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GENETICA DELLE DISTONIE

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	Dystonia type	Pattern of inheritance	Chromosome region	Gene locus	Protein
Oppenheim's torsion dystonia	PTD	Autosomal dominant	9q34	DYT1	TorsinA
Early-onset (unconfirmed)	PTD	Autosomal recessive	Not mapped	DYT2	Not identified
Lubag (X-linked dystonia-parkinsonism)	Heredo-degenerative dystonia	X-linked recessive	Xq13.1	DYT3	Multiple transcript system
Whispering dystonia (one family only)	PTD	Autosomal dominant	Not mapped	DYT4	Not identified
Dopa-responsive dystonia	Dystonia-plus	Autosomal dominant	14q22.1	DYT5	GTP cydohydrolyase I
Cranio-cervical dystonia (Mennonite/Amish)	PTD	Autosomal dominant	8p21-q22	DYT6	Not identified
Familial torticollis	PTD	Autosomal dominant	18p	DYT7	Not identified
Paroxysmal dystonic choreoathetosis (non-kinesigenic; Mount-Rebak)	Paroxysmal dystonia	Autosomal dominant	2q33-q35	DYT8	Myofibrillogenesis regulator 1
Paroxysmal dyskinesias with spasticity	Paroxysmal dystonia	Autosomal dominant	1p21	DYT9	Not identified
Paroxysmal kinesigenic dyskinesia	Paroxysmal dystonia	Autosomal dominant	16p11.2-q12.1	DYT10	Not identified
Myodonus-dystonia	Dystonia-plus	Autosomal dominant	7q21-q23	DYT11	Epsilon-sarcoglycan
Rapid-onset dystonia-parkinsonism	Dystonia-plus	Autosomal dominant	19q13	DYT12	Na ⁺ /K ⁺ -ATPase alpha3
Cervical-cranial-brachial	PTD	Autosomal dominant	1p36	DYT13	Not identified
Dopa-responsive dystonia	Dystonia-plus	Autosomal dominant	14q13	DYT14	Not identified
Myodonus-dystonia	Dystonia-plus	Autosomal dominant	18p11	DYT15	Not identified

PTD=primary torsion dystonia.

Table: Classification of genetic dystonias

Geyer HL and Bressman SB, Lancet Neurol, 2006

Camargos S, et al. DYT 16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress response protein PRKRA.

Lancet Neurol 2008; 7: 207-15

Seibler P, et al. A heterozygous frameshift mutation in PRKRA (DYT16) associated with generalized dystonia in a German patient.

Lancet Neurol 2008; 7: 380-1.

Panel 3: Causes of secondary dystonia

Hereditary disorders associated with neurodegeneration

Autosomal dominant

Huntington's disease
Machado-Joseph disease (SCA3)
Other SCA subtypes (SCA2, SCA6, SCA17)
Familial basal ganglia calcification (Fahr's disease)
Dentatorubral-pallidoluysian atrophy
Neuroferritinopathy
Frontotemporal dementia
Neuronal intranuclear inclusion disease (inheritance not well-established)

Autosomal recessive

Juvenile Parkinson's disease (parkin)
Wilson's disease
Aceruloplasminaemia
Pantothenate kinase-associated neurodegeneration (formerly Hallervorden-Spatz)
Neuroacanthocytosis
Ataxia with vitamin E deficiency
Ataxia-telangiectasia
Ataxia with oculomotor apraxia
Sulfite oxidase (molybdenum cofactor) deficiency
Triosephosphate isomerase deficiency
Guanidinoacetate methyltransferase deficiency
Infantile bilateral striatal necrosis
Cockayne's disease

Lysosomal storage disorders

GM1 gangliosidosis
GM2 gangliosidosis (hexosaminidase A deficiency)
Niemann-Pick type C (juvenile dystonia lipidosis)
Metachromatic leukodystrophy
Krabbe's disease
Neuronal ceroid lipofuscinosis

Amino and organic acidurias

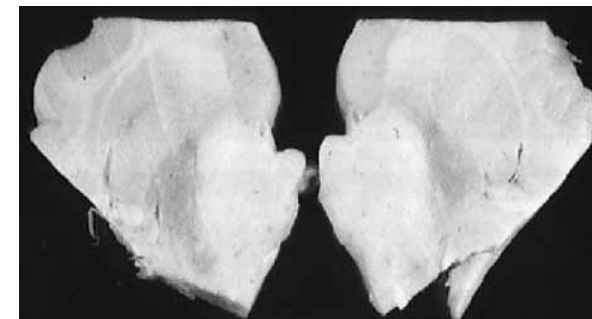
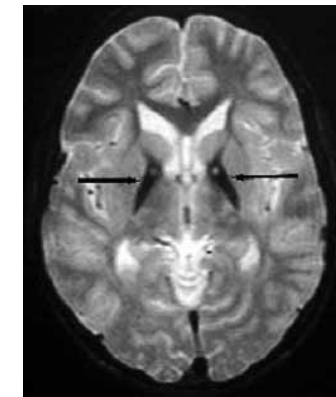
Glutaric acidaemia type I
Homocystinuria
Propionic acidaemia
Methylmalonic aciduria
Fumarase deficiency
Hartnup disease

X-linked recessive

Lubag (X-linked dystonia-parkinsonism)
Lesch-Nyhan syndrome
Deafness-dystonia-optic atrophy syndrome (Mohr-Tranebjaerg syndrome)
Pelizaeus-Merzbacher disease
Rett's syndrome

Mitochondrial

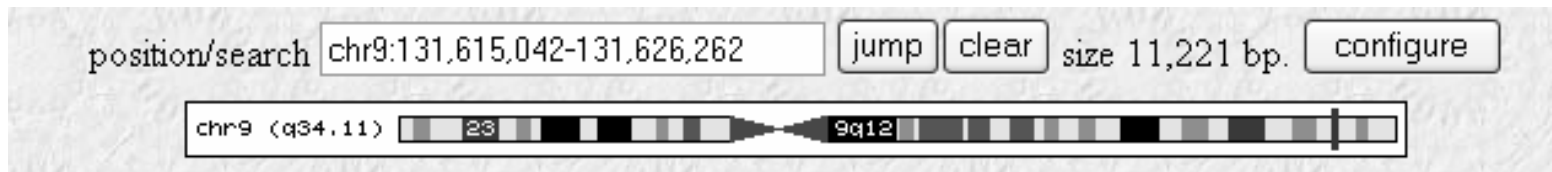
Leber's hereditary optic neuropathy
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Myoclonic epilepsy with ragged-red fibres (MERRF)
Leigh's syndrome



Early-onset, torsion dystonia (DYT1)

- Prevalenza: 1/10000 – 1/15000 tra i non ebrei, 1/3000 – 1/5000 tra gli ebrei
- Esordio: media 12.5 anni (range 3 -64).
- Esordio nel 94% dei casi in un arto (> inferiore), 2/3 dei casi generalizzazione
- Variabilità fenotipica inter- e intrafamiliare
- Ereditarietà autosomica dominante con ridotta penetranza (30%)
- Casi sporadici rari
- Mutazioni gene TOR1A (DYT1) → Torsin A: analogie con Superfamiglia di AAA+ ATPasi, funzione di chaperoni. Regolazione dell'esocitosi vescicolare. Maggiore espressione nella *pars compacta* della sostanza nera

Torsin A (TOR1A)



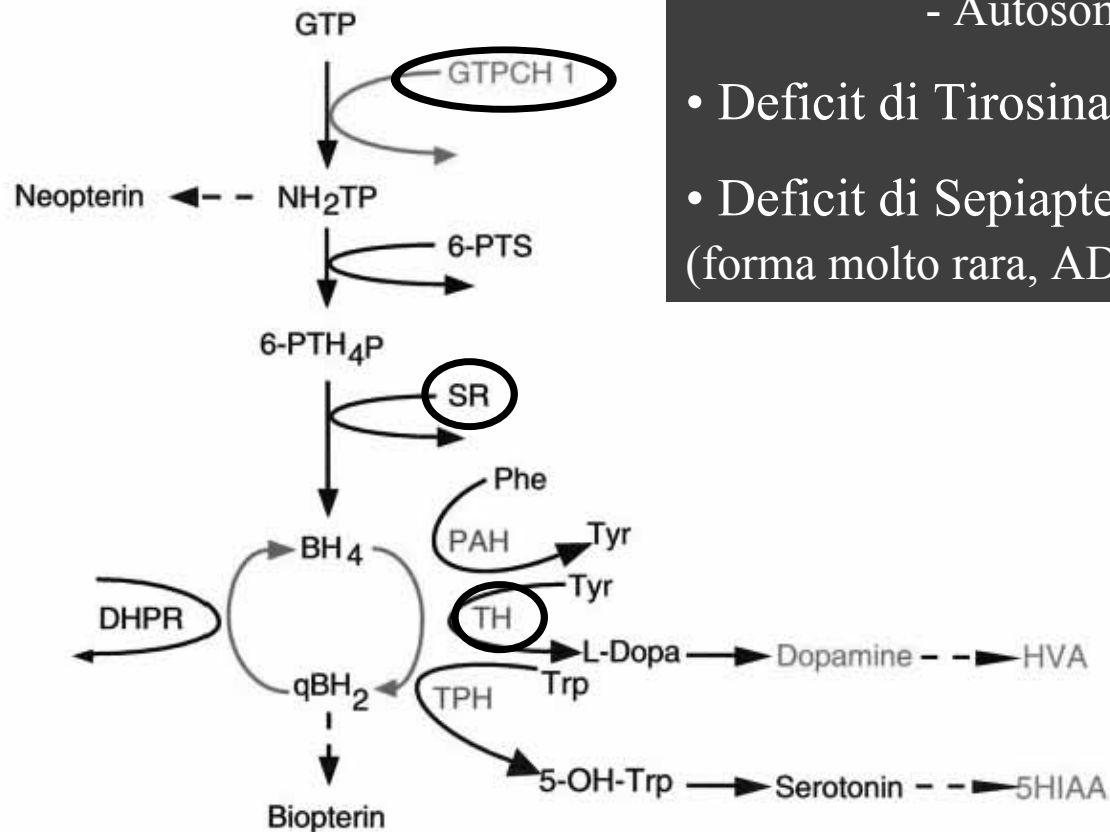
- Delezione di una sequenza GAG nell'esone 5 con perdita di un Acido Glutammico

GAG deletion:	
Wild type torsin AGTGGCTGAGGAGATGAC.....
Mutant torsin AGTGGCTGAGATGAC.....

- 90% degli Ebrei Ashkenazi, 50- 70% dei non Ebrei
- Polimorfismo 216H: ridotta penetranza (Risch et al., 2007)

- Delezione di 18 bp nell'esone 5, caso con distonia ad esordio precoce e mioclono (Leung et al., 2001) → mutazione del gene SGCE (Klein et al., 2002)
- Paziente con mutazione puntiforme G>A (arginina per glutammina) nell'esone 5 (Zirn et al., 2008)

Dopa-responsive dystonia (DYT5)



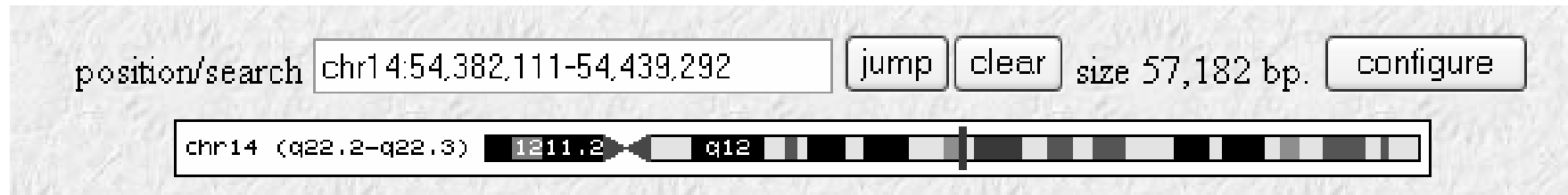
- Deficit di GTP cicloidrolasi 1(GTPCH1):
 - Autosomica dominante
 - Autosomica recessiva
- Deficit di Tirosina Idrossilasi (TH)
- Deficit di Sepiapterina Reduttasi (SR) (forma molto rara, AD)

Fig. 3 The aromatic amino acid hydroxylases and the function of tetrahydrobiopterin. BH₄ = tetrahydrobiopterin; DHPR = dihydropteridine reductase; GTP = guanosine triphosphate; GTPCH I = guanosine triphosphate cyclohydrolase I; 5HIAA = 5-hydroxyindoleacetic acid; HVA = homovanillic acid; NH₂TP = dihydroneopterin triphosphate; 5-OH-Trp = 5-hydroxy tryptophan; PAH = phenylalanine hydroxylase; 6-PTH₄P = 6-pyruvoyl-tetrahydropterin; 6-PTS = 6-pyruvoyl-tetrahydropterin synthase; qBH₂ = q-dihydrobiopterin; SR = sepiapterin reductase; TH = tyrosine hydroxylase; TPH = tryptophan hydroxylase.

Deficit di GTPCH1 (Malattia di Segawa)

- Prevalenza $\approx 0.5-1/1000000$
- Sex ratio: F:M = 3:1
- Esordio: media 6aa (range 1 – 50)
- Esordio con distonia d'azione \rightarrow parkinsonismo
- Variabilità fenotipica inter- e intrafamiliare
- Disturbi psichiatrici e del sonno
- Peggioramento diurno dei sintomi in circa il 75% dei casi
- Generalizzazione in 76% dei casi
- Risposta drammatica al trattamento con L-Dopa
- Ereditarietà autosomica dominante
- Penetranza 30%, 40 - 100% se vengono considerati segni clinici sfumati

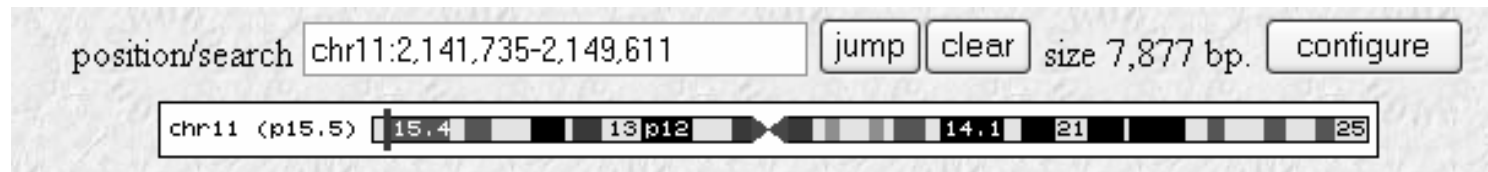
Deficit di GTPCH1 (Malattia di Segawa)



- Mutazioni puntiformi (missenso e nonsense)
 $\approx 60\%$ dei casi (20 – 80%)
- Delezioni
 $\approx 5 – 10\%$ dei casi
- Descritti casi ‘de novo’
- Forma autosomica recessiva: rara, esordio neonatale con deficit di suzione e deglutizione, ipotonia, epilessia, RPM, iperfenilalaninemia allo screening neonatale.
Tp: L-dopa/carbidopa, BH4 e 5-idrossitriptofano.

Deficit di Tirosina Idrossilasi (TH)

- Spettro fenotipico ampio: da forme di distonia Dopa-responsiva a forme di parkinsonismo infantile fino a gravi encefalopatie infantili.
- Attività enzimatica residua correla con il quadro clinico



- Omozigoti o eterozigoti *compound*
- Sostituzioni nucleotidiche (missenso) e, più raramente, delezioni di singoli nucleotidi (frameshift)
- Genitori portatori asintomatici o, molto raramente, con rigidità indotta dall'esercizio responsiva alla Dopa

Paroxysmal nonkinesigenic dyskinesia (DYT8)

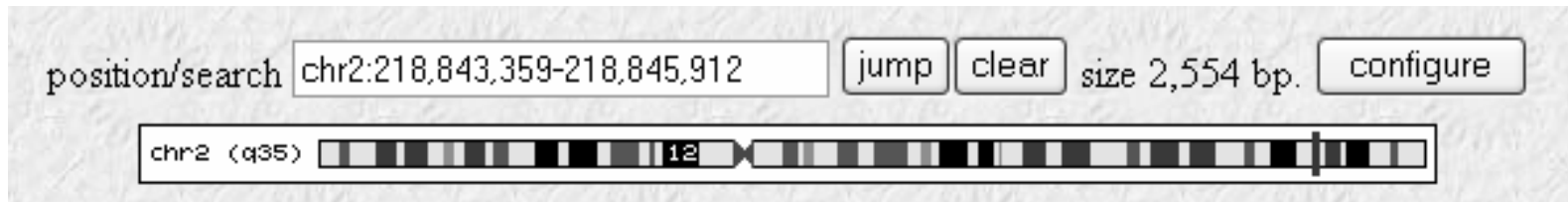
Criteria diagnostici:

- 1. Hyperkinetic involuntary movement attacks, with dystonia, chorea, or combination of these, typically lasting 10 minutes to 1 hour, but up to 4 hours*
- 2. Normal neurologic examination results between attacks, and exclusion of secondary causes*
- 3. Onset of attack in infancy or early childhood*
- 4. Precipitation of attacks by caffeine and alcohol consumption*
- 5. Family history of movement disorder meeting Criteria 1 through 4*

Bruno et al., Neurology, 2007

- Esordio: media 12 aa
- Frequente aura
- Ereditarietà autosomica dominante
- Penetranza incompleta (Bruno et al., su 49 pz 98%)
- Casi sintomatici: sclerosi multipla, sofferenza pre-perinatale, traumi, disendocrinopatie, HIV, lesioni vascolari dei nuclei della base

Myofibrillogenesis regulator-1 (MR-1)

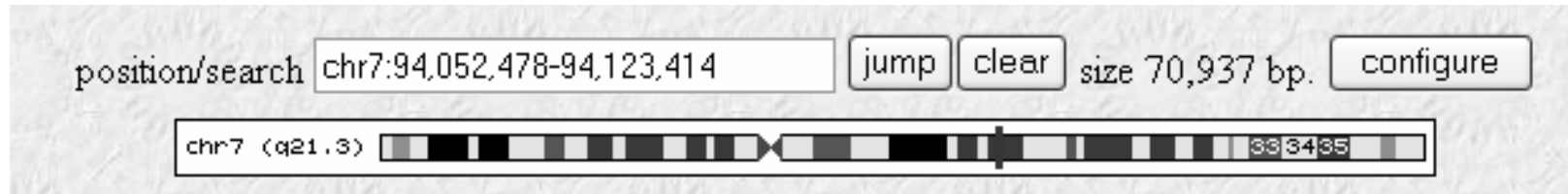


- Funzione ignota
- MR-1 omologo dell'Idrossiacilglutazione Idrolasi (HAGH), enzima che degrada il metilgliossale (acido lattico + glutazione ridotto), sostanza tossica presente in alta quantità nel caffè e nel vino ed elevata in risposta allo stress. Il metilgliossale ha attività mutagena e cancerogena oltre ad effetti tossici sulle cellule neuronali.
- In DYT8 tossine e stress + attività MR-1 anomala potrebbero concorrere alla tossicità neuronale
- Mutazioni: sostituzioni A7V e A9V

Myoclonus-Dystonia (DYT11)

- Prevalenza ignota
- Esordio in infanzia o adolescenza (range 6 mesi – 38 anni)
- Mioclono arti superiori e muscoli assiali (occasionalmente arti inferiori).
Distonia focale o segmentale nel 54% dei casi, occasionalmente unica manifestazione.
- Disturbi psichiatrici e abuso di alcool
- Decorso relativamente benigno
- Ereditarietà autosomica dominante
- Variabilità fenotipica inter- e intrafamiliare
- Penetranza ridotta per imprinting materno: < 5% degli affetti eredita la mutazione dalla madre (soppressione incompleta)
- Descritti casi sporadici

ϵ -sarcoglycan (SGCE)



- Parte del complesso distrofina-glicoproteina che fissa il citoscheletro alla matrice extracellulare. Due isoforme: a) ubiquitaria; b) SNC (> neuroni dopaminergici)
- Descritte sostituzioni (mutazioni missenso e nonsenso), delezioni e inserzioni (mutazioni frameshift e errori di splicing). 95% delle mutazioni negli esoni 1-7, 5% nell'esone 9. Descritti casi con delezione di esoni
- Detection rate al sequenziamento: nei casi familiari $\approx 30 - 50\%$, nei casi sporadici $\approx 10 - 15\%$. Detection rate per delezioni: $\approx 9\%$ (Han et al., Mov Disord, 2008; Grünewald et al, Hum Mut, 2008)
- Altri geni candidati :
 - DRD2 (recettore dopaminergico D2): mutazione missenso
 - DYT1: delezione 18 bp carbossiterminale
 - DYT1: delezione tripletta GAG
 - DYT15: locus su 18p11

} Mutazione SGCE

Rapid-Onset Dystonia Parkinsonism (DYT12)

Criteri diagnostici:

- *Abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days*
- *A clear rostrocaudal (face>arm>leg) gradient of involvement*
- *Prominent bulbar findings*

Brashear et al., Brain, 2007

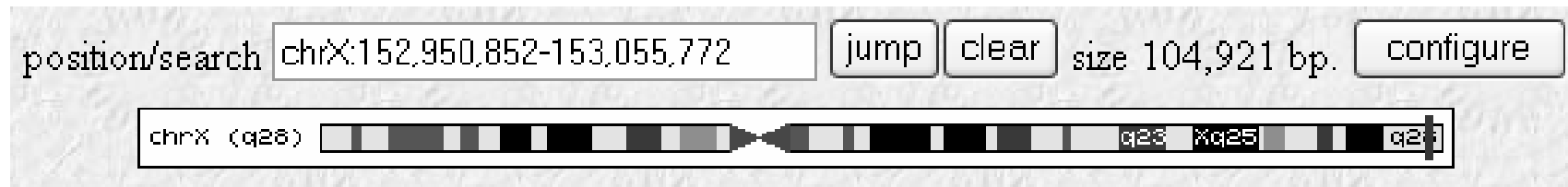
- Prevalenza ignota
- Esordio: 4 – 55 aa
- Minima risposta alla L-Dopa
- Ereditarietà autosomica dominante con penetranza incompleta
- Mutazioni (6 missenso) gene *Na⁺/K⁺ ATPasi α 3 subunit (ATP1A3)*



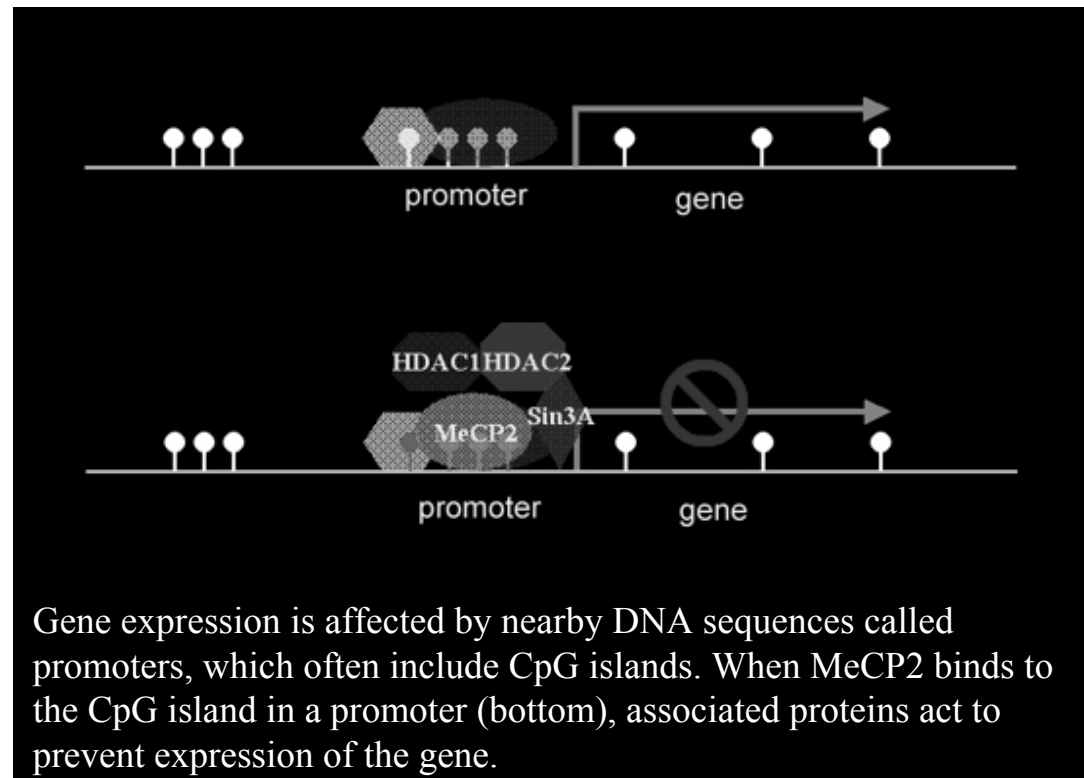
- Subunità α 3 espressa solo nei neuroni
- Nel SNC: reuptake di glutammato e altri neurotrasmettitori, regolazione concentrazione Ca^{+} intracellulare, regolazione del volume cellulare
- Descritti casi *de novo*

MECP2 (methyl-CpG-binding protein 2) Related Disorders

- Prevalenza nella popolazione generale femminile 1/10000
- Verosimilmente seconda causa di RM nelle femmine dopo Sindrome di Down.
- 90-95% dei casi con mutazione di MECP2: missenso, nonsense, delezioni ($\approx 15\%$)



- Regolatore della trascrizione
- Ruolo nella sinaptogenesi



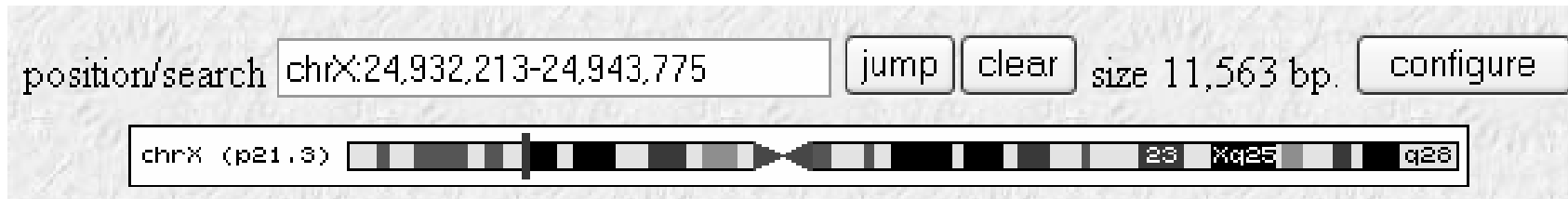
‘The frequency of potentially disease-causing MECP2 mutations in the population of mentally retarded male patients is thus between 1.3% and 1.7%. This is an important figure, considering that the incidence of fragile X syndrome, the most frequent familial cause of MR in males, is 2.8% in the same population’.

Villard, J Med Genet, 2007

Disturbi del movimento:

- Stereotipie
 - Atassia
 - **Distonia**
 - Tremore
 - Corea
 - Mioclono
 - Sindrome rigido-acinetica
- } CRITERI DIAGNOSTICI SPECIFICI

ARX (X-linked aristaless-related homeobox gene)



article

Mutation of *ARX* causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans

m/naturegenetics

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nature genetics • volume 32 • november 2002

Nel corso dello sviluppo corticale regola la proliferazione e la migrazione degli interneuroni GABAergici

Expansion of the first PolyA tract of *ARX* causes infantile spasms and status dystonicus

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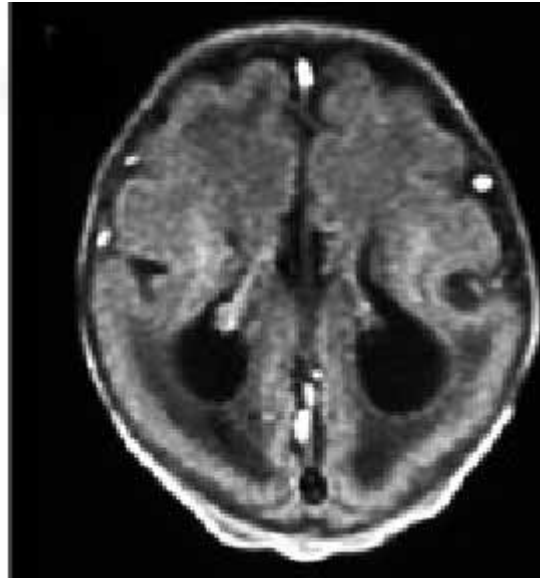
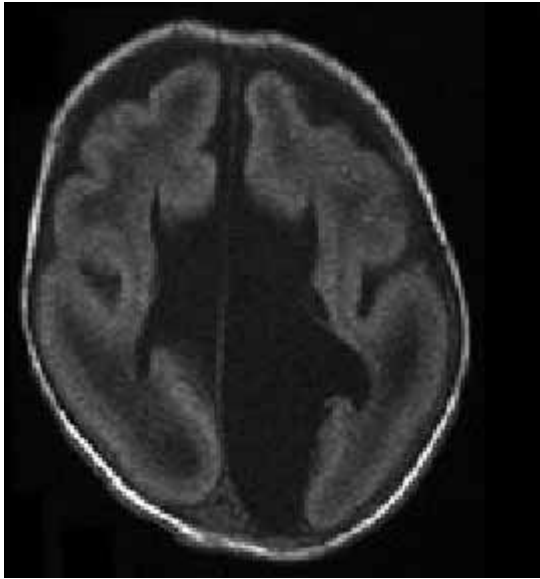
VIDEO

ABSTRACT **Background:** *ARX* is a paired-type homeobox gene located on the X chromosome that contains five exons with four polyalanine (PolyA) tracts, a homeodomain, and a conserved C-terminal aristaless domain. Studies in humans have demonstrated remarkable pleiotropy: malformation phenotypes are associated with protein truncation mutations and missense mutations in the homeobox; nonmalformation phenotypes, including X-linked infantile spasms (ISS), are associated with missense mutations outside of the homeobox and expansion of the PolyA tracts. **Objective:** To investigate the role of *ARX*, we performed mutation analysis in 115 boys with cryptogenic ISS. This included two pairs of brothers. **Results:** We found an expansion of the trinucleotide repeat that codes for the first PolyA tract from 10 to 17 GCG repeats (c.333_334ins[GCG]7) in six boys (5.2%) ages 2 to 14, from four families, including the two pairs of brothers. In addition to ISS, all six boys had severe mental retardation and generalized dystonia that appeared around the age of 6 months and worsened, eventually leading to stable severe quadriplegic dyskinesia within age 2 years. Three children experienced recurrent, life-threatening status dystonicus. In four children brain MRI showed multiple small foci of abnormal cavitation on T1 and increased signal intensity on T2 in the putamina, possibly reflecting progressive multifocal loss of tissue. **Conclusion:** The phenotype of infantile spasms with severe dyskinetic quadriparesis increases the number of human disorders that result from the pathologic expansion of single alanine repeats. *ARX* gene testing should be considered in boys with infantile spasms and dyskinetic cerebral palsy in the absence of a consistent perinatal history. **NEUROLOGY 2007;69:427-433**

Table Phenotypes and genotypes associated with ARX mutations		
	Phenotype (gender)	ARX genotypes
Syndromes with malformations	XLAG with HYD (M)	Large intragenic deletions, frameshifts or null mutations (exons 1-4), nonconservative missense mutations in homeobox
	XLAG (M)	
	Proud syndrome (ACC-AG) (M)	
	ACC with MR, seizures (F)	
	ACC with normal intelligence (F)	
Syndromes without malformations	infantile epileptic-dyskinetic encephalopathy (this report) (M)	PolyA expansion (1st PolyA tract [GCG]7)
	Infantile spasms (M)	PolyA expansion (1st [GCG]7 and 2nd PolyA tracts), deletion of exon 5
	XMESID (M)	Rarely, conservative missense mutations in homeobox
	Partington syndrome (XLMR, seizures, mild distal dystonia) (M)	PolyA expansion (2nd PolyA tract)
	XLMR with or without seizures (M)	PolyA expansion (1st [GCG]1, 2, 3 and 2nd PolyA tracts), missense mutations outside homeobox
	Normal (F)	PolyA expansion, missense mutation

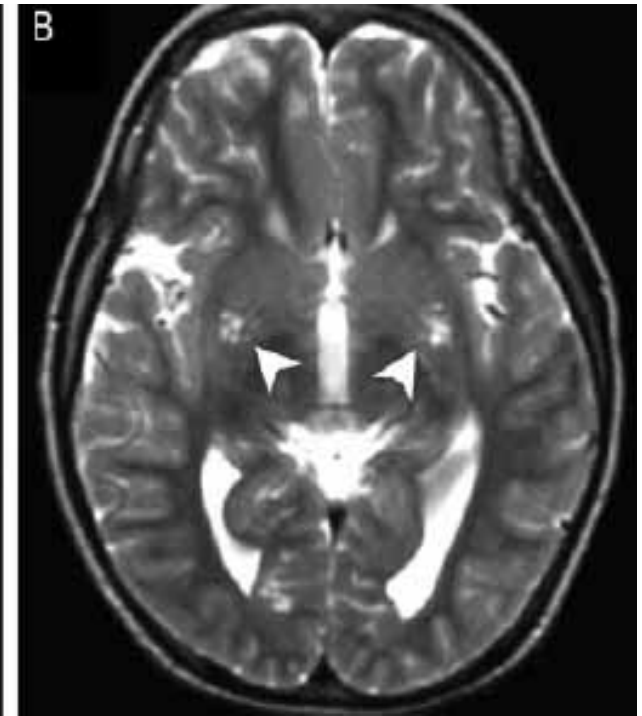
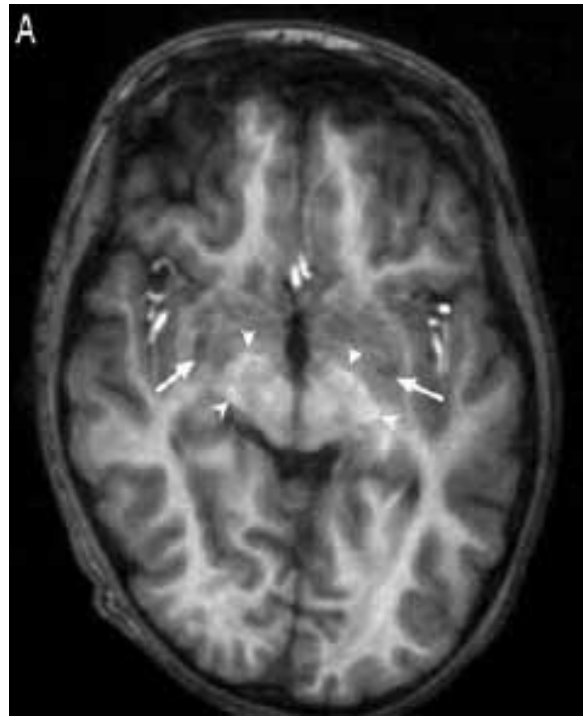
ACC = agenesis of the corpus callosum; AG = abnormal genitalia; HYD = hydrocephalus; XLMR = X-linked mental retardation; XLAG = X-linked lissencephaly with abnormal genitalia; XMESID = X-linked myoclonic epilepsy with spasticity and intellectual disability.

Guerrini et al., Neurology, 2007



Dobyns et al., Am J Med Genet, 1999

(A) Axial T1-weighted inversion recovery image of Patient 3 shows lucencies (arrows) in the posterior lentiform nuclei. Foci of hyperintensity (arrowheads) are seen in the cerebral peduncles; these are of unknown significance. (B) Axial T2-weighted image of Patient 4 shows multiple hyperintense foci (arrowheads) in the posterior putamina. There is overall increase in the size of ventricles and cisterns, suggesting cerebral volume loss.



Guerrini et al., Neurology, 2007