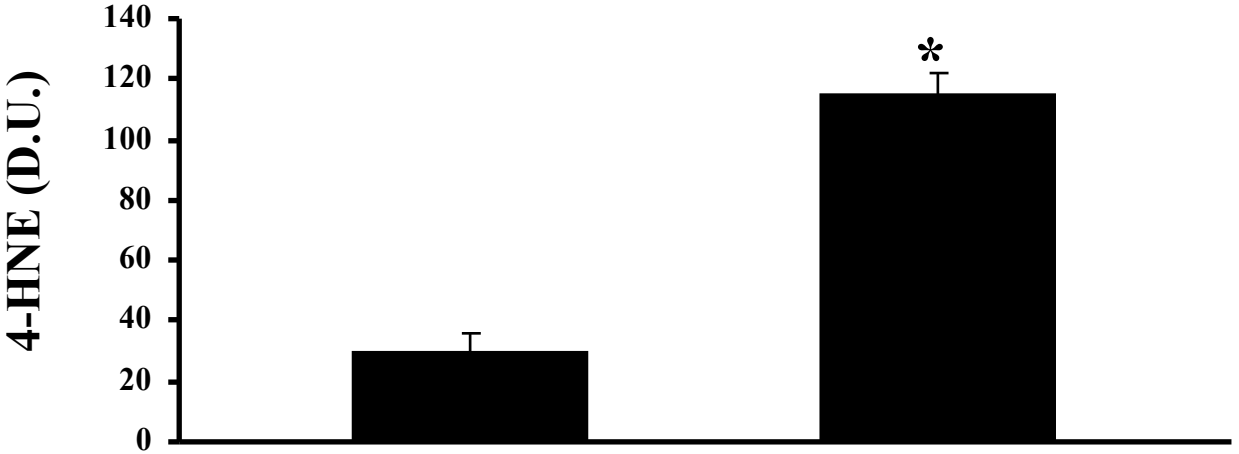


* p<0.01 vs ctrl

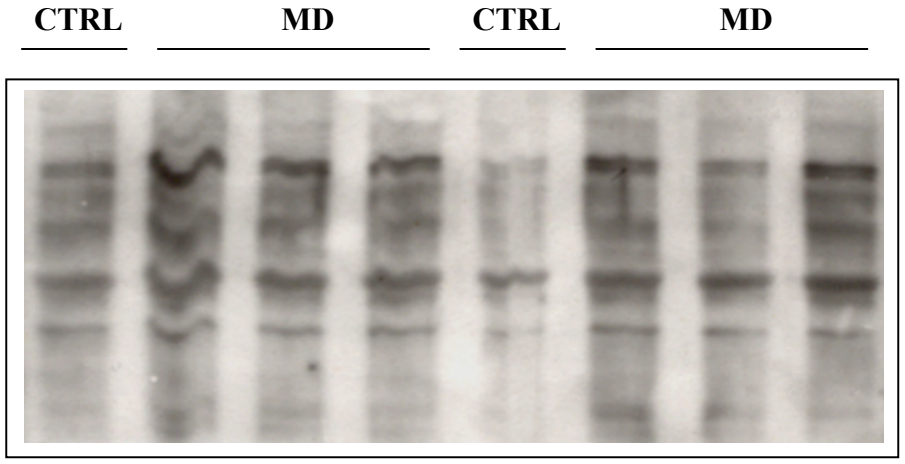
Fig 3

4-HNE IN LYMPHOCYTES OF CONTROL HEALTHY VOLUNTEERS (CTRL) AND MENIERE' DISEASED PATIENTS (MD)

A)



B)

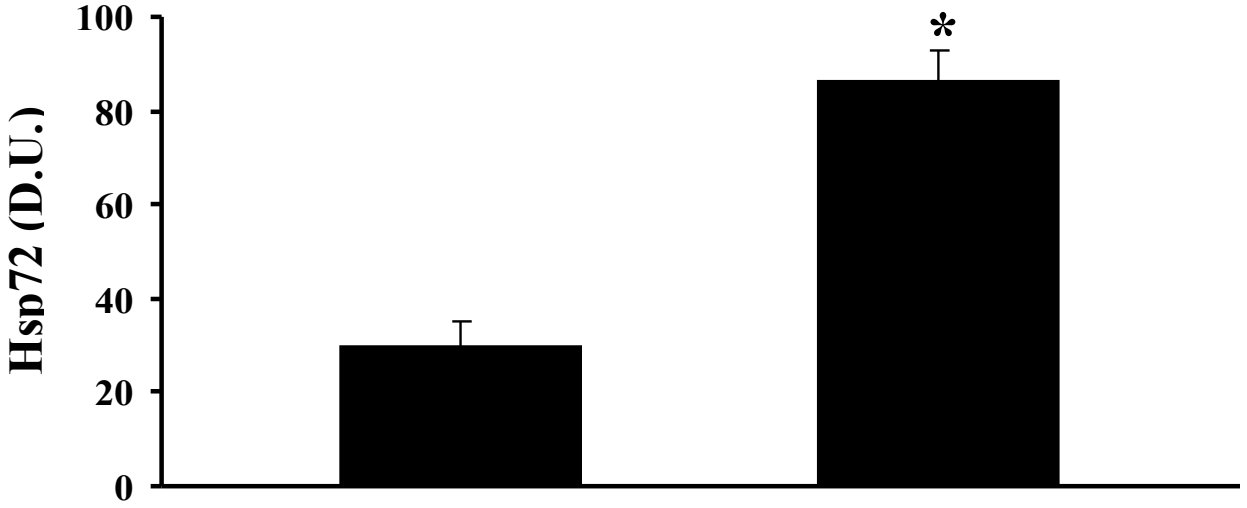


*** p<0.01 vs ctrl**

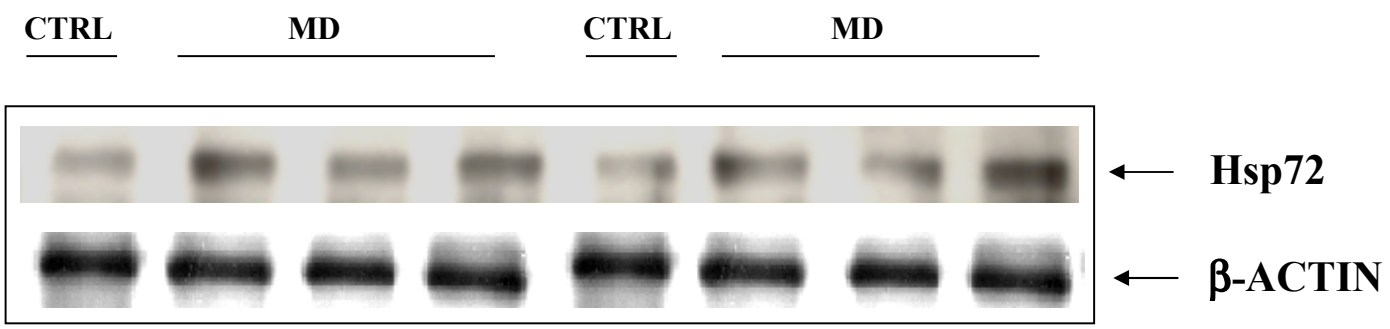
Fig 4

Hsp72 EXPRESSION IN LYMPHOCYTES OF CONTROL HEALTHY VOLUNTEERS AND MENIERE' DISEASED PATIENTS (MD)

A)



B)

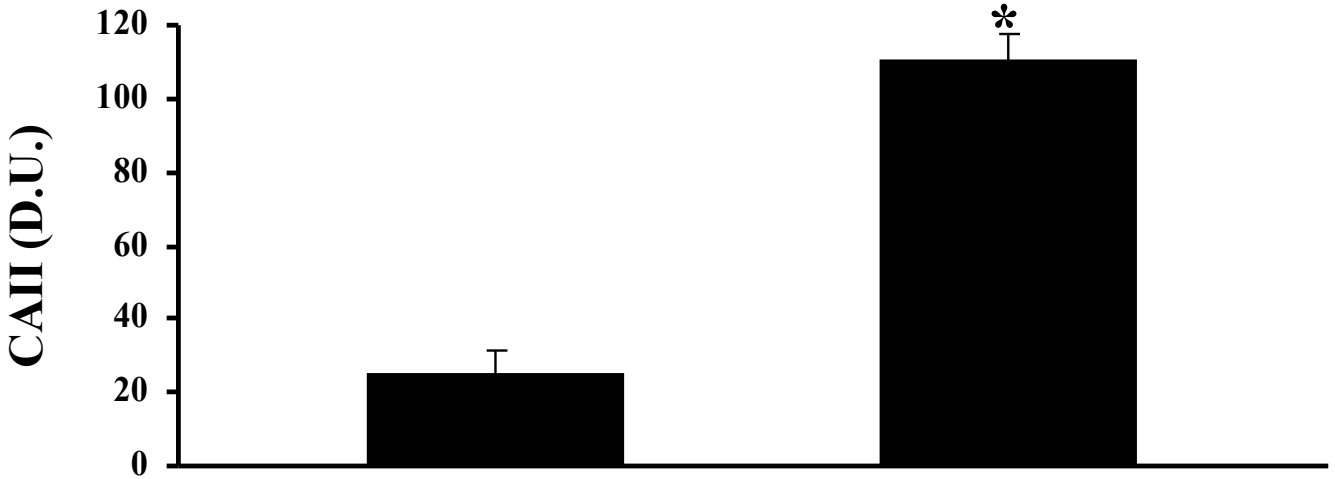


* p<0.01 vs ctrl

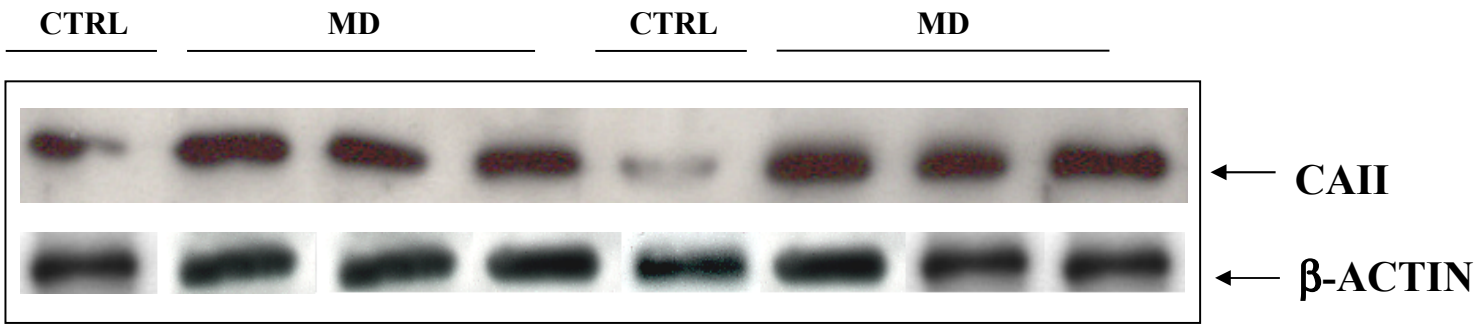
Fig 5

ANHYDRASE CARBONIC II (CAII) EXPRESSION LEVELS IN LYMPHOCYTES OF CONTROL HEALTHY VOLUNTEERS AND MENIERE' DISEASED PATIENTS (MD)

A)



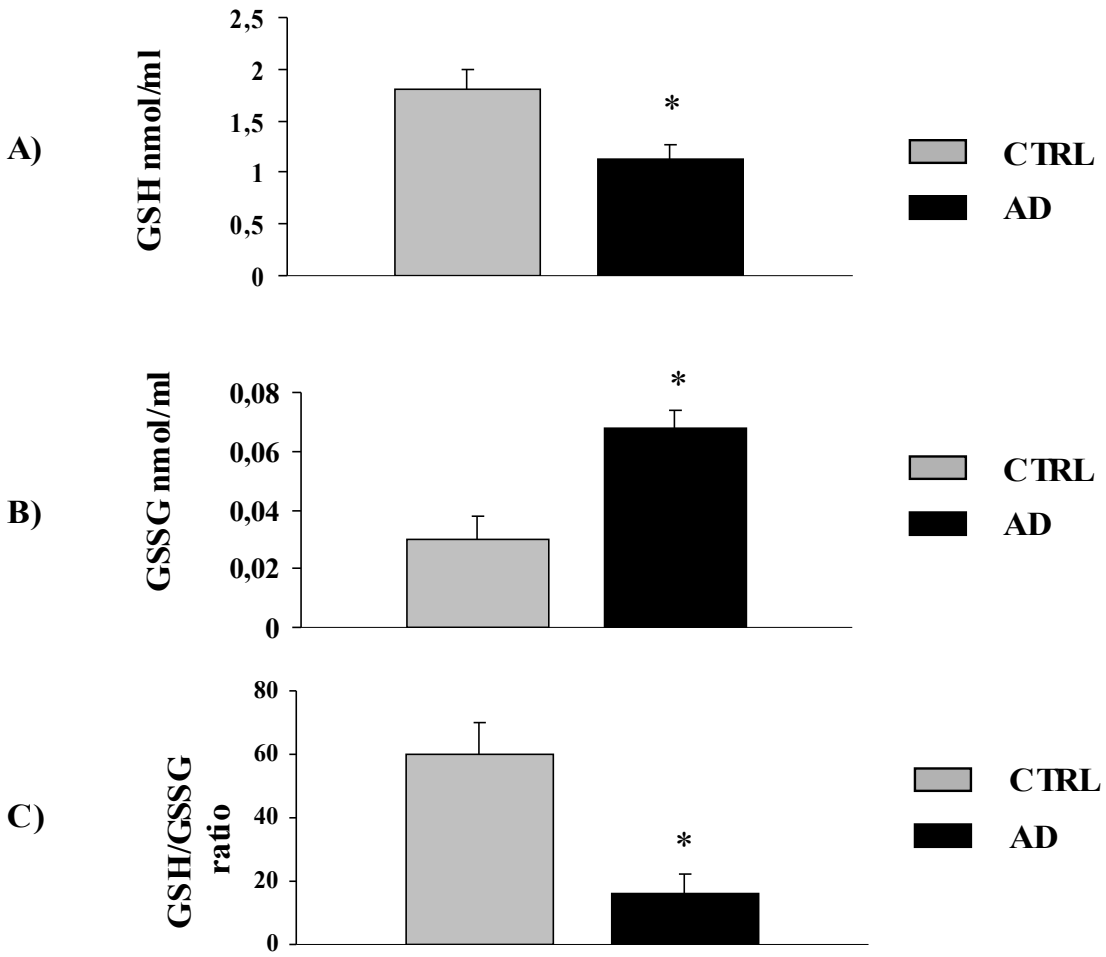
B)



* p<0.01 vs ctrl

Fig 6

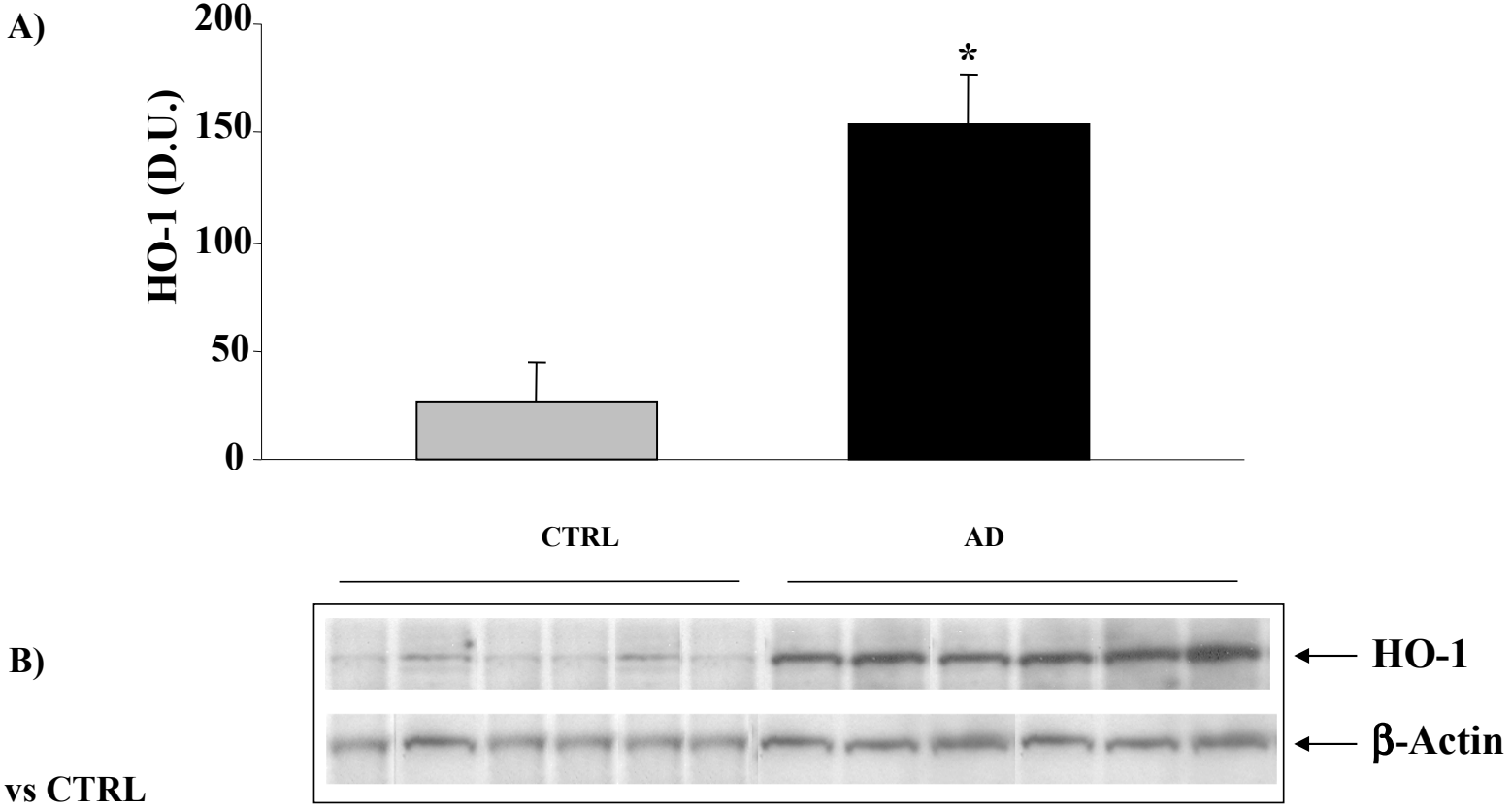
THIOL STATUS IN LYMPHOCYTES OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS



*p<0.05 vs CTRL (A,B), *p<0.01 vs CTRL (C)

Fig 7

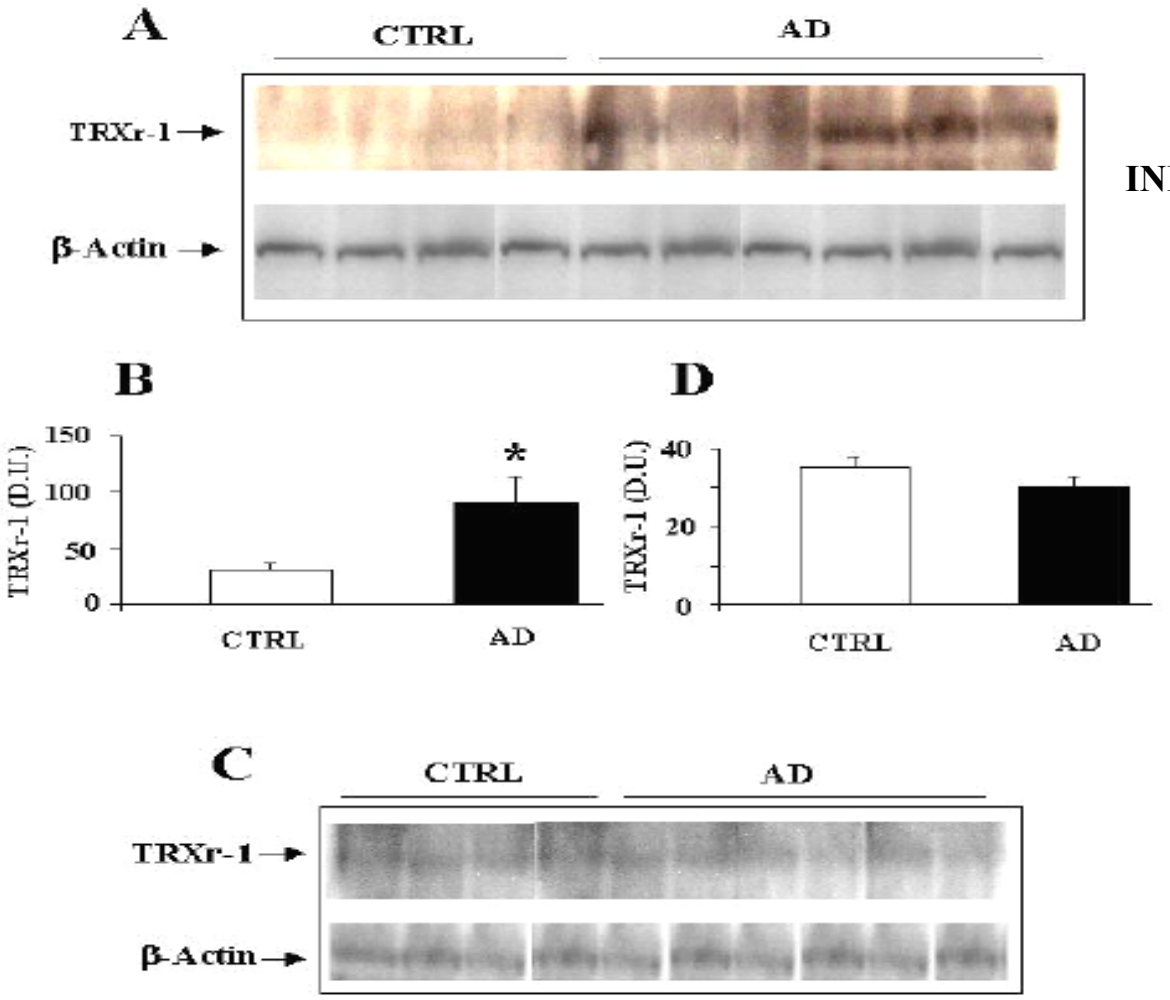
HO-1 EXPRESSION LEVELS IN INFERIOR PARIETAL LOBULE OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS



*p<0.01 vs CTRL

Fig 8

TRXr-1 EXPRESSION LEVELS IN INFERIOR PARIETAL LOBULE AND CEREBELLUM OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS



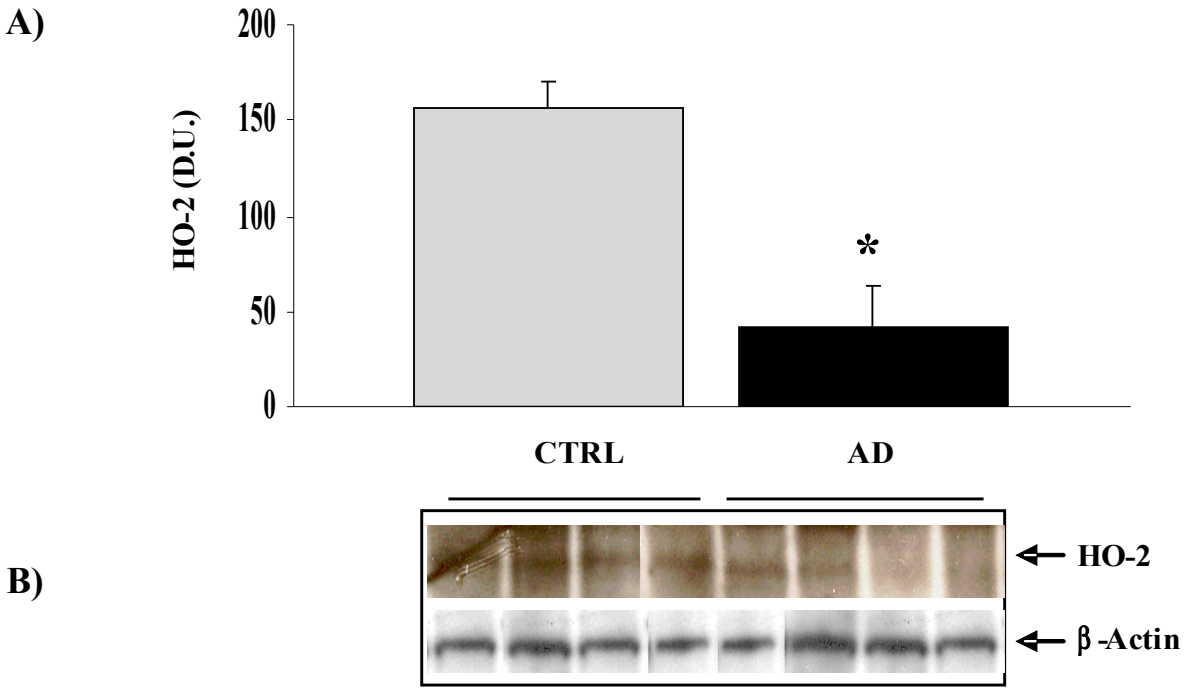
INFERIOR PARIETAL LOBULE

CEREBELLUM

*p<0.01 vs CTRL (B)

Fig 9

HO-2 EXPRESSION LEVELS IN INFERIOR PARIETAL LOBULE OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS

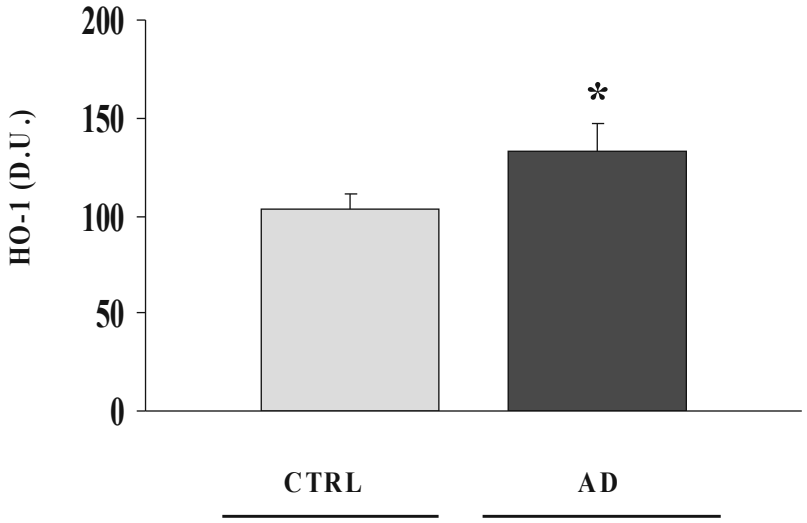


*p<0.01 vs CTRL

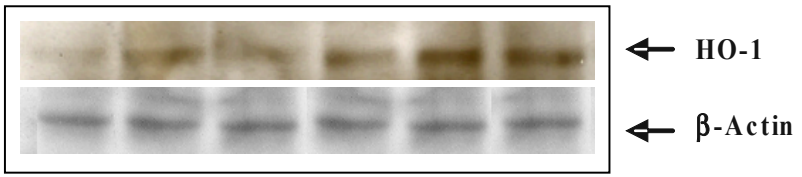
Fig 10

PLASMA HO-1 EXPRESSION LEVELS OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS

A)



B)

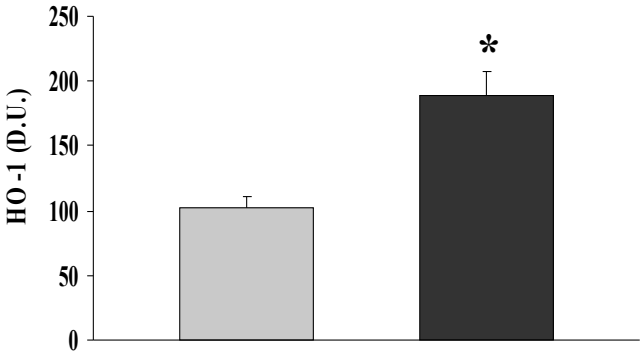


***p<0.05 vs CTRL**

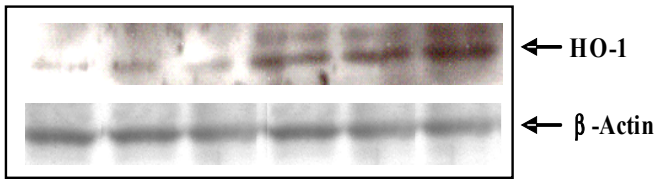
Fig 11

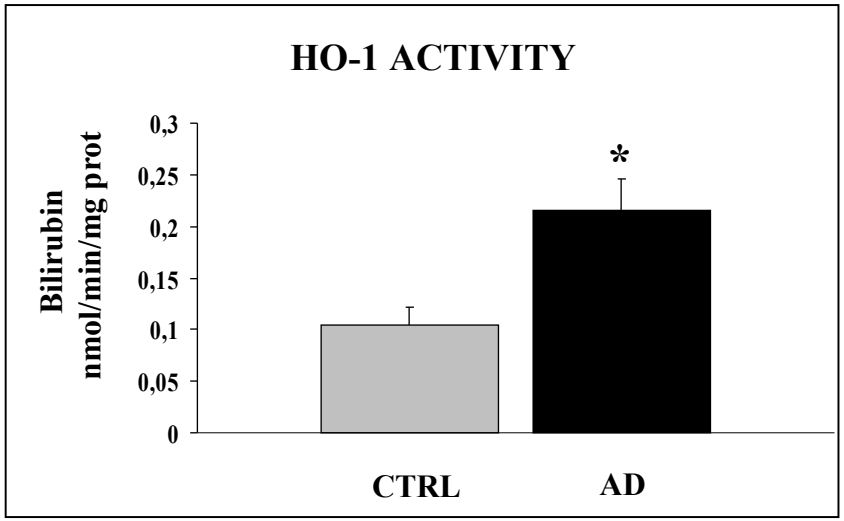
LYMPHOCYTES HO-1 EXPRESSION LEVELS AND ACTIVITY OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS

A)



B)



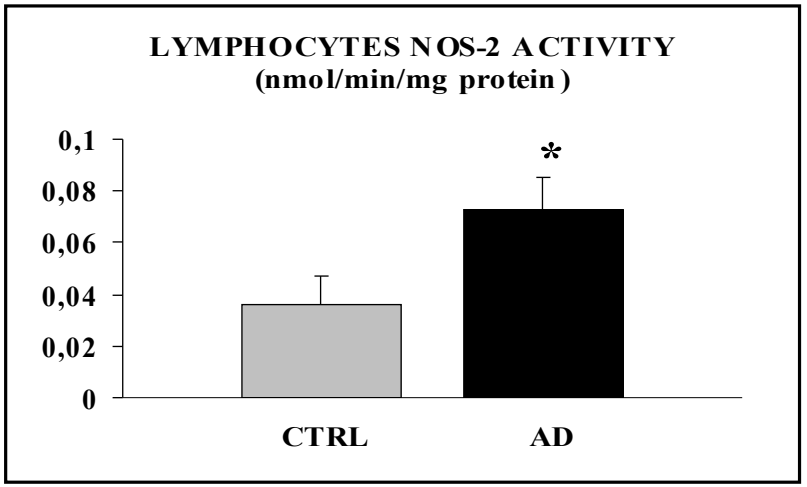


C)

*p<0.01 vs CTRL

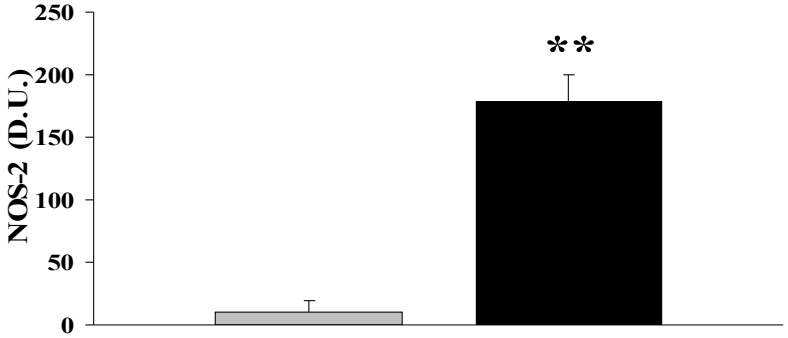
Fig 12

LYMPHOCYTES NOS-2 EXPRESSION LEVELS AND ACTIVITY OF CONTROL HEALTHY VOLUNTEERS AND ALZHEIMER DISEASED PATIENTS

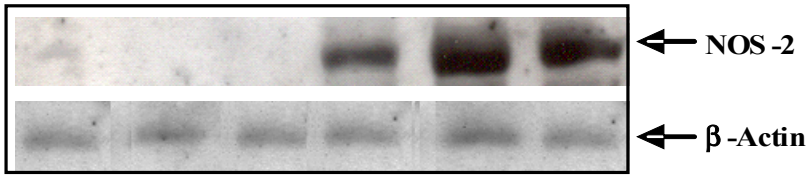


C)

A)



B)

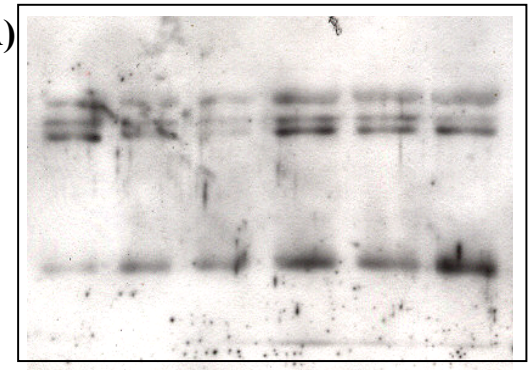


**p<0.01 vs CTRL, *p<0.05 vs CTRL

Fig 13

PLASMA NITROTYROSINE

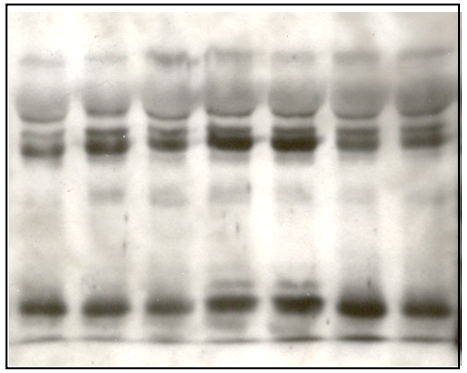
A)



CTRL AD

PLASMA 4-HNE

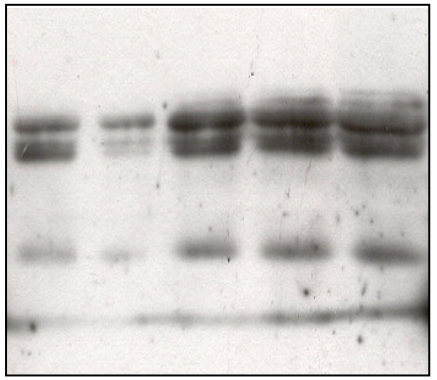
C)



CTRL AD

PLASMA DPNH

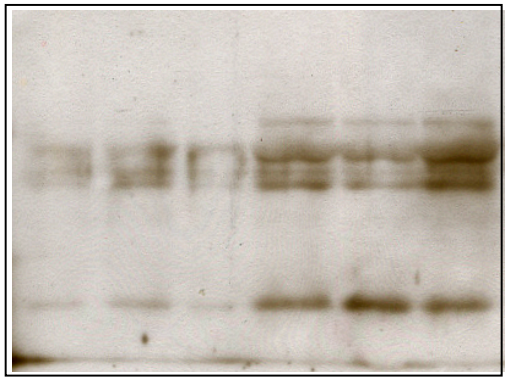
E)



CTRL AD

LYMPHOCYTES NITROTYROSINE

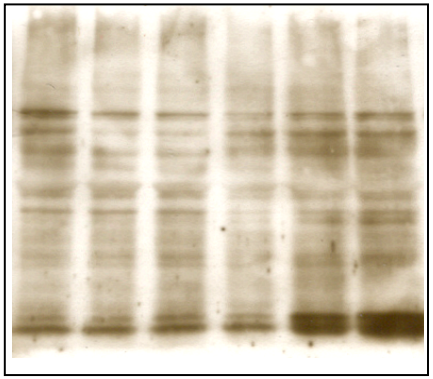
B)



CTRL AD

LYMPHOCYTES 4-HNE

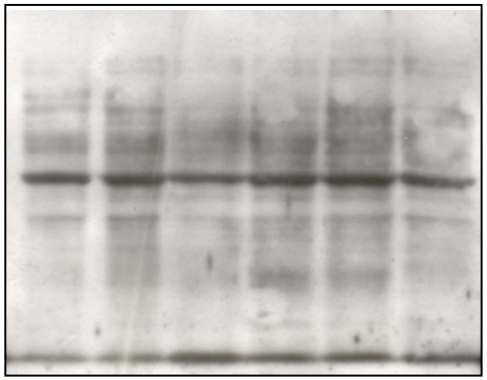
D)



CTRL AD

LYMPHOCYTES DPNH

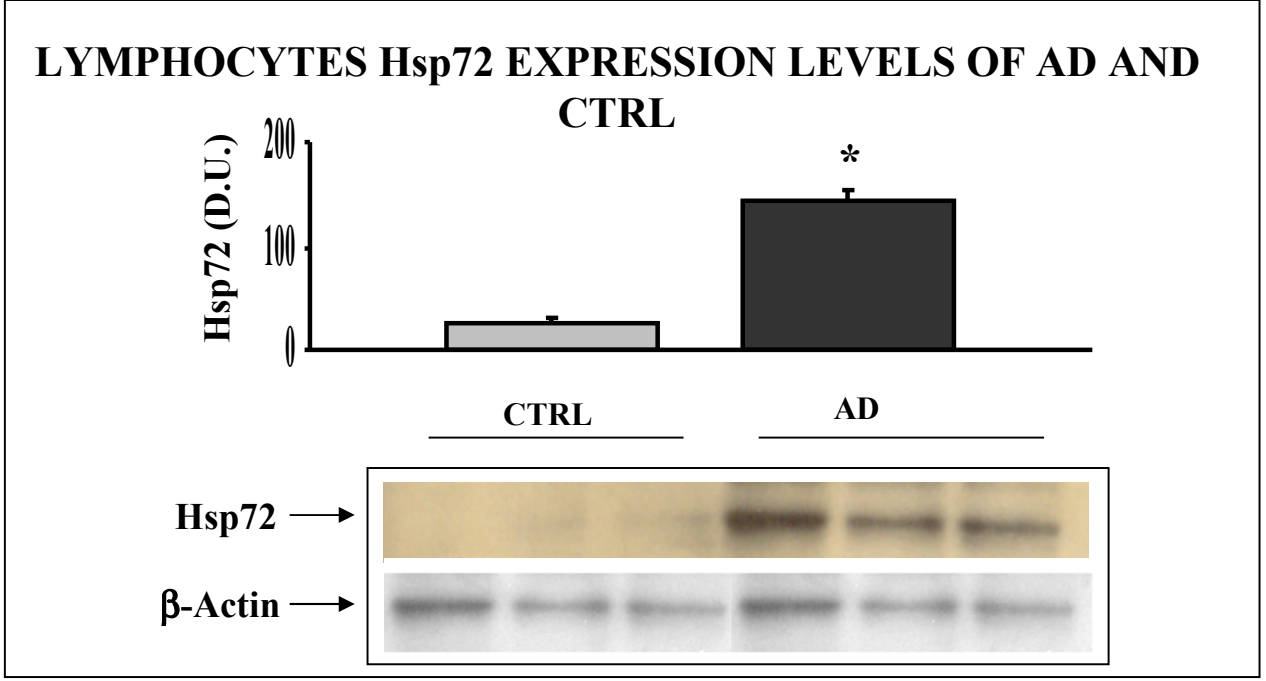
F)



CTRL AD

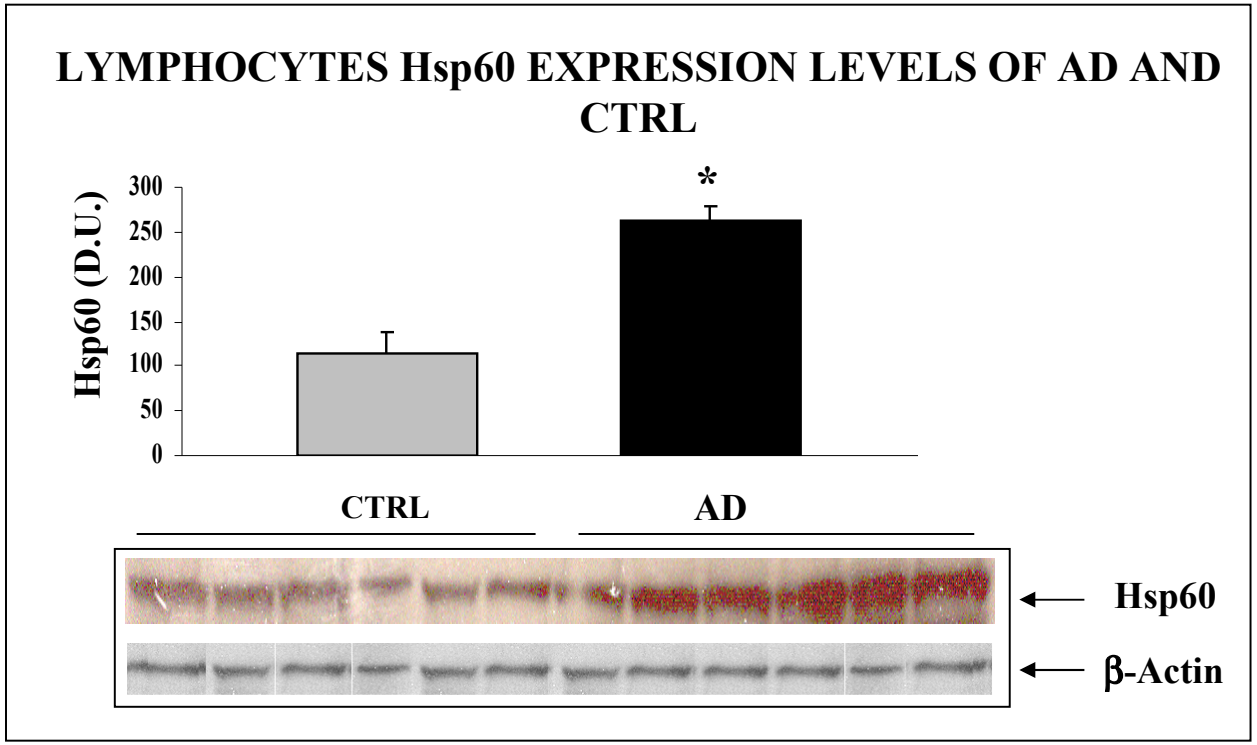
Fig 14

A)



*p<0.01 vs CTRL

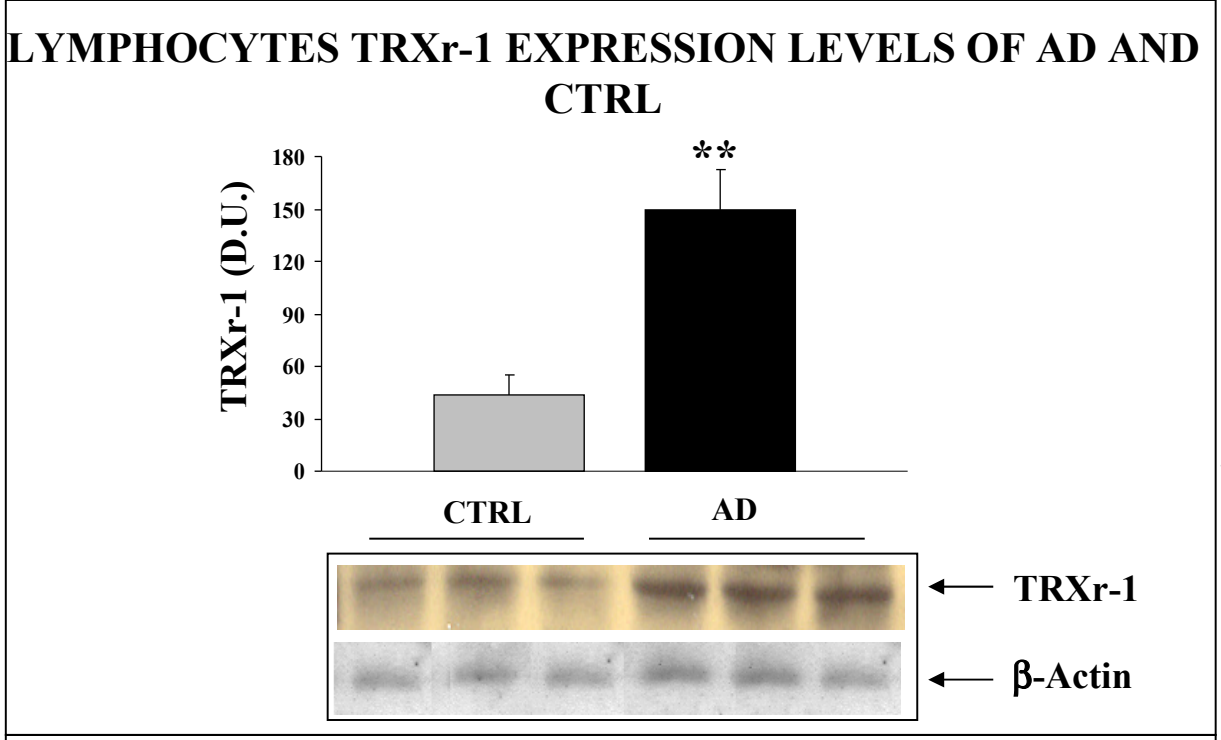
B)



*p<0.01 vs CTRL

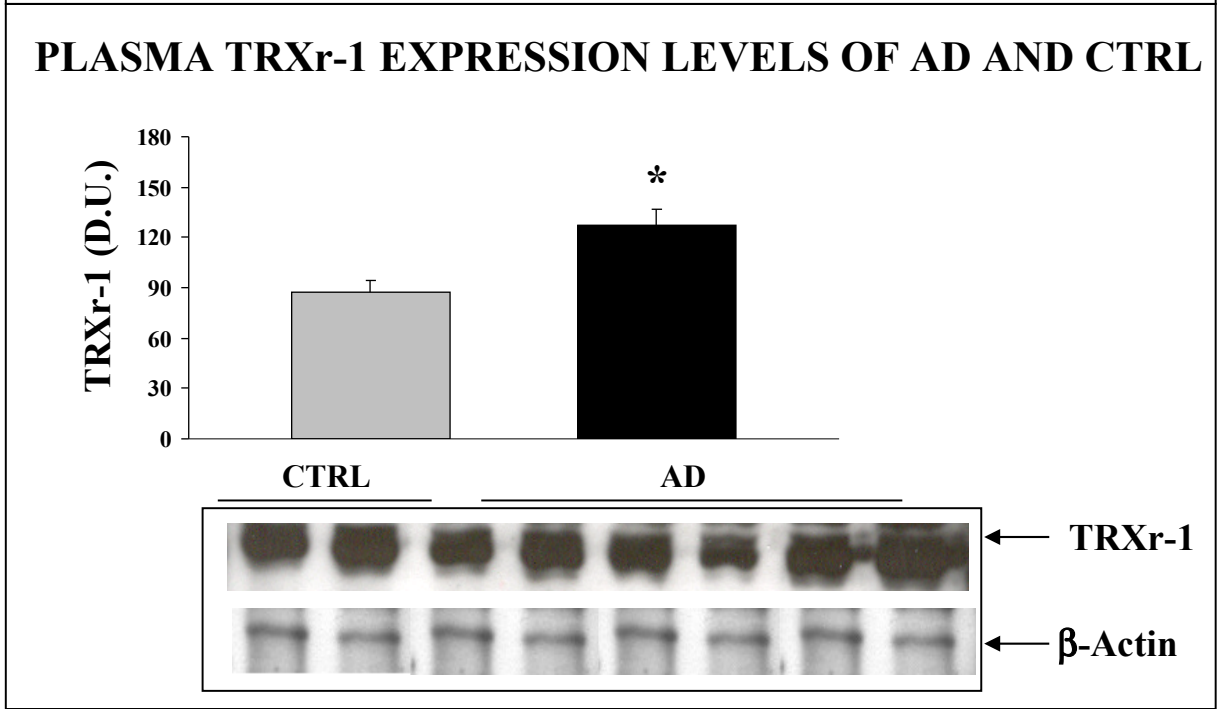
Fig 15

A)



**p<0.01 vs CTRL

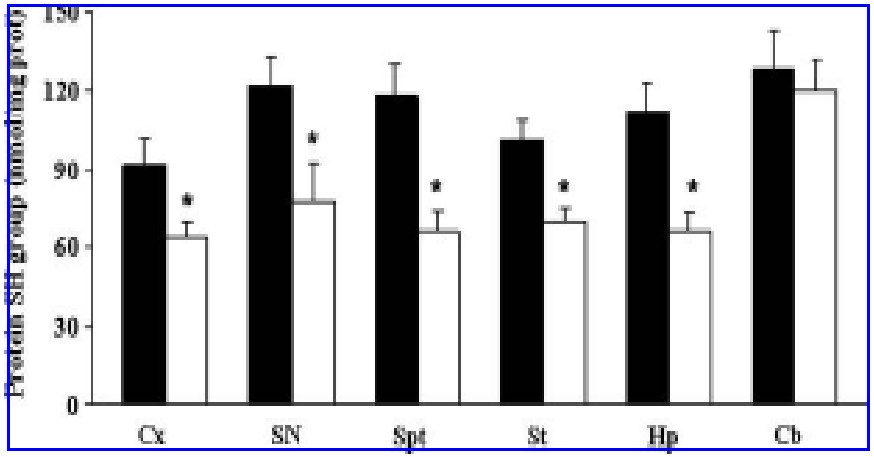
B)



*p<0.05 vs CTRL

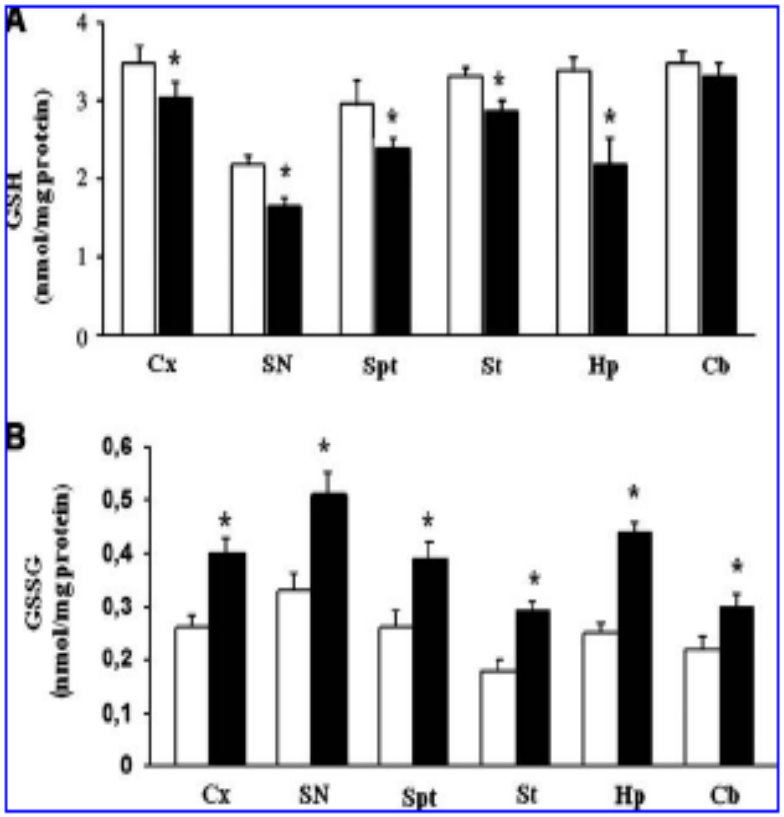
Fig 16

REGIONAL DISTRIBUTION OF TOTAL SULFHYDRYL GROUPS IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS



*p<0.05 vs aged (12 month) rats

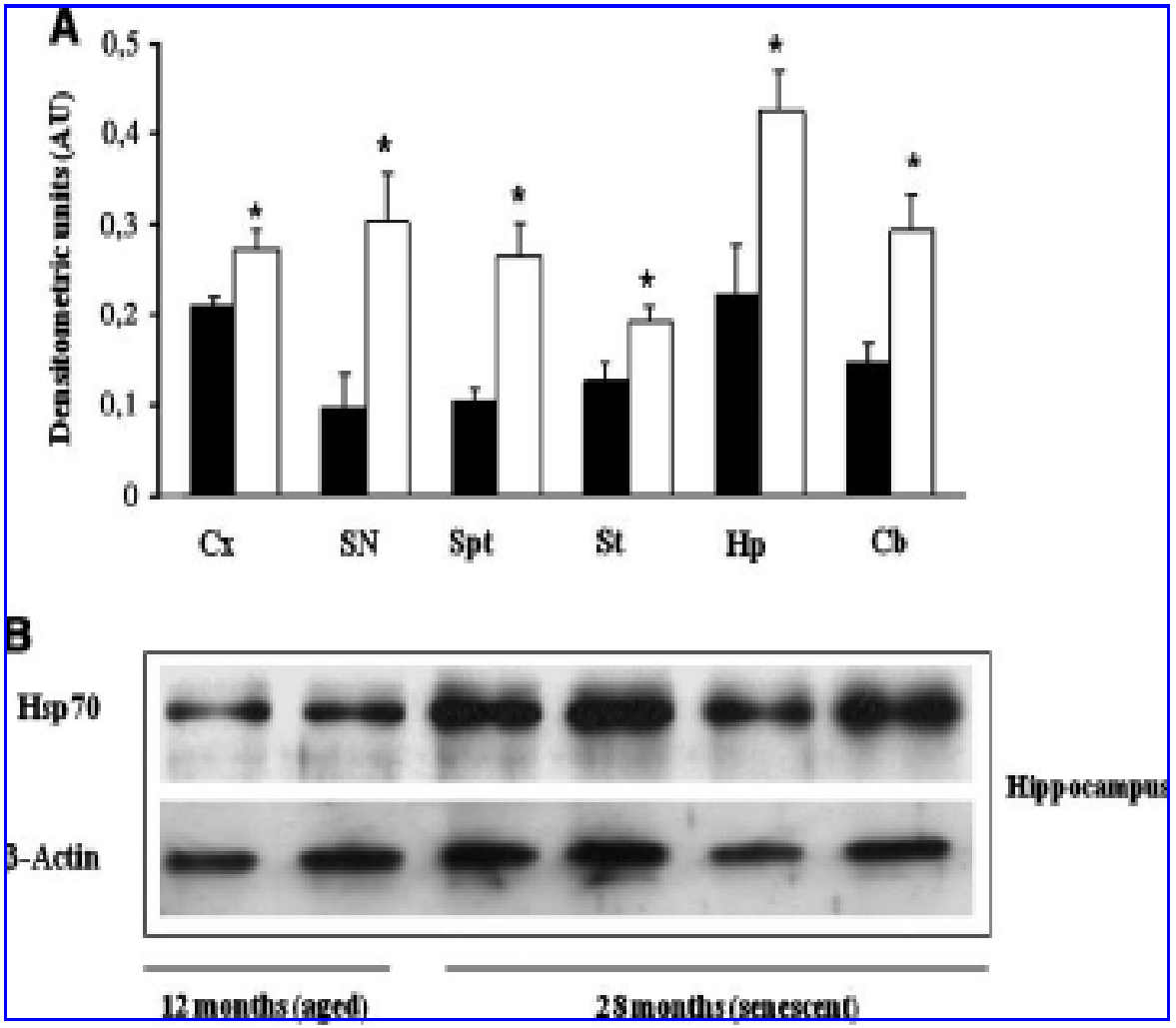
Fig 17



REGIONAL DISTRIBUTION OF REDUCED (GSH) AND OXIDIZED (GSSG) GLUTATHIONE IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS

Fig 18

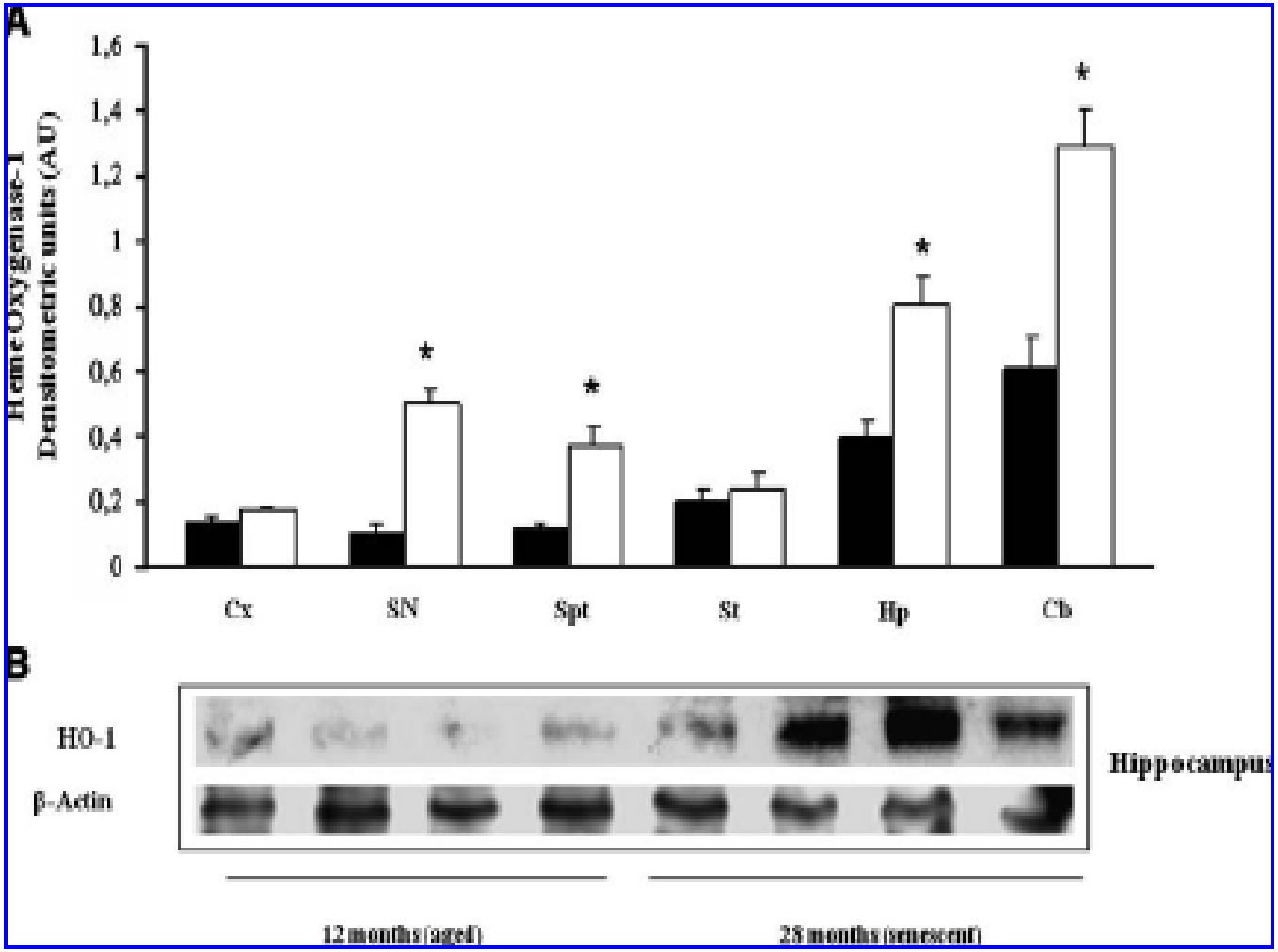
REGIONAL DISTRIBUTION OF Hsp72 IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS



*p<0.05 vs aged (12 month) rats

Fig 19

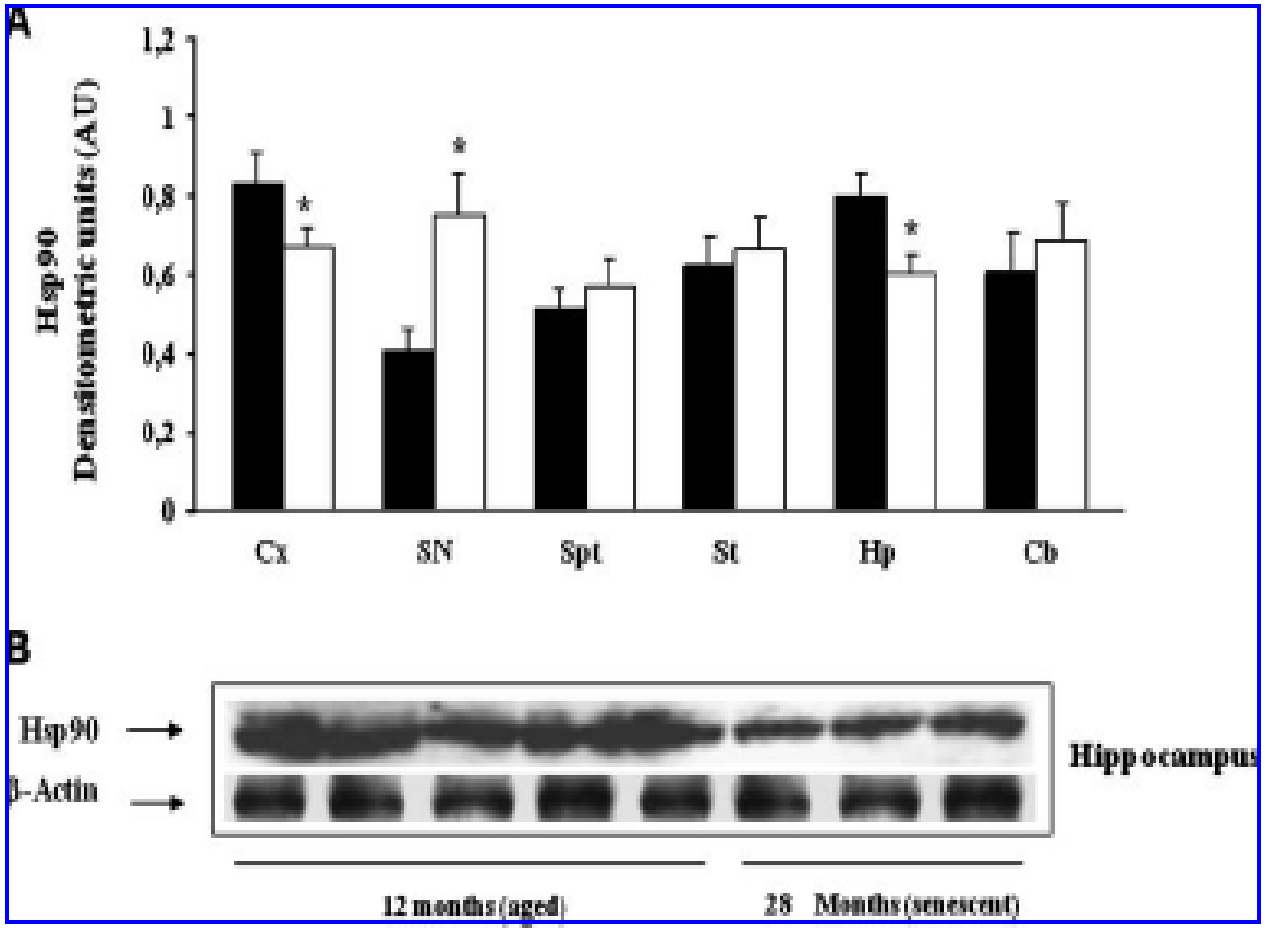
REGIONAL DISTRIBUTION IN THE LEVELS OF HO-1 IMMUNOREACTIVITY IN DIFFERENT BRAIN REGIONS OF AGED AND SENESCENT RATS



*p<0.05 vs aged (12 month) rats

Fig 20

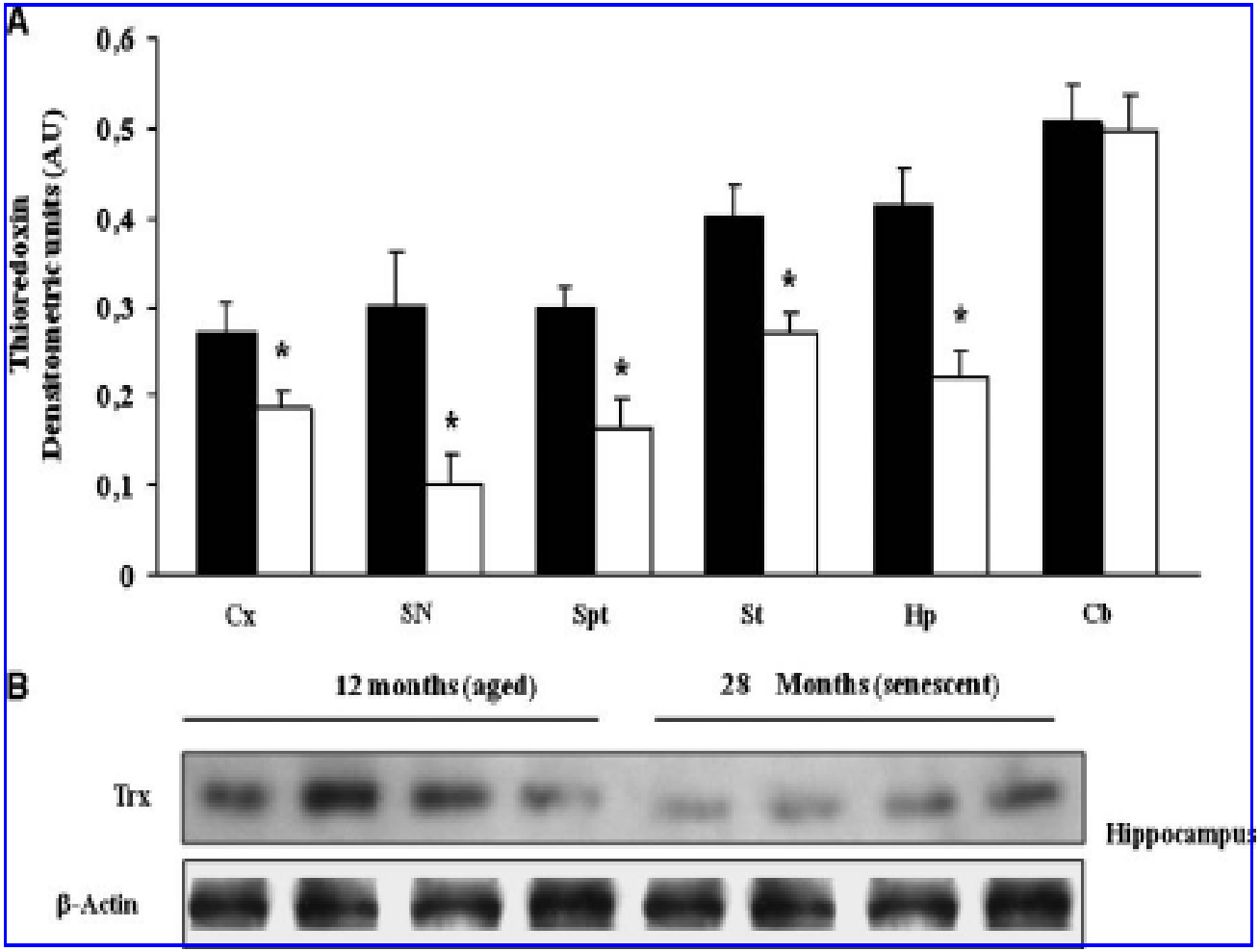
REGIONAL DISTRIBUTION OF Hsp90 IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS



*p<0.05 vs aged (12 month) rats

Fig 21

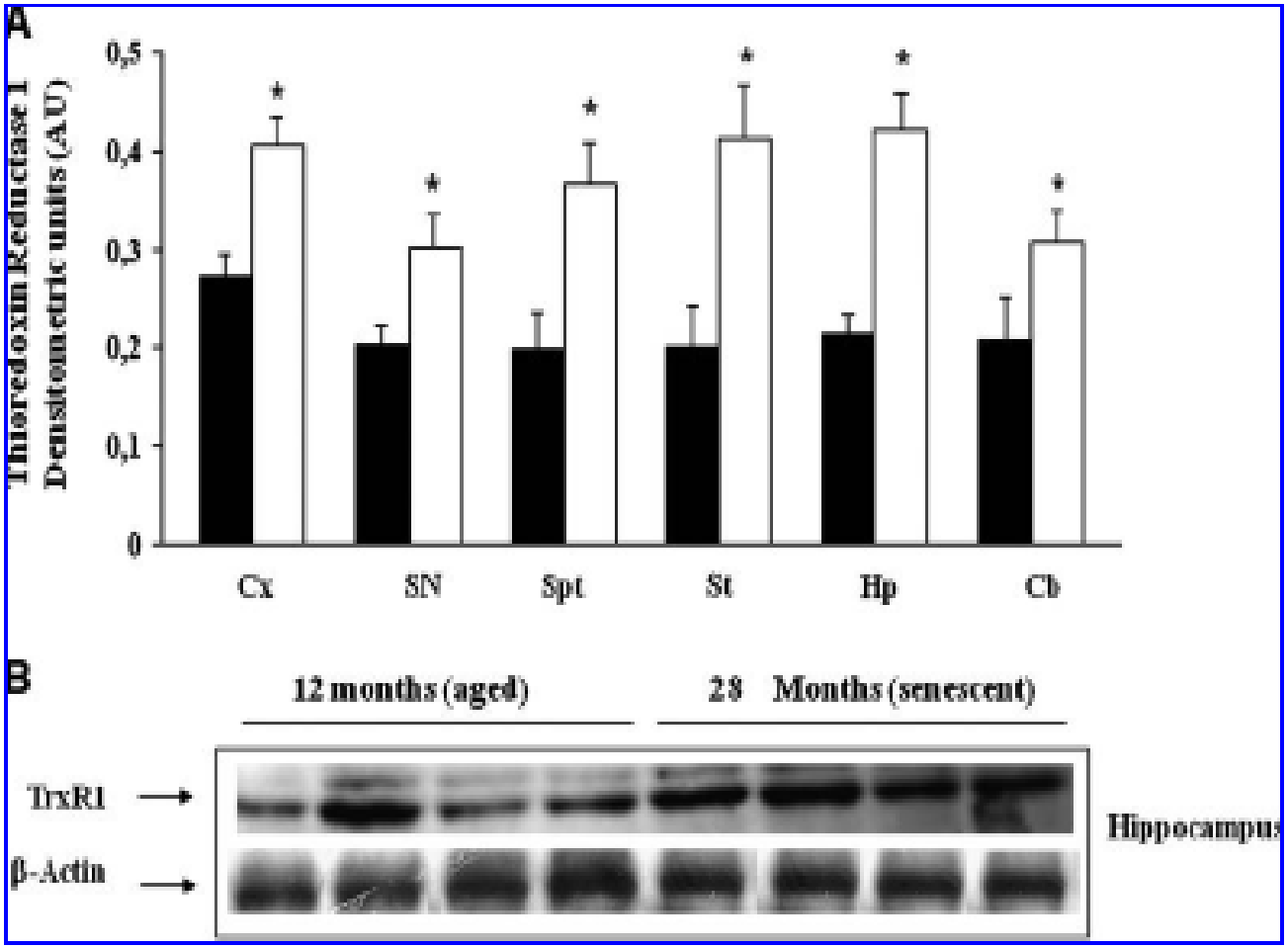
REGIONAL DISTRIBUTION OF Trx PROTEIN IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS



*p<0.05 vs aged (12 month) rats

Fig 22

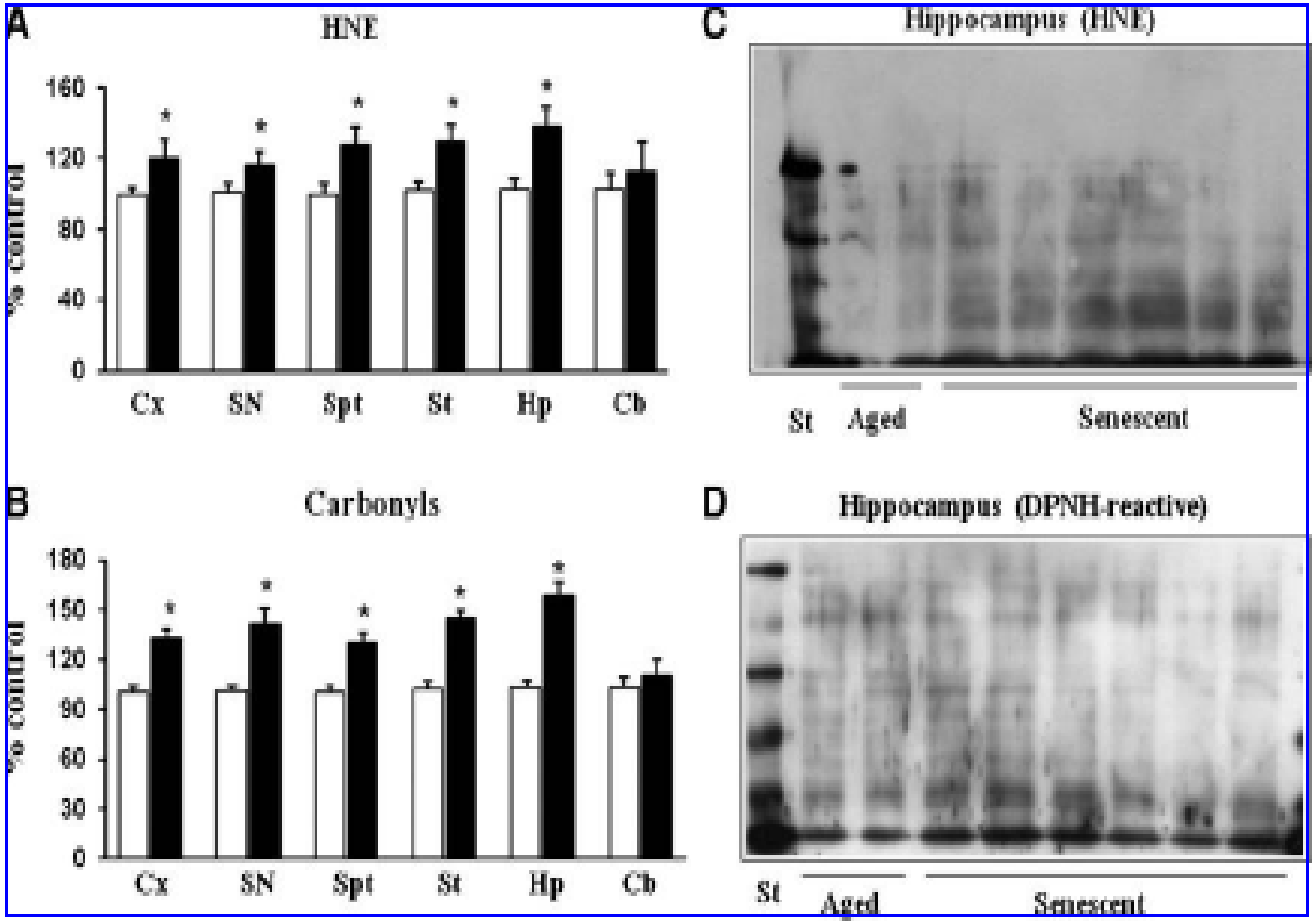
REGIONAL DISTRIBUTION OF THIOREDOXIN REDUCTASE (TrxR-1) IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS



*p<0.05 vs aged (12 month) rats

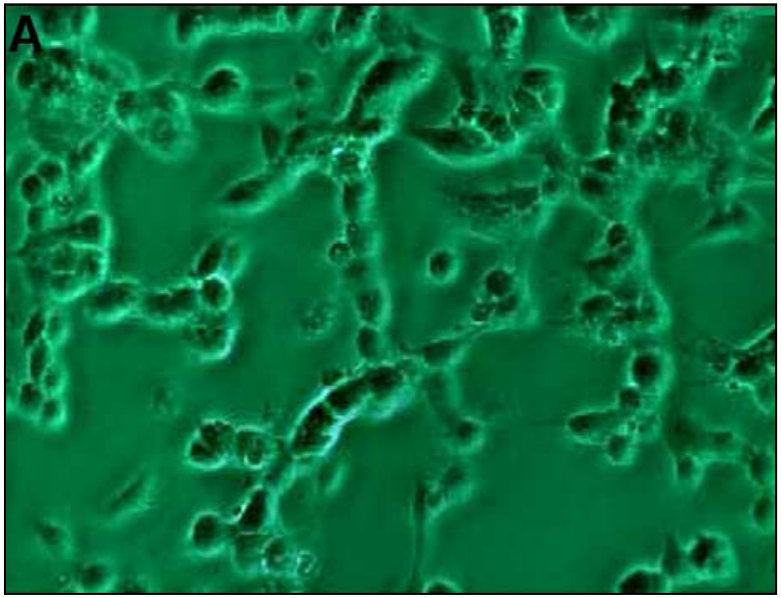
Fig 23

4-HNE AND CARBONYL LEVELS IN DIFFERENT BRAIN REGIONS OF SENESCENT AND AGED RATS



*p<0.05 vs aged (12 month) rats

NEUROBLASTOMA SH-SY5Y CELL LINE



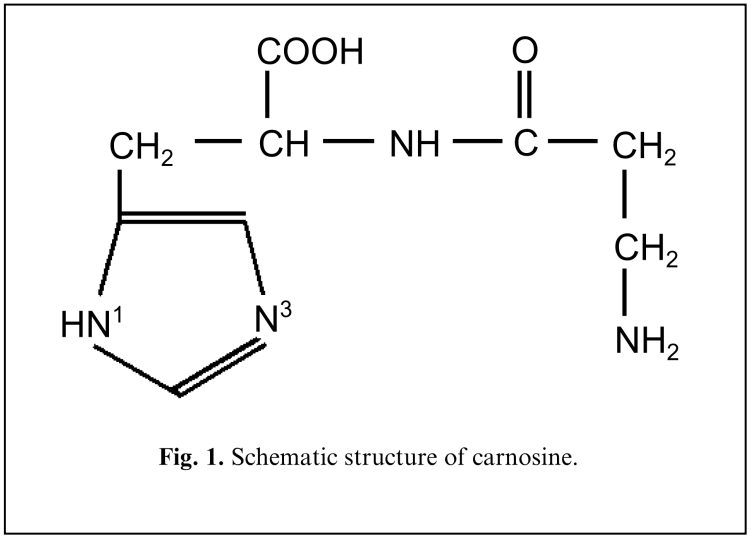


Fig. 1. Schematic structure of carnosine.

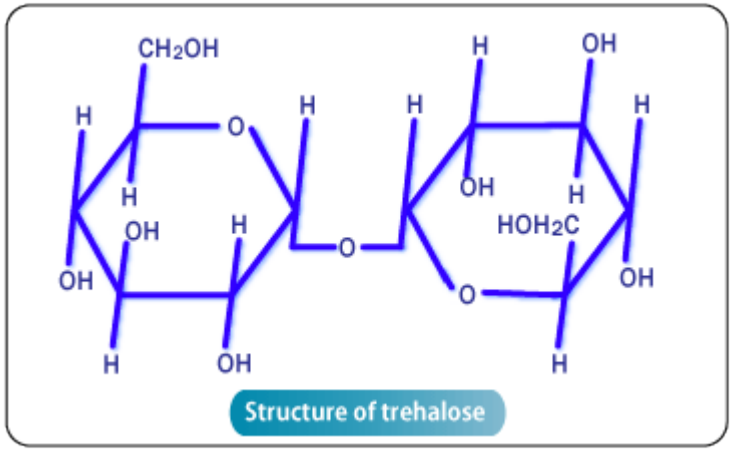
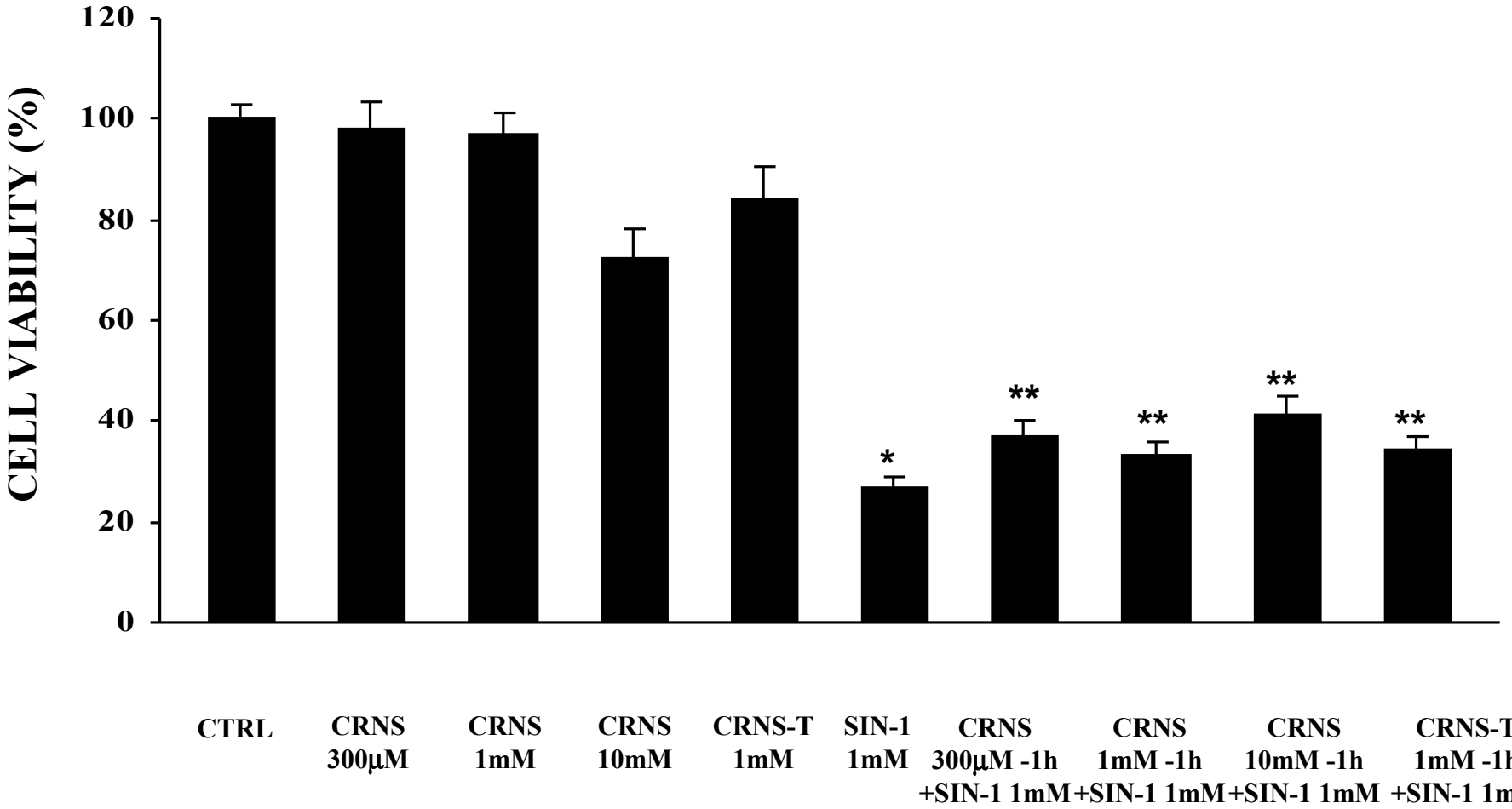


Fig 24

NEUROBLASTOMA SH-SY5Y CELL VIABILITY AFTER SIN-1 (4h) TREATMENT IN PRESENCE AND ABSENCE OF CRNS

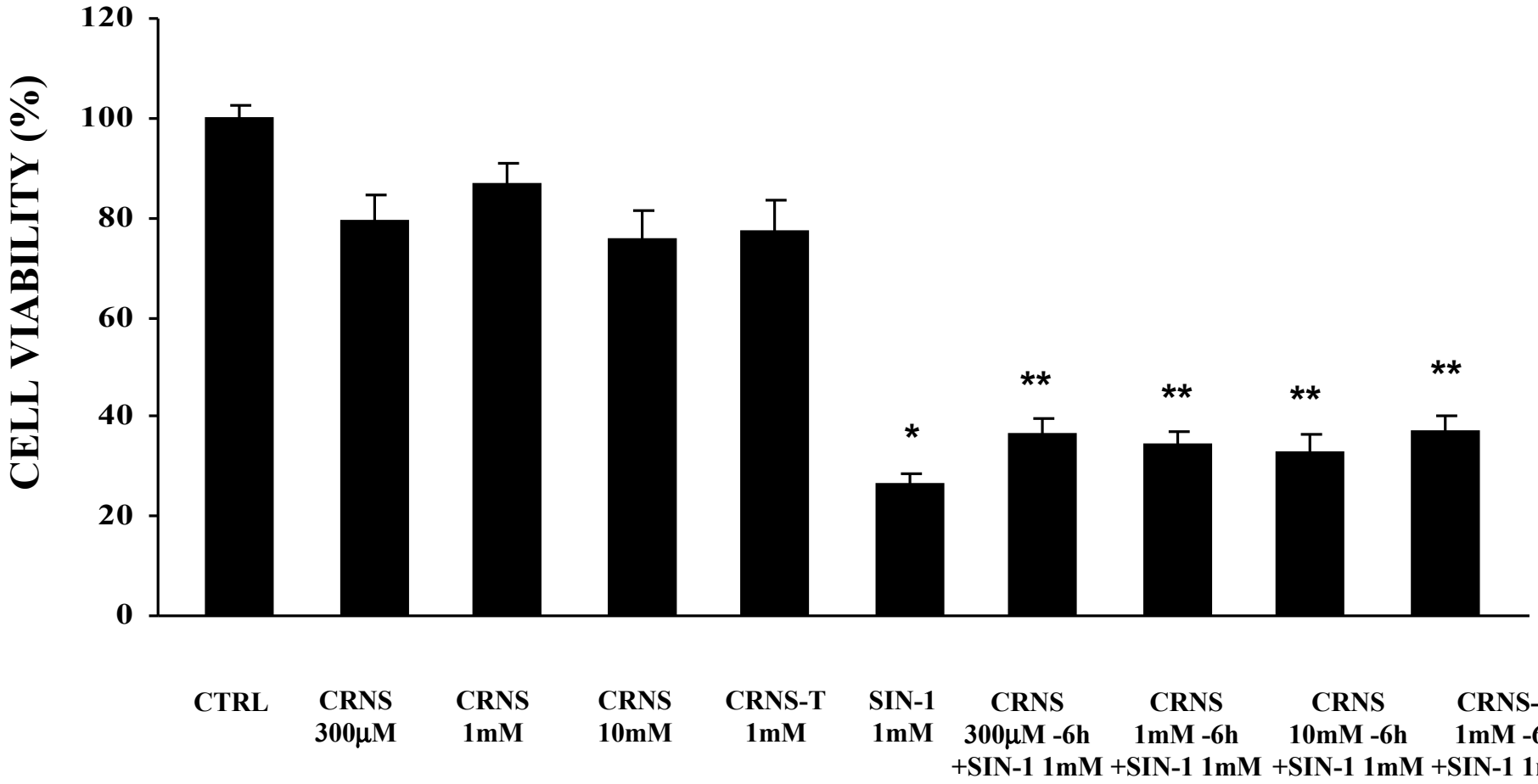


*** p<0.05 vs CTRL; ** p<0.05 vs SIN-1**

CRNS (-1h) pretreatment

Fig 25

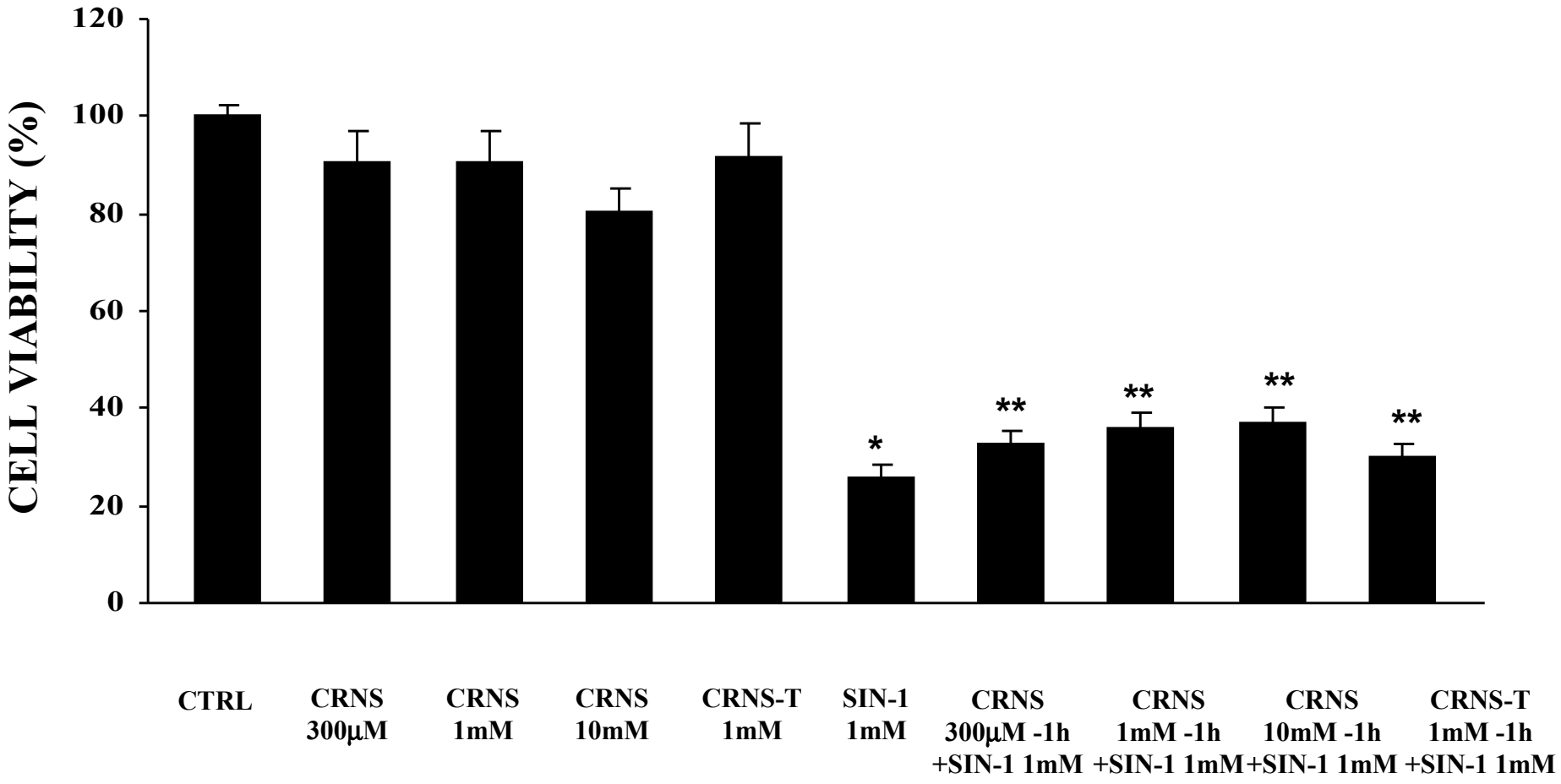
NEUROBLASTOMA SH-SY5Y CELL VIABILITY AFTER SIN-1 (4h) TREATMENT IN PRESENCE AND ABSENCE OF CRNS



* Significant vs control ($p<0.05$); **significant vs SIN-1 ($p<0.05$)

Fig 26

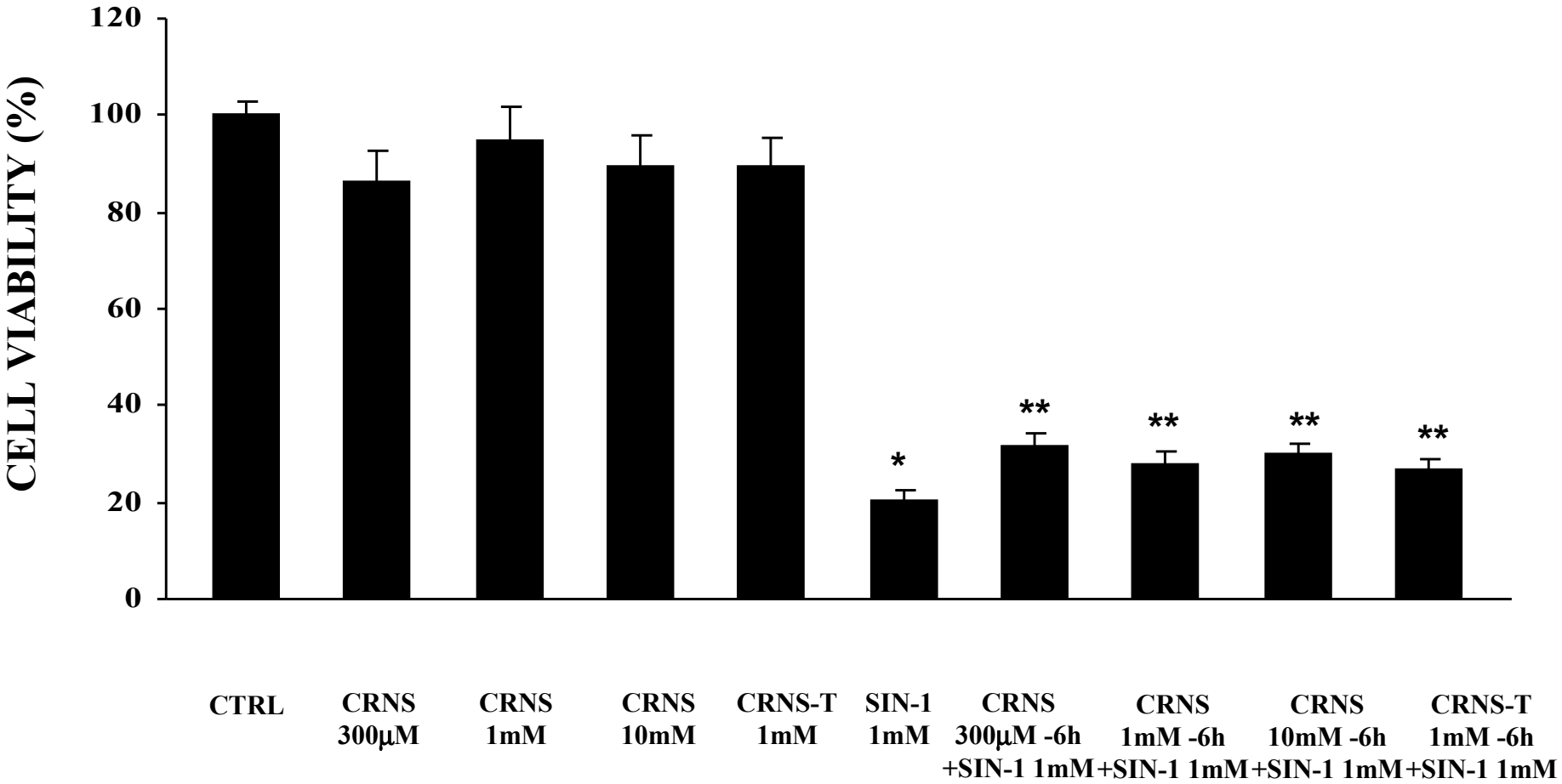
NEUROBLASTOMA SH-SY5Y CELL VIABILITY AFTER SIN-1 (7h) TREATMENT IN PRESENCE AND ABSENCE OF CRNS



* Significant vs control (p<0.05); **significant vs SIN-1 (p<0.05)

Fig 27

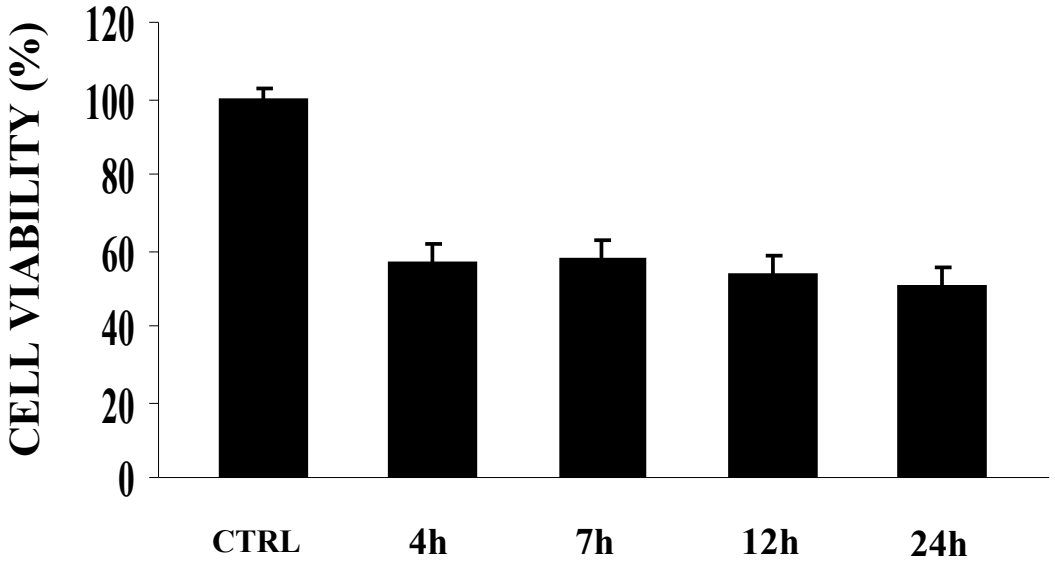
NEUROBLASTOMA SH-SY5Y CELL VIABILITY AFTER SIN-1 (7h) TREATMENT IN PRESENCE AND ABSENCE OF CRNS



* Significant vs control (p<0.05); **significant vs SIN-1 (p<0.05)

Fig 28

NEUROBLASTOMA SH-SY5Y CELL VIABILITY AFTER SIN-1 (1mM) TREATMENT AT DIFFERENT TIMES



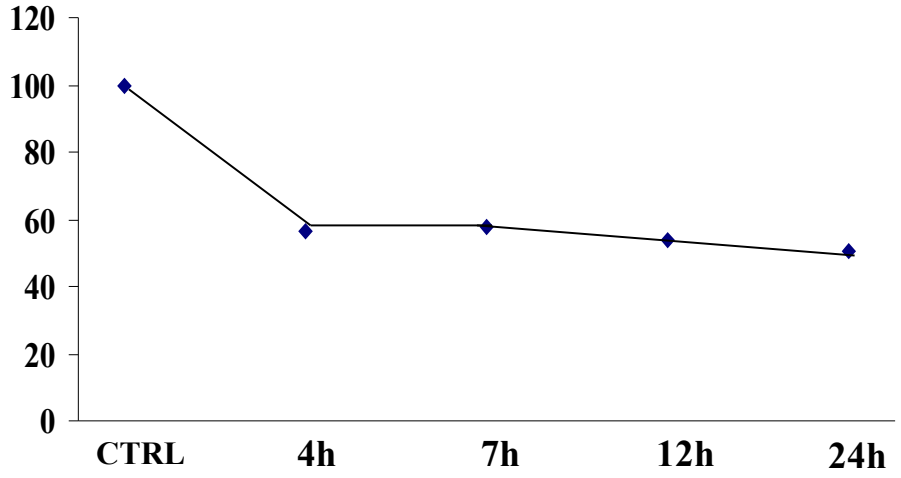
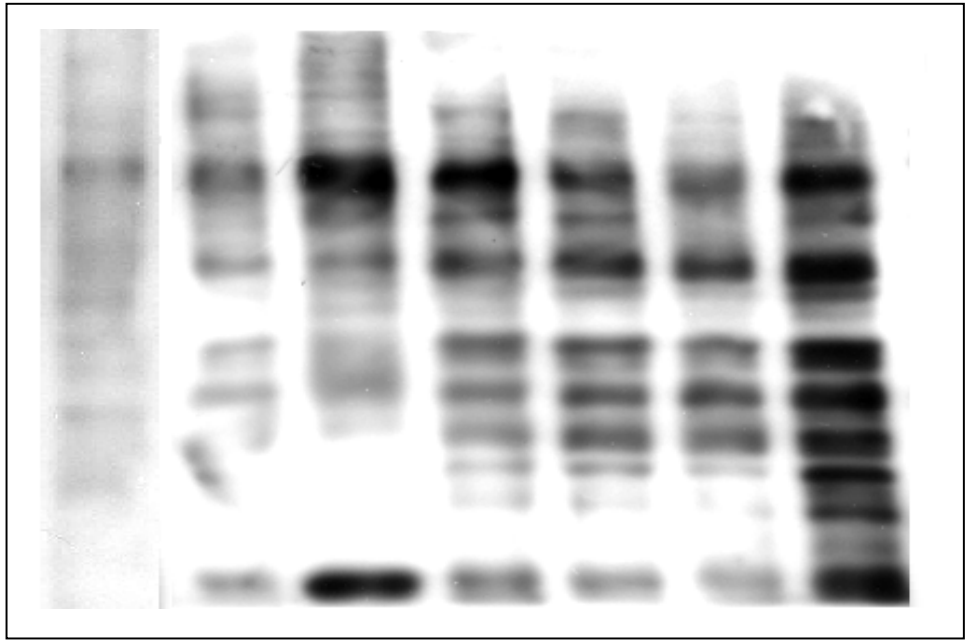


Fig 29

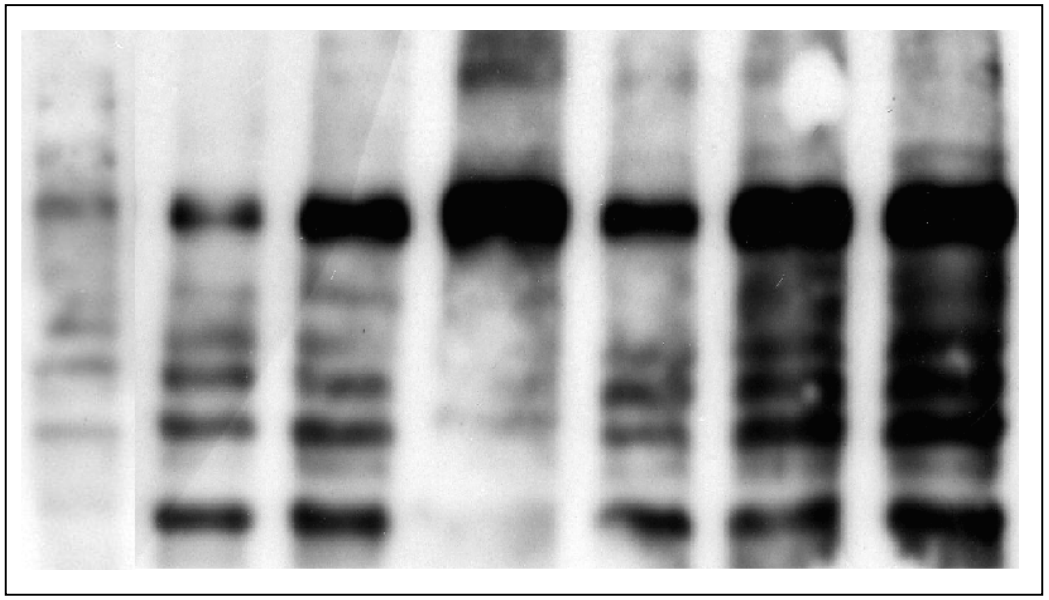
CARBONYL GROUPS CONTENT (DPNH) IN NEUROBLASTOMA SH-SY5Y CELL LINE AFTER SIN-1 TREATMENT AT DIFFERENT CONCENTRATIONS AND TIMES



CTRL	SIN-1 0.5mM 7h	SIN-1 1mM 7h	SIN-1 2mM 7h	SIN-1 0.5mM 24h	SIN-1 1mM 24h	SIN-1 2mM 24h

Fig 30

4-HNE EXPRESSION LEVELS IN NEUROBLASTOMA SH-SY5Y CELL LINE AFTER SIN-1 TREATMENT AT DIFFERENT CONCENTRATIONS AND TIMES

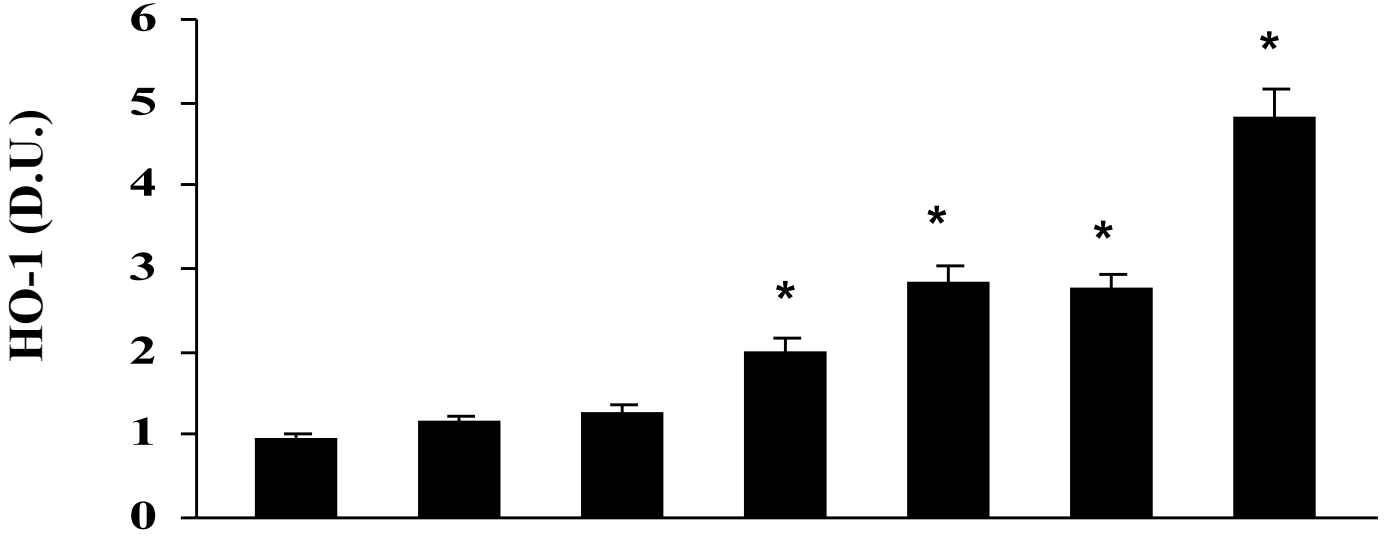


CTRL	SIN-1 0.5mM 7h	SIN-1 1mM 7h	SIN-1 2mM 7h	SIN-1 0.5mM 24h	SIN-1 1mM 24h	SIN-1 2mM 24h

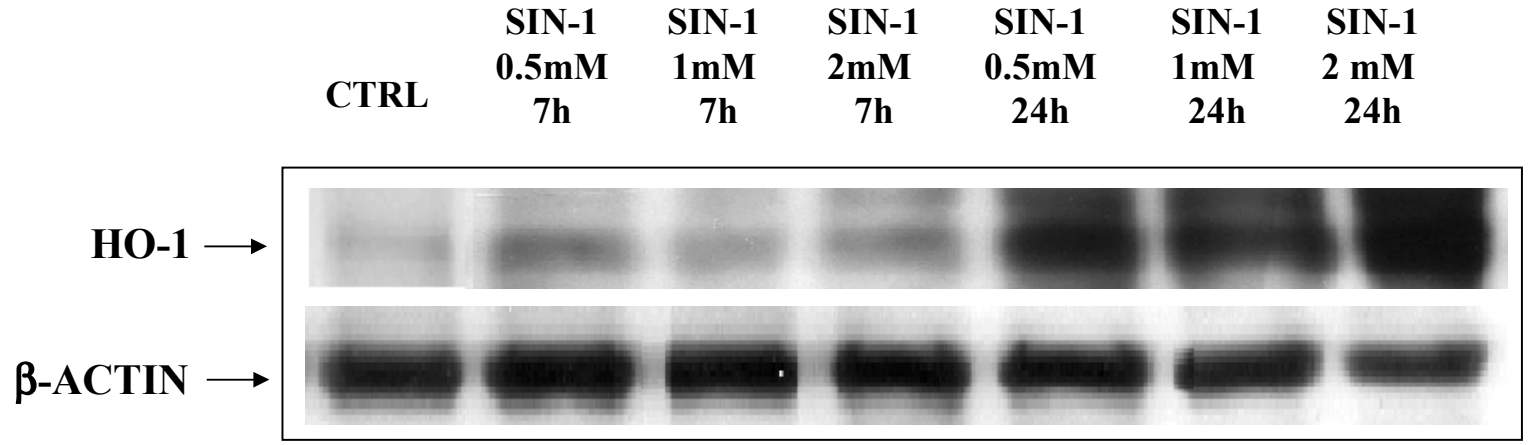
Fig 31

HO-1 INDUCTION IN NEUROBLASTOMA SH-SY5Y CELL LINE AFTER SIN-1 TREATMENT AT DIFFERENT CONCENTRATIONS AND TIMES

A)



B)

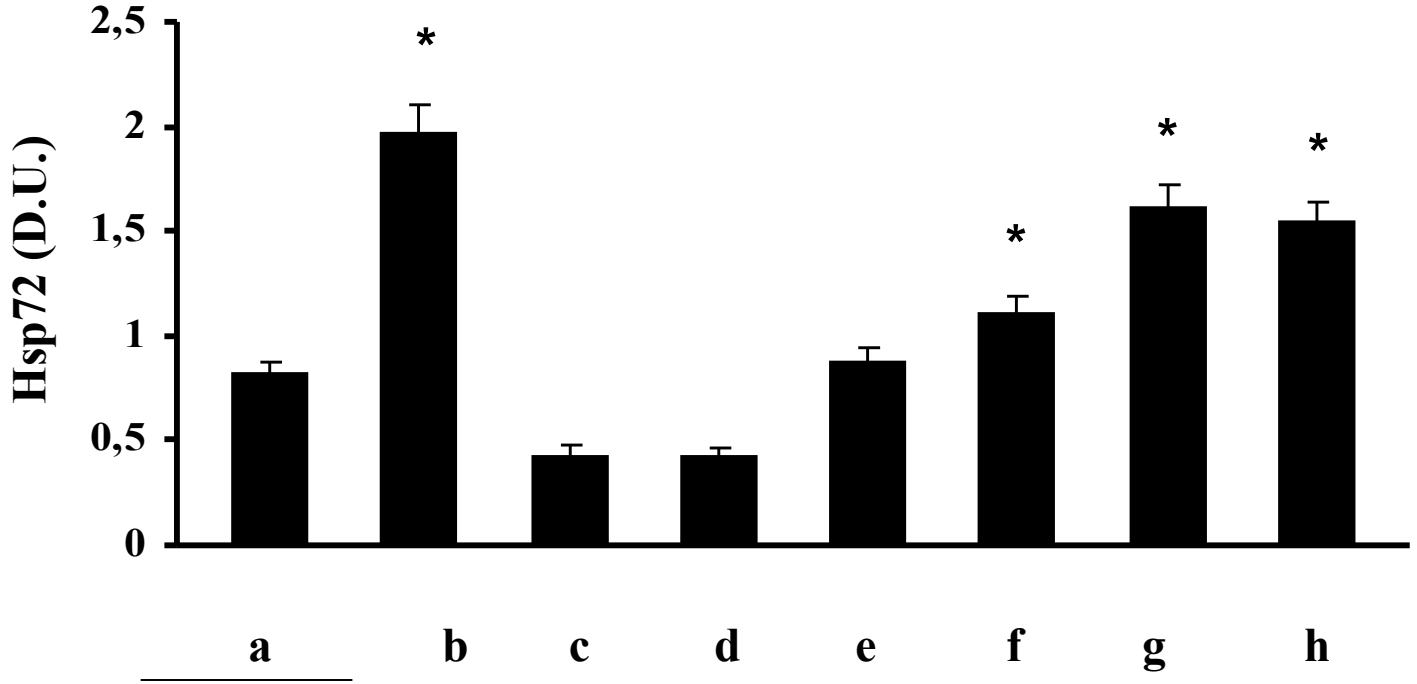


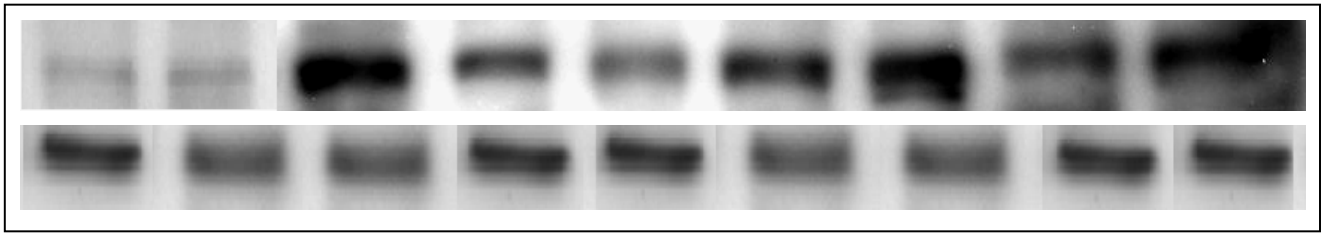
* Significant vs CTRL ($p<0.01$)

Fig 32

Hsp72 EXPRESSION LEVELS IN NEUROBLASTOMA SH-SY5Y CELL LINE AFTER SIN-1 (1mM) TREATMENT IN PRESENCE AND ABSENCE OF CRNS AT DIFFERENT CONCENTRATIONS

A)





B)

LEGEND

a CTRL
b SIN-1 1mM
c CRNS 300µM
d CRNS 1mM
e CRNS 10mM
f CRNS 300µM -1h+SIN-1 1mM
g CRNS 1mM -1h+SIN-1 1mM
h CRNS 10mM -1h+SIN-1 1mM

* Significant vs CTRL ($p<0.01$)

Fig 1A

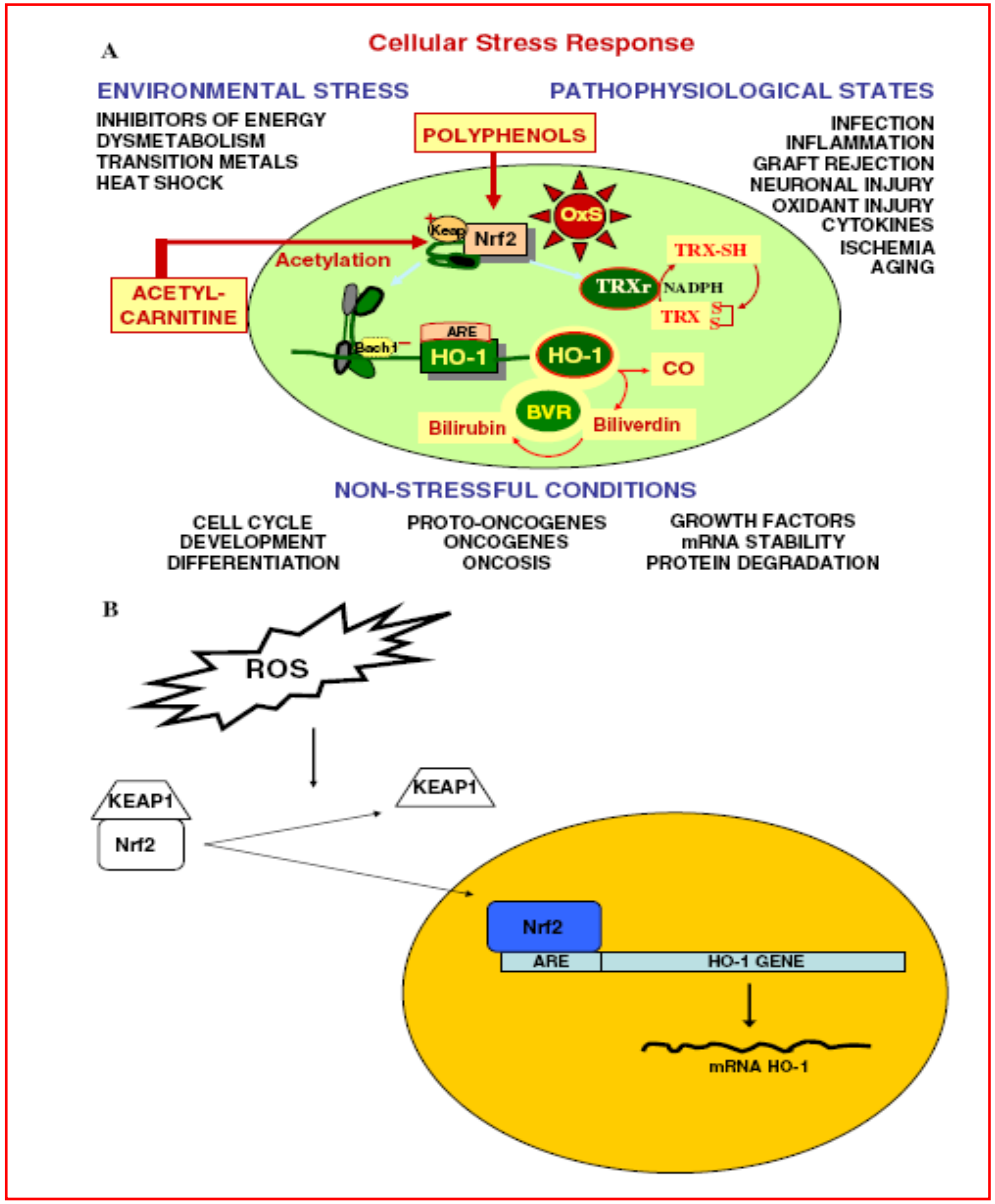
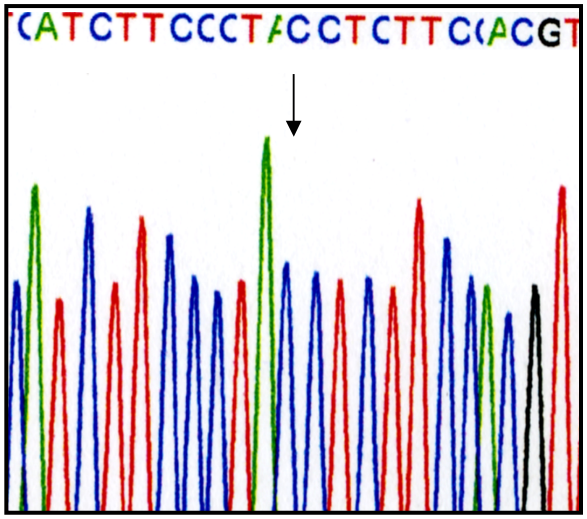

A
Cellular Stress Response
ENVIRONMENTAL STRESS
INHIBITORS OF ENERGY
DYSMETABOLISM
TRANSITION METALS
HEAT SHOCK
PATHOPHYSIOLOGICAL STATES
INFECTION
INFLAMMATION
GRAFT REJECTION
NEURONAL INJURY
OXIDANT INJURY
CYTOKINES
ISCHEMIA
AGING
POLYPHENOLS
ACETYL-CARNITINE
Acetylation
Keap
Nrf2
OxS
TRX-SH
TRXr
NADPH
TRX
S
S
ARE
Bach1
HO-1
HO-1
CO
BVR
Bilirubin
Biliverdin
NON-STRESSFUL CONDITIONS
CELL CYCLE
DEVELOPMENT
DIFFERENTIATION
PROTO-ONCOGENES
ONCOGENES
ONCOSIS
GROWTH FACTORS
mRNA STABILITY
PROTEIN DEGRADATION
B
ROS
KEAP1
Nrf2
KEAP1
Nrf2
ARE
HO-1 GENE
mRNA HO-1

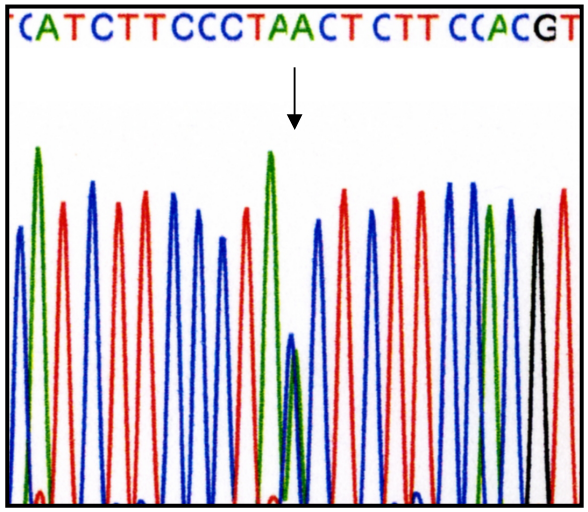
Fig 34

NF1 HETEROZYGOUS *NONSENSE* MUTATION IN EXON 41



CTRL

CATCTTCCCTACCTCTTCCACGT



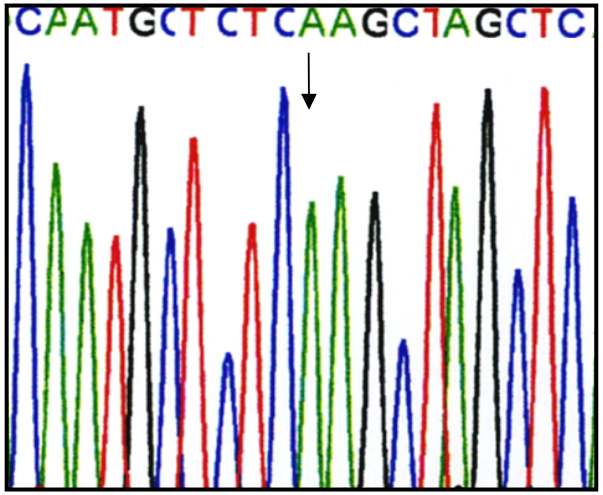
NF1

CATCTTCCCTAACTCTTCCACGT

c.6243C>A
p.Y2081X

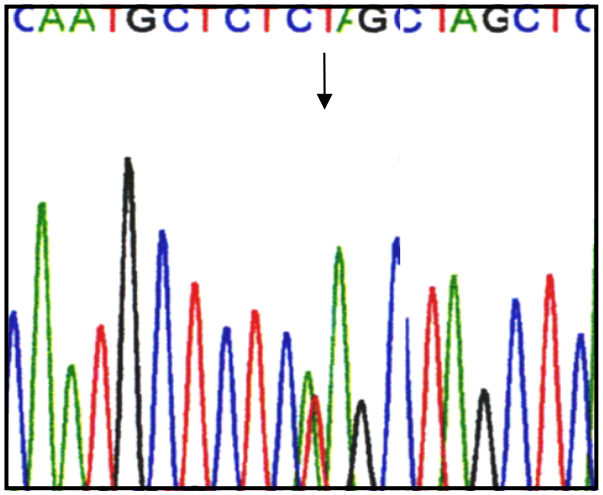
Fig 35

NF1 HETEROZYGOUS *NONSENSE* MUTATION IN EXON 36



CTRL

CAATGCTCTCAAGCTAGCTC



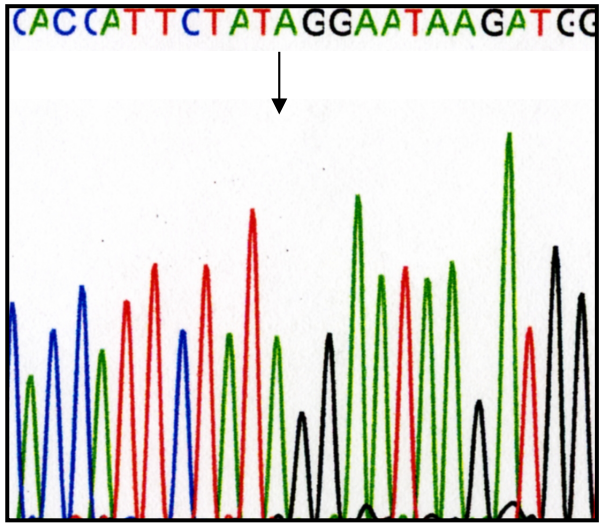
NF1

CAATGCTCTCTAGCTAGCTC

c.5170A>T
p.K1724X

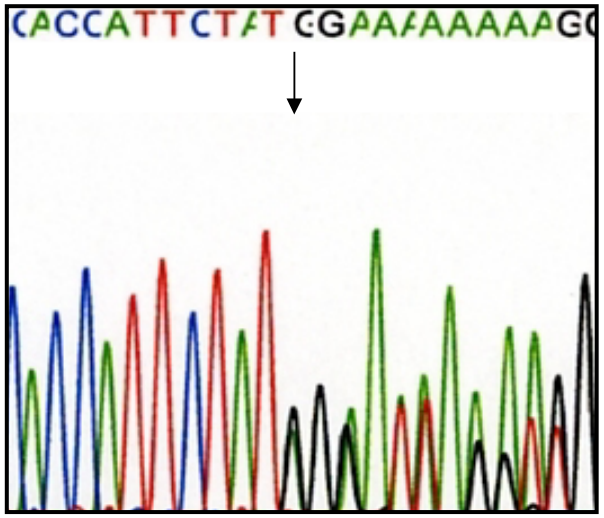
Fig 36

NF1 HETEROZYGOUS *SPLICING* MUTATION IN INTRON 23 (ACCEPTOR-SITE) CAUSING EXON 24 SKIPPING



CTRL

CACCATTCTATAGGAATAAGATGG



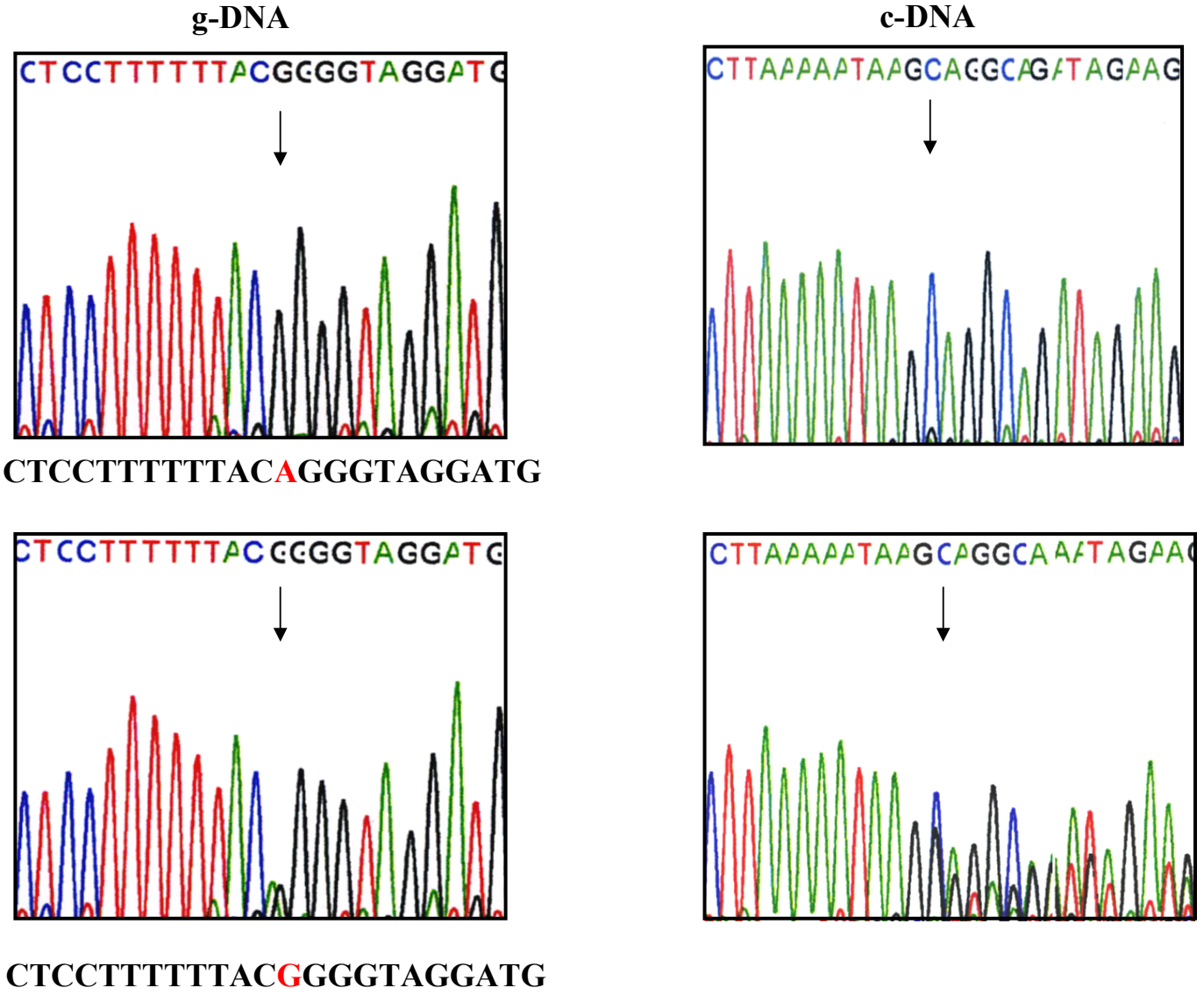
NF1

CACCATTCTATGGAATAAGATGG

IVS23-2delA
c.3114-2delA

Fig 37

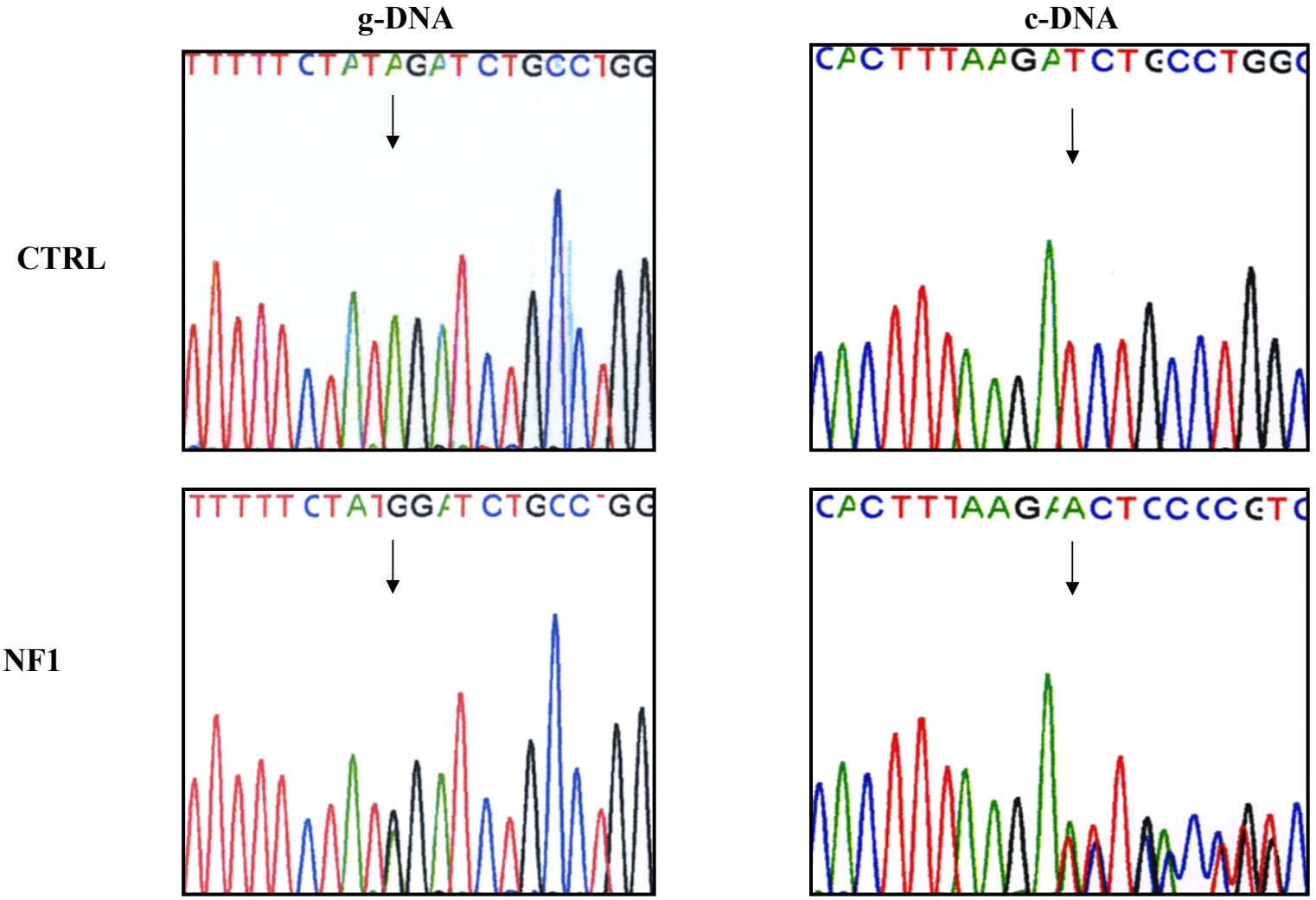
NF1 HETEROZYGOUS *MISSENSE* MUTATION IN EXON 17 ACTIVATING A *CRIPTIC SPLICING* SITE



Gasparini P. et al., Hum. genet. 1996 97(4):492-495

Fig 38

NF1 HETEROZYGOUS *SPLICING* MUTATION IN EXON 11 (ACCEPTOR SITE) CAUSING FIVE CODONS *IN-FRAME* DELETION

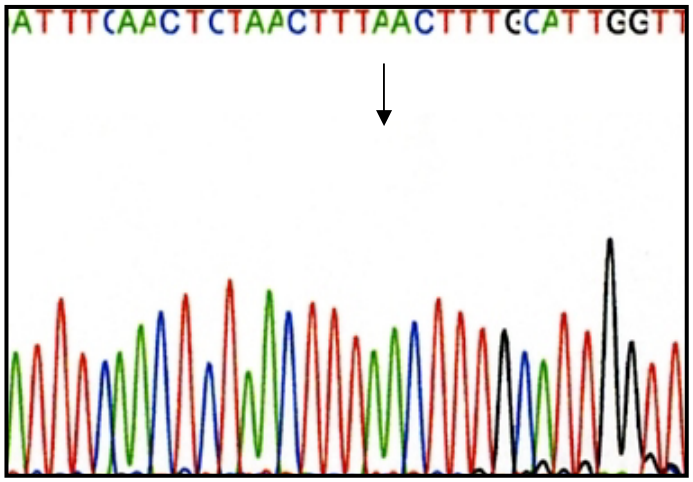


IVS10-2A>G

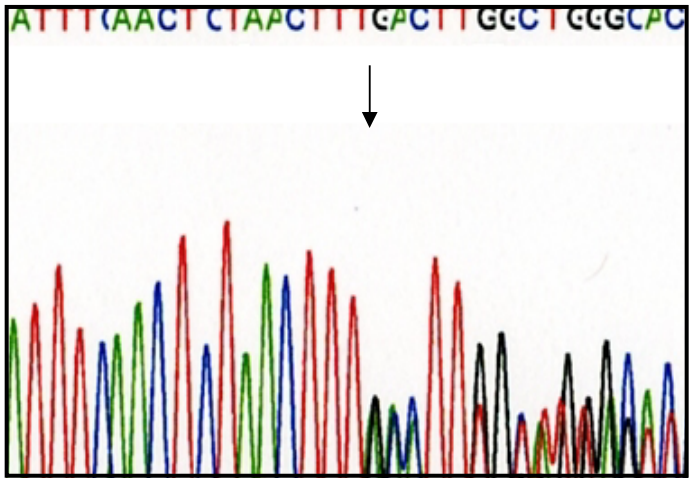
Ars E. et al., J. Med. Genet. 2003, 40(6):e 82

Fig 39

NF1 HETEROZYGOUS *IN-FRAME* MICRODELETION MUTATION IN EXON 47



CTRL



NF1

ATTTCAACTCTAACTTTAACTTTGCATTGGTT

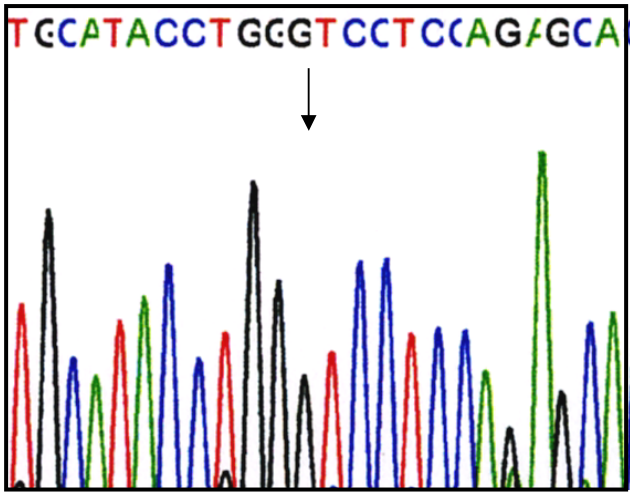
ATTTCAACTCTAACTTTAACTTTGCATTGGTT

c.7097-7101delAACTTT
p.2366-2367Asn-Phedel

Abernathy et al., Human Mutation 3:347-352, 1994

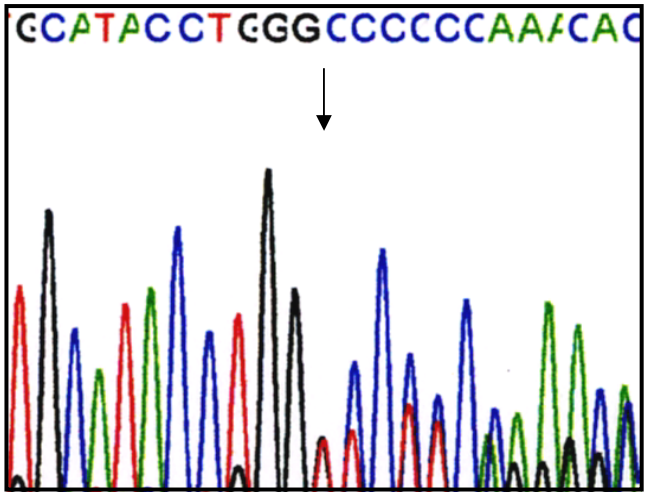
Fig 40

NF1 HETEROZYGOUS *FRAMESHIFT* MICRODELETION MUTATION IN EXON 34 CAUSING A PREMATURE STOP CODON



CTRL

TGCATACCTGGGTCCTCCAGAGCA



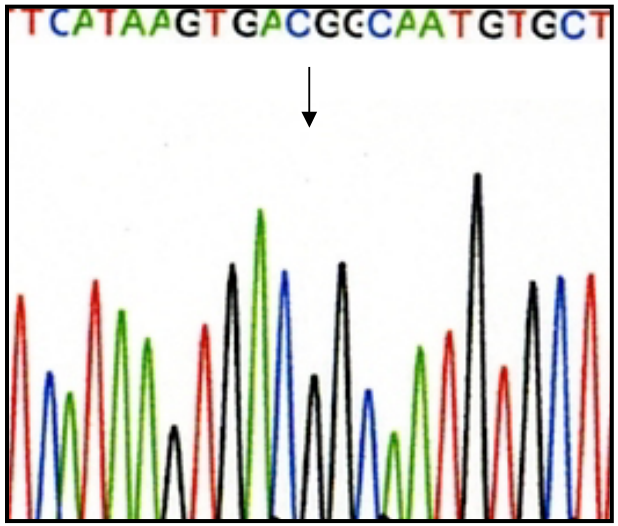
NF1

TGCATACCTGGGTCCTCCAGAGCA

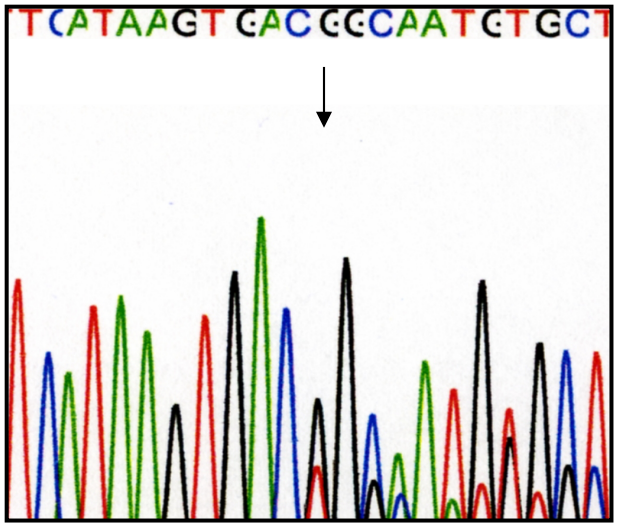
c.4577delG
p.1525fs1552X

Fig 41

NF1 HETEROZYGOUS *FRAMESHIFT* MICROINSERTION MUTATION IN EXON 33 CAUSING A PREMATURE STOP CODON



CTRL



NF1

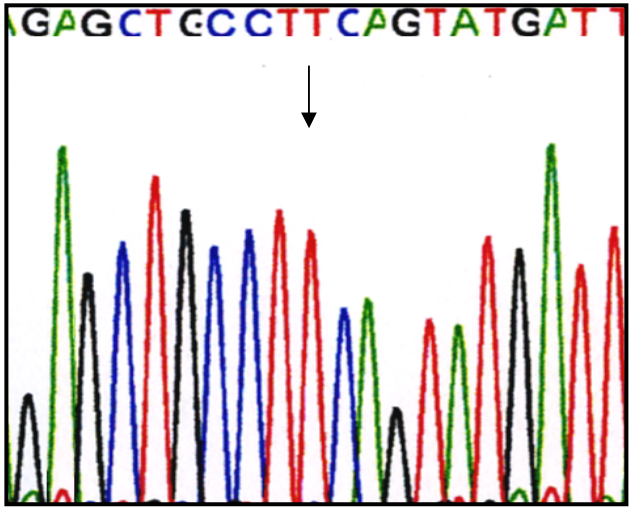
TCATAAGTGACGGCAATGTGCT

TCATAAGTGACTGGCAATGTGCT

c.4441 insT
p.1480Aspfs1508X

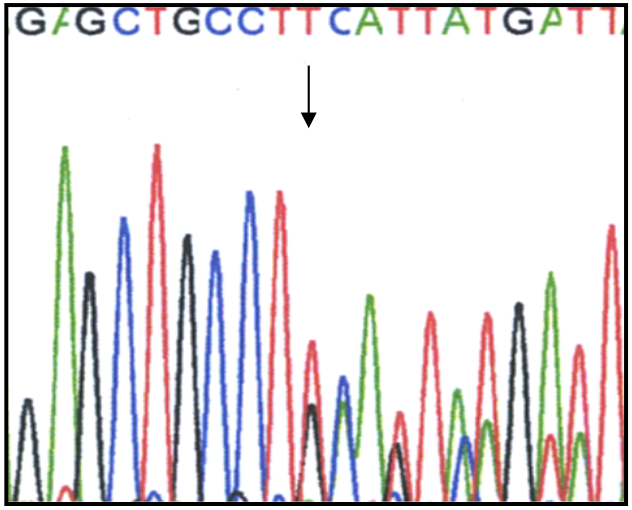
Fig 42

NF1 HETEROZYGOUS *FRAMESHIFT* MICROINSERTION MUTATION (insATTC) IN EXON 22 CAUSING A PREMATURE STOP CODON



GAGCTGCCTTCAGTATGATT
(REVERS STRAND)

CTRL



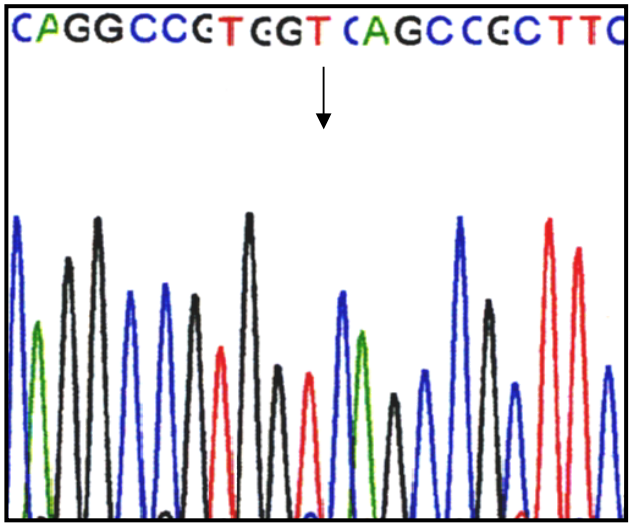
GAGCTGCCTGAATTCAGTAT
(REVERS STRAND)

NF1

c.2930-2931insATTC
p.Gly978Phefs982X

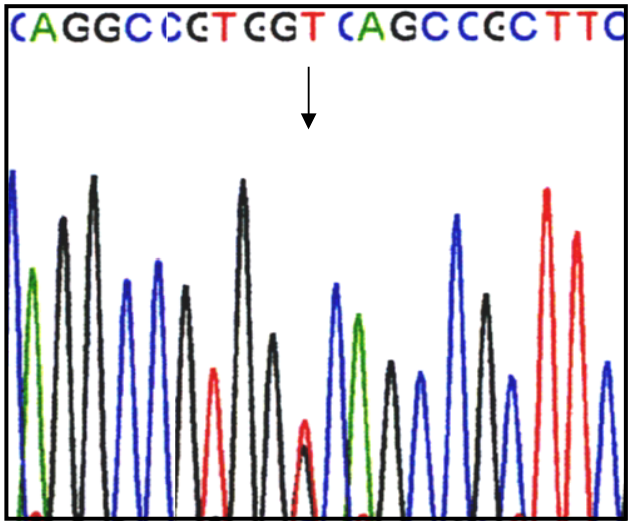
Fig 43

NF1 HETEROZYGOUS *MISSENSE* MUTATION IN EXON 1



CTRL

CAGGCCTGGTCAGCCGCTTC



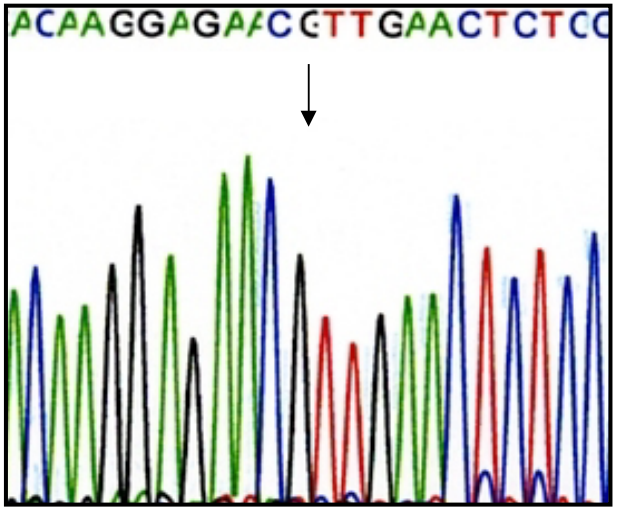
NF1

CAGGCCTGGGCAGCCGCTTC

c.41T>G
p.V14G

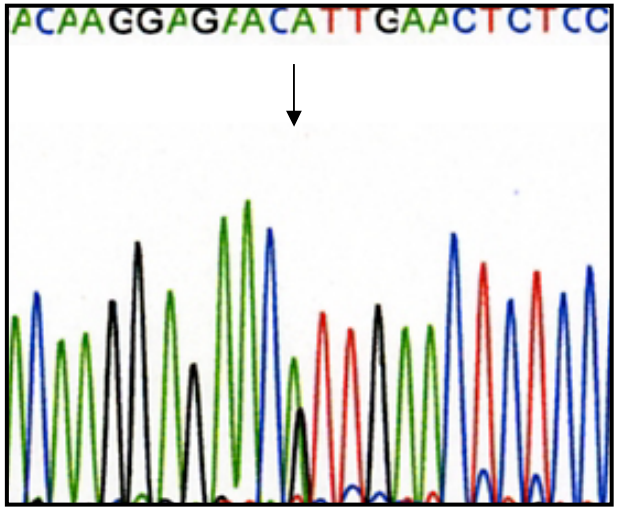
Fig 44

NF1 HETEROZYGOUS *MISSENSE* MUTATION IN EXON 57



CTRL

ACAAGGAGAACGTTGAACTCTCC



NF1

ACAAGGAGAACATTGAACTCTCC

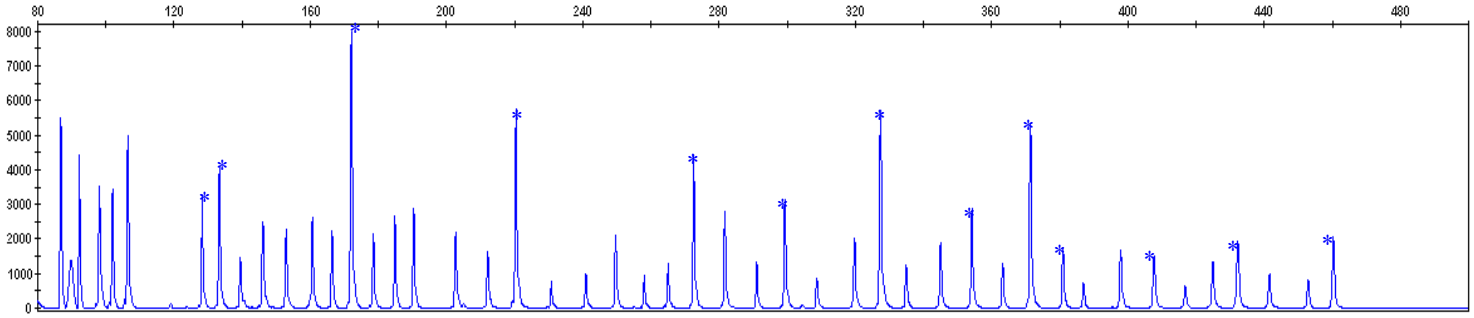
c.8332G>A
p.V2778I

Fig 45

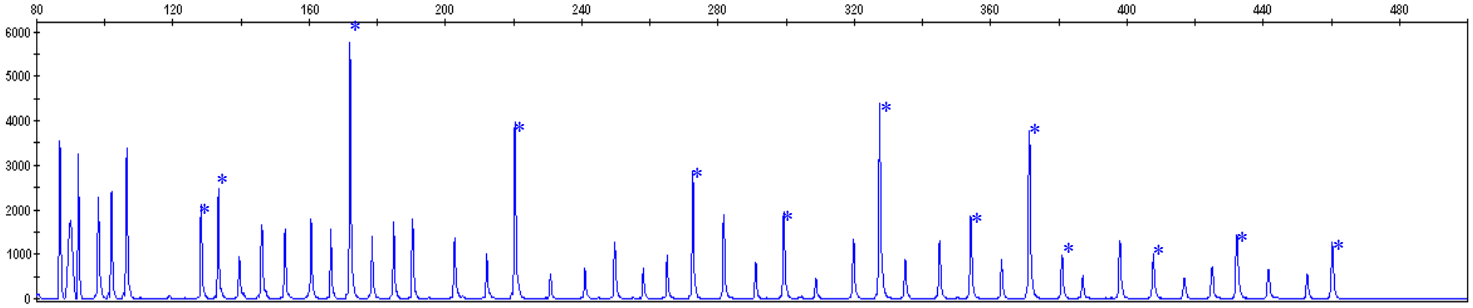
MLPA-NF1

GENOMIC DELETION OF GENE NF1

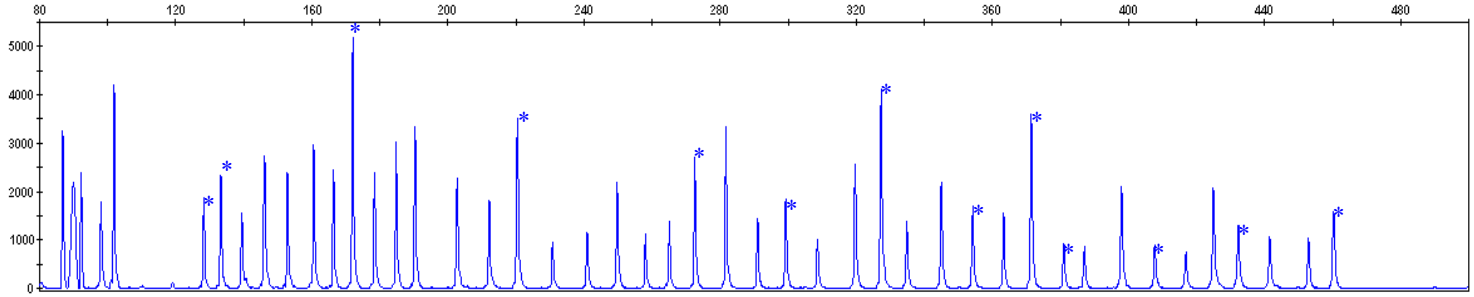
PROBAND NF1



NF1 PARENT



CTRL

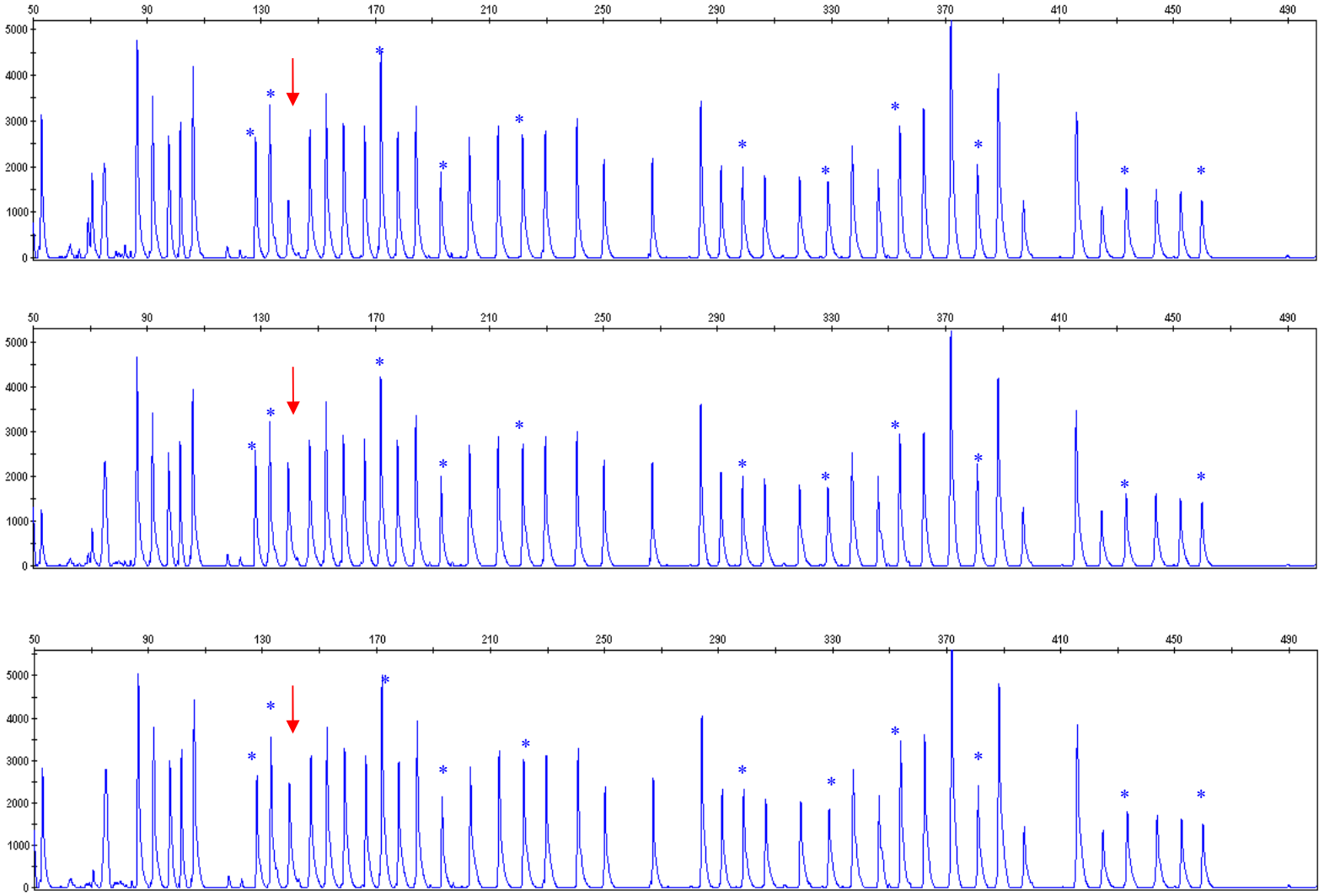


* *REFERENCE PROBE*

Fig 46

MLPA-NF1

EX1 DELETION OF GENE NF1



* *REFERENCE PROBE*

SUMMARY OF THE NOVEL MUTATIONS IDENTIFIED

CLINIC CASES	EXONS	MUTATION
NF-1	41	c.6243C>A p.Y2081X
NF-1	23	IVS23-2delA c.3114-2delA
NF-1	33	c.4441insT p.1480Aspfs1508X
NF-1	47	c.7095-7101delAACTTT p.2366-2367Asn-Phedel
NF-1	34	c.4577delG p.1525 fs1552X
NF-1	57	c.8332G>A p.V2778I
NF-1	1	c.41T>G p.V14G
NF-1	11	IVS10-2A>G
NF-1	17	c.1885G>A
NF-1	36	c.5170A>T p.K1724X
NF-1	21	c.2693T>C p.L898P
NF-1	22	c.2930-2931insATTC p.Gly978PheFs982X
NF-1	54	c.7978A>G p.I2660V
NF-1	Deletion Ex1 (MLPA)	Deletion Ex1 (MLPA)
NF-1	Genomic deletion (MLPA)	Genomic deletion (MLPA)

ALZHEIMER'S DISEASE

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS

Sample (n=6)	*Age (years)*	*Gender (M/F)*	*Postmortem Interval (h)*
Control	85.8 ± 4.1	4/2	2.9 ± 0.23
AD	84.5 ± 5.2	4/2	2.1 ± 0.47

MENIERE'S DISEASE

Table 1 Crisis frequency in a year

Crisis frequency		Crisis duration	
2 crisis per year	3 patient (7.6%)	Less than 1 h	8 (20.4%)
4 crisis per year	19 patients (48.71%)	From 1 to 7 h	18 (46.1%)
5 crisis per year	8 patients (20.4%)	From 8 to 21 h	10 (25.6%)
7 crisis per year	6 patients (15,3%)	More than 30 h	3 (7.7%)
8 crisis per year	3 patient (7,6%)		

Table 2 Staging of patients with MD at admission

Stage of MD	Tone average (dB)	Numbers of patients	Percentage
Mild hearing threshold	20–40	7	17.9
Milder hearing threshold	40–70	21	53.8
Severe hearing threshold	70–90	11	28.2