[Frontiers in Bioscience E2, 701-710, January 1, 2010]

The aristaless (*Arx*) gene: one gene for many "interneuronopathies"

Martino Ruggieri[1], Piero Pavone[2], Giovanni Scapagnini[3], Loriana Romeo[1], Ilaria Lombardo[4], Giovanni Li Volti [5,6], Giovanni Corsello[7], Lorenzo Pavone[4]

[1] Institute of Neurological Science (ISN), National Research Council (CNR), Catania, Italy, [2] Unit of Pediatrics, University Hospital "Vittorio Emanuele", Catania, Italy,[3] Department of Health Sciences, University of Molise, Campobasso, Italy,[4] Unit of Clinical Pediatrics, Department of Pediatrics, University of Catania, Italy,[5] Department of Biological Chemistry, Faculty of Pharmacy, University of Catania, Italy,[6] IRCCS Associazione Oasi Maria S.S.- Institute for Research on Mental Retardation and Brain Aging, Troina (EN), Italy,[7] Maternal-Infantile Department, University of Palermo, Italy

TABLE OF CONTENTS

1. ABSTRACT

The *ARX* [Aristaless-related (X-linked) homeobox] gene is not only present in arthropods and their ancestors, but also in vertebrates including humans (*ARX* orthologs). The gene is composed of 5 coding exons and it is expressed predominantly in foetal and adult brain and skeletal muscle. In this review we report on our experience and review the existing literature on the genotype and phenotype heterogeneity associated with *ARX* abnormalities in humans ranging from severe neuronal migration defects (e.g., lissencephaly), to mild forms of X-linked mental retardation without apparent brain abnormalities. The *ARX*-related disorders are reviewed focusing on their clinical features and on the role of the *ARX* gene. It has yet to be established whether the molecular defect alone could cause a given cerebral abnormality and/or malformation or an additional or related molecular or environmental event could contribute to a given phenotype in molecularly predisposed individuals.

2. THE "ARISTA" AND THE ARISTALESS (AL)-RELATED FAMILY OF HOMEOBOX GENES

An overwhelming multiplicity of species is found in the insect world, as documented by the enormous variety of different sizes, puzzling shapes, and intricate patterns of their outer manifestations (1,2). Two developmental characteristics of the arthropod phylum are the tendency toward regional specification and the segmented body, with each segment bearing a pair of ventrally located and articulated appendages (e.g., legs) (3). Thus, it is commonly accepted that insects have evolved from an annelid-like ancestor, consisting of an array of fairly similar segments, to their current specialised forms through the grouping of adjacent segments into three body parts (tagmosis) and a high degree of specification of single segment that is reflected for example, by the variety in external morphology of insect appendages, including legs and antennas (4).

One of the anatomic parts of the antennas is known as "arista", which is a simple or variously modified apical or sub-apical bristle, arising from the third antennal segment. The arista may be bare, sometime appearing no more than a simple bristle, pubescent (i.e., covered in short hairs), or plumose (i.e., covered in long hairs). The arista is the evolutionary remains of antennal segments, and may sometimes show signs of segmentation. These segments are called aristameres (2).

Detailed molecular studies, coupled with genetic tools, have focused on the events of pattern formation (segmentation) and morphogenesis in a member of the family of insects, Drosophila melanogaster (3, 4). Such studies showed that genes like Distal-less (Dll), formerly called Brista, and rotund (rn), play an important role in establishing the pattern along the proximo-distal axis of appendages, including the aristameres (4). These genes belongs to the family of the homeotic homeobox-genes [a homeobox (from the Greek "homoios" = like; and "box") is a small DNA sequence (i.e., a small DNA tract of approximately 180 base pairs long acting as a gene), highly conserved across vast evolutionary distances, which is contained within longer DNA tracts (i.e., within larger genes known as homeobox-containing genes) that are involved in the regulation of patterns of development (morphogenesis) in animals, fungi and plants. Some of the homeobox genes act by regulating which parts of the body forms what body part (homeotic homeobox-genes) - among the homeotic genes there is a group of related homeobox genes, known as Hox genes, which regulates the anterior-posterior axis and segment identity of metazoan organisms during early embryonic development]. One of the members of this family of homeotic/hox genes is known as aristaless (al) (ARX) gene (5). Mutations in the Drosophila ARX gene, besides causing minor effects on wing venation and size of the scutellum, reduce or remove the most distal part of the antennae and legs (i.e., the arista and claws). Of more interest, the al (ARX) gene is also transcribed during embryogenesis and apart from its function(s) in the ontogeny of specific larval head and tail organs (see above), its embryonic transcript pattern suggested possible (higher) roles in early imaginal disc development (4). This is further supported by the fact that this gene belongs to the (group-II) aristaless-related family of aristaless-related genes (which include ISSX; MRX29; MRX32; MRX33; MRX36; MRX38; MRX43; MRX54; MRXS1; and PRTS genes), which is a subset of the Paired-related homeobox-containing genes whose members are expressed primarily in the central and/or peripheral nervous systems during development (6, 7).

3. THE ARX (ARISTALESS-RELATED) GENES AND THEIR HOMEODOMAIN PROTEIN PRODUCTS

The (homeotic/hox) ARX [Aristaless-related (X-linked) homeobox] gene (OMIM # 300382) is not only present in arthropods and their ancestors, but also in vertebrates including man (ARX orthologs) (6)

The gene is composed of 5 coding exons and encompasses a genomic region of roughly 12.5 kb (8, 9). ARX is located in the vicinity of - approximately 6.7 kb from - the 3-prime end of the gene encoding DNA polymerase-alpha (POLA gene; OMIM # 312040), which maps to Xp22.3-p21.1. The ARX and POLA genes are in tail-to-tail orientation.

The open reading frame spans 1,686 bp and encodes a protein (a transcription factor and sequence-specific DNA-binder) of 562 amino acids, which contains two conserved homeo-domains (a homeodomain is a protein sequence and structure which has evolved, function, and exist independently of the rest of the protein chain): (1) a (paired Q/50 or paired/K50) C-terminal domain of 16 aminoacids (called the aristaless homeodomain); and (2) an octapeptide in the N-terminus, which functions as in transcriptional repression. The aristaless domain is highly conserved in the Otp (orthopedia) homeoprotein, a member of a family of proteins thought to be important in regionalisation of the ventral diencephalons. Deletion of the aristaless domain in the Otp reduces the transactivation activity. In addition to these main homeodomains, ARX contains four distinct polyalanine (polyA) tracts (aminoacids 100-115, 144-155, 275-281, and 432-440) (10, 11). Their function is still debated, but it has been suggested that they suppress transcription. Interestingly, these domains are not 100% conserved between mouse and human.

The ARX gene is expressed predominantly in foetal and adult brain and skeletal muscle (8). Stromme detected a single 2.8-kb ARX mRNA isoform in brain and 2 additional, smaller ARX mRNAs in skeletal muscle (9).

The mouse and zebra fish (and human) ARX orthologs are expressed predominantly in forebrain (cerebral cortex) and floor plate [especially in g-aminobutirric (GABA)-interneurons], which suggests that the ARX protein, is important for the maintenance of specific neuronal subtypes (i.e., interneurons) in the cerebral cortex and axonal guidance in the floor plate (12-15) and is involved in nervous system (and pancreas) development (16-18).

Specifically, ARX interacts via its protein homeodomain with importin 13 (IPO13; OMIM # 610411), a member of the importin-beta super family, which mediate translocation through nuclear pore complexes: cooperation with the RanGTPase system allows IPO13 (and other members of this super family) to bind and subsequently release their substrates on opposite sides of the nuclear envelope ensuring direct nuclear vs. cytoplasm transport and vice versa (19). Additional functions of ARX include regulation of transcription DNA-dependent (5). Thus, ARX acts as a regulator of proliferation and differentiations of neuronal progenitors and is involved in the tangential migration of interneurons from ventral regions to the developing cortex (20,21).

As recently demonstrated by *in utero* electroporation to knock down or over-express ARX the targeted inhibition of ARX causes cortical progenitor cells to exit the cell cycle prematurely and impairs their

migration toward the cortical plate(21). In contrast, ARX over-expression increases the length of the cell cycle. In addition, RNA interference-mediated inactivation of ARX prevents cells from acquiring multipolar morphology in the sub-ventricular and intermediate zones, resulting in decreased neuronal motility (20,21). In contrast, ARX over-expression appears to promote the development of tangentially oriented processes of cells in the sub-ventricular and intermediate zones and affects radial migration of pyramidal neurons. As recorded by Friocourt the level of ARX expression is important for tangential migration of GABA-containing interneurons, because both inactivation and over-expression of the gene impair their migration from the ganglionic eminence (21).

The function of ARX and its orthologs have been investigated in humans as well as in different model systems, besides Drosophila melanogaster, including Caenorhabditis elegans, Xenopus laevis, and Mus musculus.

In this review, we will focus the findings concerning the role and anomalies of ARX in human brain development.

4. PHENOTYPIC HETEROGENEITY ASSOCIATED WITH ARX ABNORMALITIES

It is well-established that the ARX gene has an important role in the development of the brain, and its mutations can cause structural anomalies in the cerebrum and several other structures (12, 22, 23). The human ARX (Xp22.13) gene is responsible for a number of disorders, including a wide spectrum of syndromes ranging from phenotypes with severe neuronal migration defects, such as lissencephaly, to mild forms of X-linked mental retardation without apparent brain abnormalities (5, 24-40). Malformation phenotypes are usually associated with protein truncation mutations and missense mutations in the homeobox; non-malformation phenotypes, including X-linked infantile spasms (ISS), are associated with missense mutations outside of the homeobox and expansion of the polyA tracts. The variety of signs and/or symptoms recorded in the neurological clinical manifestations associated to ARX impairment are compatible with the loss of cortical interneurons and altered basal ganglia-related activities (23).

4.1. Ohtahara syndrome

Ohtahara syndrome, (which thus far includes two forms (the early infantile epileptic encephalopathy-1 [**EIEE1**], also known as X-linked infantile spasm syndrome-1 [ISSX1] or West syndrome (WS) X-linked (OMIM # 308350), caused by mutations in the ARX gene; and the early infantile epileptic encephalopathy-4 [**EIEE4;** OMIM # 612164], caused by mutations in the STXBP1 gene [OMIM # 602926]); this encephalopathy is a genetically heterogeneous severe form of epilepsy first reported by Ohtahara and characterized by frequent tonic seizures or spasms beginning in very early infancy with a specific electroencephalographic (EEG) finding of suppression-burst patterns, characterized by high-voltage bursts alternating with almost flat suppression phases (41). Approximately 75% of EIEE1 and EIEE4 patients progress to WS, which is characterized by tonic spasms with clustering, arrest of psychomotor development, and hypsarrhythmia on EEG (15, 31, 32). The two EIEE1 and EIEE4 Ohtahara variants should be distinguished from the other two forms of EIEE, i.e., the **EIEE2** (also known as X-linked infantile spasms syndrome-2 [ISSSX-2] or Rett syndrome variant with infantile spasms or Rett syndrome with CDKL5 mutations; OMIM # 300672), an X-linked disorder caused by mutation in the CDKL5 gene (OMIM # 300203), and the **EIEE3** (also known as neonatal myoclonic epilepsy with suppression-burst pattern or early myoclonic encephalopathy [EME; OMIM # 609304], caused by mutation in the SLC25A22 gene [OMIM # 609302]).

4. 1.1. Clinical features of Ohtahara syndrome

Age at onset of seizures is in the very early infantile periods. Notably, in one study about 30% of cases first manifested seizures within 10 days of life, whereas in approximately 70% of children by the age of 1 month (42, 43). The main seizure pattern is tonic spasms, which usually appears in clustering. In addition to tonic spasms, partial motor seizures, hemiconvulsions, or generalised tonic seizures can be recorded in about 30% of cases. The daily frequency of seizures remains very high, ranging from around 100-300 episodes in children with isolated seizures, and from 10-20 clusters in individuals with clusters of seizures. Myoclonic seizures are rather rarely recorded.

4.1.2. Interictal EEG findings

The most specific EEG feature is the suppression burst (SB). This pattern is characterised by high voltage bursts of slow waves mixed with multifocal spikes alternating with almost flat (isoelectric) suppression phases at an approximately regular rate. Among the distinguishing features, is the consistent appearance in both waking and sleeping status and regular appearance of periodicity.
Electroencephalographically, the suppression-burst pattern gradually begins to disappear from age 3 months and usually disappears by 6 months, transforming to hypsarrhythmia in most cases from 2-6 months of age, or showing further transition to diffuse slow spike-and-waves or multiple independent spike foci in some other cases at 1 year of age or later (44). Occasionally, some patients can demonstrate a persistent suppression-burst on multiple EEGs.

4.1.3. Brain imaging

The most common structural abnormalities thus far recorded include pachigyria, agyria, hemimegalencephaly, corpus callosum hypo- or a-genesis, dysgenesis of the collicoli, and posterior fossa anomalies. There is also hypo-dysmyelination and diffuse to localised cortical atrophy.

4.2. Clinical features of infantile spasms and WS

The association of infantile spasms (IS) with delay of psychomotor regression and a peculiar type of

EEG called hypsarrhythmia is defined as West syndrome (WS), according to many authorities in this topic (45-48). The incidence of IS ranges from 2-5/10,000 newborns and the prevalence is estimated to be 1-2/10,000 by the 10th year of life. The male-to-female ratio is 6:4 and in 90% of the cases, the clinical manifestation happens within the 1st year of life with a peak between 4 and 6 months.

In general, the IS shows some peculiar aspect concerning the age of onset, characteristic of the spasms, psychomotor delay, and EEG interictal activity, but although these signs and symptoms are an essential part of the syndrome, they nevertheless show a wide range of variability (49).

In the recent new classification of epilepsy, WS has been enclosed in the group of epileptic encephalopathies in which the "epileptiform abnormalities may contribute to progressive cerebral dysfunction" (50).

In most cases, the spasms manifest themselves with sudden muscular contractions of short duration which affect the trunk and extremities in a bilateral and symmetric way and in clusters. In one-third of patients, other types of epileptic crises may occur. The crisis may manifest as flexion, extension, mixed (flexion and extension), symmetric or asymmetric, and an atypical form (eye deviation, nystagmus, and autonomic dysfunction). The great variability of the symptoms put the pediatricians to a severe test to give a prompt diagnosis; for weeks the diagnosis may be delayed and the crisis misdiagnosed as gastrointestinal symptoms (49).

In classical hypsarrhythmia, the basal tracing is chaotic and disorganized; specifically, the slow waves and spikes are asynchronous, not rhythmic in duration and topography, and the spikes may be focal, multifocal, and generalized. In the EEG atypical pattern, frequent interhemispheric synchronizations, a phase of electrodecrement, presence of foci, asymmetry, and a burst suppression may be observed. Recently, hypsarrhythmia has been thought to be a form of non-convulsive status epilepticus (51).

From an etiologic point of view, the IS are distinguished as three different types (secondary, cryptogenetic, and idiopathic). The nature of the idiopathic form has been questioned. According to some researchers, the idiopathic form involves about 10% of all cases of IS; this is the most benign form and almost never associated with severe mental retardation. The cryptogenetic form represents about 20% of the cases of IS; it is presumably an organic involvement of the brain that cannot be detected with current imaging techniques. The secondary form is the most severe form of IS, representing about 70%-80% of the cases.

The most frequent causes of IS are the hypoxic-ischemic encephalopathies. In our large experience with IS, in the last 20 years we have collected > 300 cases of IS. The distribution of IS cases according to the etiologic event is as follows: ischemic hemorrhagic encephalopathies, 52%; infective pre- and post-natal, 12%; cerebral and vascular malformations, 18%; neurometabolic and toxic, 8%; hemorrhagic post-natal and traumatic, 5%; and miscellaneous, 5%.

Familial cases of IS have been reported. In the past, one of us (L.P.) reported IS in male monozygotic twins. The onset occurred at the same time in both of the twins when they were 6 months of age. Both twins showed on a TC scan, areas of low density in the right frontoparietal region, which resolved in both twins 8 months later. At follow-up, these children showed a quite good outcome, both with respect to epilepsy and mental retardation (52).

According to a recent study by Hemminki IS have the highest risk for any subtype (10%) when a co-sibling is diagnosed with any form of epilepsy (53).

In the field of neurocutaneous syndromes, IS is very well-represented. This is particularly true with respect to tuberous sclerosis, in which the chances of children having IS is very high and is reported to be > 50% of the patients with different types of seizures. In our experience, in neurofibromatosis type 1, Sturge-Weber syndrome, and epidermal nevus syndrome the chances of IS are higher than the general population, but they represent an unusual event (54).

The major concern of IS is to know the pathophysiology of the crisis in association with the EEG hypsarrhythmic pattern. In particular, it is difficult to establish for what reason an infant with severe perinatal damage manifests IS plus hypsarrhythmia and another infant with similar brain damage presents with tonic and/or clonic seizures, but no hypsarrhythmic pattern.

Price developed the first genetic mouse model of ISS that spontaneously recapitulates salient phenotypic features of the human triplet repeat expansion mutation (55). In this animal model Arx((GCG)10+7) ("Arx plus 7") pups displayed abnormal spasm-like myoclonus and other key EEG features, including multifocal spikes, electrodecremental episodes, and spontaneous seizures persisting into maturity. The neurobehavioral profile of Arx mutants was remarkable for lowered anxiety, impaired associative learning, and abnormal social interaction. Laminar decreases of Arx+ cortical interneurons and a selective reduction of calbindin-, but not parvalbumin- or calretinin-expressing interneurons in neocortical layers and hippocampus indicated that specific classes of synaptic inhibition were missing from the adult forebrain, providing a basis for the seizures and cognitive disorder (55). A significant reduction of calbindin-, NPY (neuropeptide Y)-expressing, and cholinergic interneurons in the mutant striatum suggested that dysinhibition within this network may contribute to the dyskinetic motor spasms (55).

Additional models have been developed by Marsh who developed an Arx(-/y);Dlx5/6(CIG) (male) mice exhibiting a variety of seizure types beginning in early-life, including seizures that behaviourally and

electroencephalographically resembled infantile spasms, and showed evolution through development (56).

4.3. Partington (X-linked) mental retardation syndrome

Partington (X-linked) mental retardation syndrome (**PRTS**; also known as Partington X-linked mental retardation syndromic 1 [**MRXS1**] or X-linked mental retardation with dystonic movements, ataxia, and seizures; OMIM # 309510]) which is caused by 24-bp duplication, resulting in a polyA repeat expansion of the ARX gene (37). Clinically, PRTS patients have intellectual impairment, long triangular faces, focal hand dystonia, and EEG abnormalities with seizures; other variable features include dysarthria, lower limb spasticity/foot dystonia, enlargement of the testes, and subarachnoid cysts (57).

4.4. Non-specific X-linked mental retardation

Non-specific X-linked mental retardation (**MRX54**; including **MRX36**, **MRX43,** and **MRX87**; OMIM # 300419), which is a non-specific form of mental retardation with normal physical and neurologic findings; affected individuals show a variable range of intelligence in the low to normal range, possibly as a result of a heterozygous carrier status, or delayed psychomotor development (40, 58).

4.5. X-linked lissencephaly with abnormal genitalia

X-linked lissencephaly with abnormal genitalia (**XLAG**; also known as X-linked lissencephaly type 2 [**LISX2] or** ARX-related lissencephaly [ILS or SBH] or lissencephaly variant 3-layers; OMIM # 300215); the XLAG appears to be a separate type of lissencephaly (18, 29, 33, 59).

Lissencephaly is defined as a smooth or nearly smooth cerebral surface with anomalous development of cerebral gyri (60-63). The anomaly encompasses a spectrum of different malformations: from the absence of agyria or complete lissencephaly, to few, broad, flat gyri (pachygyria, incomplete lissencephaly), and merges in the subcortical band heterotopia (60.,61).

To date, mutations of six genes have been associated with lissencephaly, including LIS1, DCX, TUNA1A, RELN, VLDLR, and ARX, whereas co-deletion of YWHAE with LIS1 appears to act as a modifier locus.

Following a recent classification (64), these clinical phenotypes (also including the forms thus far unclassified and the forms caused by yet unknown genes or with an unknown pathogenesis) have been tentatively re-classified in broad clinical groups identified according to the gradient and size of the anomalies of cerebral stratification and the involvement of the following associated extracerebral structures: (a) gradient anterior versus posterior; (b) brain size; and (c) involvement of other structures beyond the brain. Classifications in this topic are always in progress since new forms and molecular data are frequently reported in the literature.

All XLAG patients to date have been genotypic males, and all have had normal head size at birth with severe microcephaly developing over the first months of life, intractable neonatal onset epilepsy, poor temperature regulation, chronic diarrhoea, and ambiguous and underdeveloped genitalia. Related females may have mental retardation and epilepsy, and in such cases often have agenesis of the corpus callosum. Imaging studies show anterior pachigyria, with only a few, shallow, sulci, and posterior agyria. The cerebral cortex is usually thicker than normal (6-7 mm in thickness), but is thin compared to that observed in lissencephaly secondary to LIS1 and DCX mutations. The corpus callosum is always completely absent and the basal ganglia are either small or dysplastic or completely absent. The brainstem and cerebellum are normal. The XLAG spectrum includes the so-called hydranencephaly with abnormal genitalia (OMIM # 300215).

4.6. Proud syndrome

Proud syndrome (also known as corpus callosum agenesis [**ACC**; and abnormal basal ganglia] with abnormal genitalia; OMIM # 300004), which has been reported in female stillbirths; manifestations in the surviving males include severe acquired microcephaly (with micrencephaly), mental retardation, limb contractures (spastic quadriplegia), scoliosis, tapered fingers with hyperconvex nails, a characteristic face with large eyes, prominent supraorbital ridges, synophrys, optic atrophy, broad alveolar ridges, seizures, renal dysplasia, cryptorchidism, and hypospadias (65).

4.7. X-linked mental retardation and epilepsy with combination of infantile spasms and non-ictal complex dyskinetic movements,

X-linked mental retardation and epilepsy with combination of infantile spasms and non-ictal complex dyskinetic movements, caused by expansion of the trinucleotide repeat in the ARX gene; this phenotype has been recorded thus far in the following: (a) 5.2% of 115 boys with familial cryptogenic infantile spasms, 2-14 years of age, who had severe mental retardation and generalized dystonia that appeared around the age of 6 months and worsened, eventually leading to stable severe quadriplegic dyskinesia by 2 years of age with or without recurrent, life-threatening status dystonicus and brain MRI appearance of multiple small foci of abnormal cavitations on T1 and increased signal intensity on T2 in the putamina (39); and (b) a 4-year-old boy who had sub-clinical spasms at 2 months of age consisting of episodes of eye rolling combined with atypical hypsarrhythmia, later evolving into severe mental retardation with polymorphic ictal episodes that consisted of nocturnal brief axial contractions followed by dyskinetic movement of all four limbs and diurnal clusters of chaotic movements combined with myoclonic jerks (16). Additional families have been reported by Shinozaki (66)).

4.8. Parietal foramina-2 syndrome

Parietal foramina-2 syndrome (**PFM-2**; OMIM # 609957) is characterized by symmetric, oval defects in the parietal bone situated on each side of the sagittal suture and separated from each other by a narrow bridge of bone. The size of the openings decrease with age and considerable

intrafamilial variability is observed. PFM-2 is caused by a mutation in the aristaless-like 4 (ALX4) gene (OMIM # 605420). From a genetic viewpoint, PFM-2 syndrome must be distinguished from **PFM-1**, which is caused by a mutation in the MSX2 gene (OMIM # 123101) on chromosome 5q. Parietal foramina also occur as part of the Potocki-Shaffer syndrome (OMIM # 601224), a contiguous gene syndrome caused by a deletion on chromosome 11p11.2 that includes the ALX4 gene. Little suggested that hereditary cranium bifidum is the same entity as symmetric parietal foramina (67).

The striking finding concerning ARX is the phenotypic heterogeneity associated with the most frequent and recurrent mutations (identified in > 5% of **XLMR** families); e.g., the in-frame 24-bp duplication (c.428_451dup24), which expands the normal 12-polyalanine tract to 20 (amino acids, 144-155) and the 21-bp insertion expanding the 16-polyalanine tract to 23 (amino acids, 100 to 115). These mutations have been associated with almost all the aforementioned phenotypes except for those associated with brain malformations (e.g., XLAG). One hypothesis for such clinical heterogeneity is the difference in genetic and environmental backgrounds that is specific to each family; an alternative hypothesis is that the polyA tract expansions at either position can result in a highly variable disease phenotype. Even with respect to mental retardation, a great deal of variability has been reported, with intellectual impairment ranging from mild-to-severe.

Additional families have been reported with severely affected males harbouring dup mutation of 27 bp, c.430_456dup(27 bp), which involves the same region of the ARX gene in exon 2, as the dup24 bp mutation: affected members in these families had infantile spasms and some of them died in early infancy (68). These phenotypes appeared more severe, when compared to the spectrum of clinical presentations associated with the dup24 bp mutation: such phenomenon was partly explained by the single, extra alanine residue (A) (21A in dup27 vs. 20A in dup24), which takes polyalanine tract 2 of ARX beyond the maximum, naturally occurring limit of 20A found in the human menome (68).

Demos reported on a novel pathogenic variant of a tandem 33 bp duplication which (likely) resulted in an expansion of polyalanine tract 2 in two brothers with mental retardation, epilepsy, dystonia, and the novel feature of intermittent hyperventilation. This pathogenic variation resulted in a "non-homogeneous" polyalanine tract expansion that is longer than predicted expansion caused by the common 24 bp duplication. The location of the novel 33 bp duplication in the same region as the common 24 bp duplication supports this region as the ARX variation "hot spot" (69).

5. ADDITIONAL EFFECTS OF ARX MUTATIONS - ARX VS. STXBP1 GENE: MUTUAL TRANSITION/EVOLUTION OF OHTAHARA SYNDROME INTO OTHER EARLY INFANTILE EPILEPTIC ENCEPHALOPATHIES (EIEE)

Ohtahara syndrome is one type, the earliest form, of the spectrum of age-dependent epileptic encephalopathies, along with WS and Lennox-Gastaut syndrome (LGS). The term “epileptic encephalopathy” characterizes epileptic syndromes with the following features: (a) the presence of serious underlying disorders; (b) extremely frequent seizures; (c) continuously and diffusely appearing marked epileptic abnormalities; and (d) mental deterioration often manifesting with the presence of seizures. Mutual transition among these syndromes is interesting and important. Approximately 75% of children with Ohtahara syndrome transform into WS with age development; these cases consist of about 3% of the cases of WS. The evolution to WS usually occurs after the age of 3-4 months. In late infancy, approximately 60% of WS evolves into LGS and 35% of LGS patients have a history of WS. These findings should strongly suggest the close relationship among these syndromes supporting the inclusive concept of the age-dependent epileptic encephalopathy.

5.1. Role of ARX gene

Consistent with the idea of mutual transition between Ohtahara syndrome, WS, and LGS, specific mutations of the ARX gene at Xp22.13 have been found in male subjects with EIEE and cryptogenic infantile spasms of the WS type. In most EIEE cases, however, no ARX mutations have been found. The severe seizures associated with less severe mutations of the ARX gene (i.e., cryptogenic infantile spasms) are presumably related to a severe deficiency of inhibitory interneurons, even though brain imaging is normal. The intractable seizures associated with more severe mutations of the gene (i.e., lissencephaly or EIEE and WS) are likely related to severe impairment of interneurons with abnormal brain imaging.

5.2. Role of Stxbp1 gene

Recently, unrelated children with EIEE have been found to harbour heterozygous missense mutations in the Stxbp1 gene, which is a gene encoding the syntaxin binding protein 1 (STXBP1; also known as MUNC18-1), a protein essential for regulating synaptic vesicle release, at least in part, by binding to syntaxin 1A (Stx1a), as well to the SNARE complex directly. STBXP1 binds to Stx1a in two different ways (binding to a closed form of Stx1a and binding to the N-terminus of an open form of Stx1a compatible with SNARE complex formation). The interaction with the N-terminus of open form Stx1a is important in synaptic vesicle release, whereas interaction with the closed form Stx1a is involved in synaptic vesicle docking. Thus, STBXP1 acts as a regulator of the synaptic vesicular machinery and ultimately regulates the kinetics of neurotransmitter release during priming of synaptic vesicles. An additional pathogenic mechanism, related to impairment of Stbxp1, to explain the spectrum of clinical and bioelectrical abnormalities seen in EIEE is the extensive cell death observed in Stbxp1 null mice; this extensive death occurs first in lower brain areas (lower brainstem areas) which are the site of origins of tonic seizures in EIEE; the delayed myelination or hypomyelination seen in some EIEE subjects could be also explained by impaired cortico-subcortical (e.g., brainstem) connections.

6. CONCLUDING REMARKS

Clearly, the ARX gene has an important role in the development of the nervous system, acting as a specific regulator in each step of neurogenesis. The relatively recent discovery of the ARX family of genes along with their most frequent mutations, such as ARXdup24, and the related studies concerning the functional consequences of the mutated structure of the ARX protein have opened new horizons, but at the same time raised several queries.

The hydrophobicity of polyA_II domain could alter the secondary structure of this portion of the ARX protein, which could switch from an alpha-helix structure to a beta-sheet. As a consequence of that, the mutated protein could assume an altered configuration which could compromise its function as a transcription factor, as occurs in several human diseases (e.g., poliQ expansion disorders) with expansions of DNA triplets, which are associated with the formation of nuclear aggregates and the increase in cellular mortality. In this latter regard, however, it is notable that in mentally retarded patients harbouring ARXdup24 mutations, there is no pathologic evidence of neuronal degeneration. Some studies are currently running on ARX-related polyA_II phenotypes, aimed to define the presence and extent of nuclear and/or cytoplasm aggregates eventually leading to an increase in cellular mortality.

Many issues still need to be clarified in the ARX-related "universe," such as the role of the ARX gene in determining neurologic abnormalities. It would be of outmost importance, clinically, to establish whether the molecular defect alone could cause a given cerebral abnormality and/or malformation or an additional or related molecular or environmental event could contribute to a given phenotype in molecularly predisposed individuals. Much work is still in need of completion, even though the progress is relentless.

7. ACKNOWLEDGEMENTS

We wish to thank the "International Science Editing", Shannon, Ireland, UK (http://www.internationalscienceediting.com) for editing the final draft of the present manuscript

8. REFERENCES

1. K. Schneitz, P. Spielmann, M. Noll: Molecular genetics of Aristaless, a prd-type homeo box gene involved in the morphogenesis of proximal and distal pattern elements in a subset of appendages in Drosophila. Genes Dev 7, 114-129 (1993)

2. E.E. Ruppert, R.S. Fox, R.D. Barnes: Invertebrates zoology: a functional evolutionary approach 7th ed. Eds: Brooks Cole, NY (2003)

3. T. Kojima, T. Tsuji, K. Saigo: A concerted action of a paired-type homeobox gene, aristaless, and a homolog of Hox11/tlx homeobox gene, clawless, is essential for the distal tip development of the Drosophila leg. Dev Biol 279, 434-45 (2005)

4. G. Campbell, A. Tomlinson: The roles of the homeobox genes aristaless and Distal-less in patterning the legs and wings of Drosophila. Development 125, 4483-9 (1998)

5. J. Gécz, D. Cloosterman, M. Partington: ARX: a gene for all seasons. Curr Opin Genet Dev 16, 308-16 (2006)

6. I. Cobos, V. Broccoli, JL. Rubenstein: The vertebrate ortholog of Aristaless is regulated by Dlx genes in the developing forebrain. J Comp Neurol 483, 292-303 (2005)

7. CT. Fulp, G. Cho, ED. Marsh, IM. Nasrallah, PA. Labosky, JA. Golden: Identification of Arx transcriptional targets in the developing basal forebrain. Hum Mol Genet Sep 16 (Epub ahead of print) (2008)

8. P. Strømme, ME. Mangelsdorf, MA. Shaw, KM. Lower, SM. Lewis, H. Bruyere, V. Lütcherath, AK Gedeon, RH. Wallace, IE.Scheffer, G. Turner, M. Partington, SG. Frints, JP. Fryns, GR. Sutherland, JC. Mulley, J .Gécz: Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy. Nat Genet 30, 441-5 (2002 a)

9. P. Strømme, ME. Mangelsdorf, IE. Scheffer, J.Gécz: Infantile spasms, dystonia, and other X-linked phenotypes caused by mutations in Aristaless related homeobox gene, ARX. Brain Dev 24,266-8 (2002 b)

10 C. Laperuta, L. Spizzichino, P. D'Adamo, J. Monfregola, A. Maiorino, A. D'Eustacchio, V. Ventruto, G. Neri, M. D'Urso, P. Chiurazzi, MV. Ursini, MG. Miano: MRX87 family with Aristaless X dup24bp mutation and implication for polyAlanine expansions. BMC Med Genet 8, 25 (2007)

11. C. Shoubridge, D. Cloosterman, E. Parkinson-Lawerence, D. Brooks, J. Gécz: Molecular pathology of expanded polyalanine tract mutations in the Aristaless-related homeobox gene. Genomics 90, 59-71 (2007)

12. K. Kitamura, Y. Itou, M. Yanazawa, M. Ohsawa, R. Suzuki-Migishima, Y. Umeki, H. Hohjoh, Y. Yanagawa, T . Shinba, M. Itoh, K. Nakamura, YI. Goto: Three human ARX mutations cause the lissencephaly-like and mental retardation with epilepsy-like pleiotropic phenotypes in mice. Hum Mol Genet Jul 15 (Epub ahead of print) (2009)

13. H. Miura, M. Yanazawa, K. Kato, K. Kitamura: Expression of a novel aristaless related homeobox gene 'Arx' in the vertebrate telencephalon, diencephalon and floor plate. Mech Dev 65,99-109 (1997)

14. LJ. McCormick, JA. Hutt, J. Hazan, C. Houart, J. Cohen: The homeodomain transcription factor drg11 is expressed in primary sensory neurons and their putative CNS targets during embryonic development of the zebrafish. Gene Expr Patterns 7, 289-96 (2007)

15. O. McKenzie, I. Ponte, M. Mangelsdorf, M. Finnis, G. Colasante, C. Shoubridge, S. Stifani, J. Gécz, V. Broccoli:

Aristaless-related homeobox gene, the gene responsible for West syndrome and related disorders, is a Groucho/transducin-like enhancer of split dependent transcriptional repressor. Neuroscience 146, 236-47 (2007)

16. K. Poirier, H. Van Esch, G. Friocourt, Y. Saillour, N. Bahi, S. Backer, E. Souil, L. Castelnau-Ptakhine, C. Beldjord, F. Francis, T. Bienvenu, J .Chelly: Neuroanatomical distribution of ARX in brain and its localisation in GABAergic neurons. Brain Res Mol Brain Res 122, 35-46 (2004)

17. P. Collombat, J. Hecksher-Sørensen, J. Krull, J. Berger, D. Riedel, PL. Herrera, P. Serup, A. Mansouri: Embryonic endocrine pancreas and mature beta cells acquire alpha and PP cell phenotypes upon Arx misexpression. J Clin Invest 117, 961-70 (2007)

18. S. Okazaki, M. Ohsawa, I. Kuki, H. Kawawaki, T. Koriyama, S. Ri, H. Ichiba, E Hai, T. Inoue, H. Nakamura, Y.Goto, K. Tomiwa, T. Yamano, K. Kitamura, M. Itoh: Aristaless-related homeobox gene disruption leads to abnormal distribution of GABAergic interneurons in human neocortex: evidence based on a case of X-linked lissencephaly with abnormal genitalia (XLAG). Acta Neuropathol 116,453-62 (2008)

19. J-M. Mingot; S. Kostka, R.Kraft, E.Hartmann, D. Gorlich,: Importin 13: a novel mediator of nuclear import and export. EMBO J 20,3685-3694 (2001)

20. G. Friocourt, K. Poirier, S. Rakić, JG. Parnavelas, J. Chell: The role of ARX in cortical development. Eur J Neurosi 23, 869-76 (2006).

21. G. Friocourt, S. Kanatani, H. Tabata, M. Yozu, T. Takahashi, M. Antypa, O. Raguénès, J. Chelly, C. Férec, K. Nakajima, JG. Parnavelas: Cell-autonomous roles of ARX in cell proliferation and neuronal migration during corticogenesis. J Neurosi 28, 5794-805 (2008).

22. G. Colasante, P. Collombat, V. Raimondi, D. Bonanomi, C. Ferrai, M. Maira, K. Yoshikawa, A. Mansouri, F. Valtorta, JL. Rubenstein, V. Broccoli: Arx is a direct target of Dlx2 and thereby contributes to the tangential migration of GABAergic interneurons. J Neurosci 28,10674-86 (2008)

23. G. Colasante, A. Sessa, S. Crispi, R. Calogero, GG. Consalez, A. Mansouri, P. Collombat, V. Broccoli: Arx acts as a regional key selector gene in the ventral telencephalon mainly through its transcriptional repression activity. Dev Biol Jul 20 (Epub ahead of print) (2009)

24. T. Bienvenu, K. Poirier, G. Friocourt, N. Bahi, D. Beaumont, F. Fauchereau, L. Ben Jeema, R. Zemni, MC. Vinet, F. Francis, P. Couvert, M. Gomot, C.Moraine, H. van Bokhoven, V. Kalscheuer, S. Frints, J. Gecz, K. Ohzaki, H. Chaabouni, JP. Fryns, V. Desportes, C. Beldjord, J. Chelly: ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. Hum Mol Genet 11, 981-91 (2002)

25. IE. Scheffer, RH. Wallace, FL. Phillips, P. Hewson, K. Reardon, G. Parasivam, P. Stromme, SF. Berkovic, J. Gecz, JC. Mulley: X-linked myoclonic epilepsy with spasticity and intellectual disability: mutation in the homeobox gene ARX. Neurology 59, 348-56 (2002).

26. S. Hirose, A. Mitsudome: X-linked mental retardation and epilepsy: pathogenetic significance of ARX mutations. Brain Dev 25, 161-5 (2003)

27. VM. Kalscheuer, J. Tao, A. Donnelly, G. Hollway, E. Schwinger, S. Kübart, C. Menzel, M. Hoeltzenbein, N. Tommerup, H. Eyre, M. Harbord, E. Haan, GR. Sutherland, HH. Ropers, J. Gécz: Disruption of the serine/threonine kinase 9 gene causes severe X-linked infantile spasms and mental retardation. Am J Hum Genet 72, 1401-11 (2003)

28. EH. Sherr: The ARX story (epilepsy, mental retardation, autism, and cerebral malformations): one gene leads to many phenotypes. Curr Opin Pediatr 15, 567-71 (2003)

29. G. Uyanik, L. Aigner, P. Martin, C. Gross, D. Neumann, H. Marschner-Schäfer, U. Hehr, J. Winkler: ARX mutations in X-linked lissencephaly with abnormal genitalia. Neurology 61, 232-5 (2003).

30. M. Kato, S. Das, K. Petras, K. Kitamura, K. Morohashi, DN. Abuelo, M. Barr, D. Bonneau, AF. Brady, NJ. Carpenter, KL. Cipero, F. Frisone, T. Fukuda, R. Guerrini, E. Iida, M. Itoh, AF. Lewanda, Y. Nanba, A. Oka, VK. Proud, P. Saugier-Veber, SL. A. Schelley, Selicorni, R. Shaner, M. Silengo, F. Stewart, N. Sugiyama, J. Toyama, A. Toutain, AL. Vargas, M. Yanazawa, EH. Zackai, WB. Dobyns: Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Hum Mutat 23, 147-59 (2004)

31. M. Kato: A new paradigm for West syndrome based on molecular and cell biology. Epilepsy Res 70 Suppl 1, S87-95 (2006)

32. M. Kato, S. Saitoh, A. Kamei, H. Shiraishi, Y. Ueda, M. Akasaka, J.Tohyama, N.Akasaka, K. Hayasaka: A longer polyalanine expansion mutation in the ARX gene causes early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome). Am. J. Hum. Genet. 81, 361-366 (2007)

33. K. Kitamura, M. Yanazawa, N. Sugiyama, H. Miura, A. Iizuka-Kogo, M. Kusaka, K. Omichi, R. Suzuki, Y. Kato-Fukui, K. Kamiirisa, M. Matsuo, S. Kamijo, M. Kasahara, H. Yoshioka, T. Ogata, T. Fukuda, I. Kondo, M. Kato, WB. Dobyns, M. Yokoyama, K. Morohashi: Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans.Nat Genet 32, 359-69 (2002).

34. H. Hartmann, G. Uyanik, C. Gross, U. Hehr, T. Lücke, M. Arslan-Kirchner, B. Antosch, AM. Das, J.Winkler: Agenesis of the corpus callosum, abnormal genitalia and

intractable epilepsy due to a novel familial mutation in the Aristaless-related homeobox gene. Neuropediatrics 35,157-60 (2004)

35. G. Wohlrab, G. Uyanik, C. Gross, U. Hehr, J. Winkler, B. Schmitt, E. Boltshauser: Familial West syndrome and dystonia caused by an Aristaless related homeobox gene mutation. Eur J Pediatr 164, 326-8 (2005)

36. ML. Stepp, AL. Cason, M. Finnis, M. Mangelsdorf, E. Holinski-Feder, D. Macgregor, A. MacMillan, JJ. Holden, J. Gecz, RE. Stevenson, CE. Schwartz: XLMR in MRX families 29, 32, 33 and 38 results from the dup24 mutation in the ARX (Aristaless related homeobox) gene. BMC Med Genet 6,16 (2005)

37. K. Szczaluba, M. Nawara, K. Poirier, J. Pilch, M. Gajdulewicz, K. Spodar, J. Chelly, J. Bal, T. Mazurczak: Genotype-phenotype associations for ARX gene duplication in X-linked mental retardation. Neurology 67, 2073-2075 (2006)

38. P. Chaste, G. Nygren, H. Anckarsäter, M. Rastam, M. Coleman, M. Leboyer, C. Gillberg, C. Betancur: Mutation screening of the ARX gene in patients with autism. Am J Med Genet B Neuropsychiatr Genet 144B, 228-30 (2007).

39. R. Guerrini, F. Moro, M. Kato, AJ. Barkovich, T. Shiihara, MA. McShane, J. Hurst, M. Loi, J. Tohyama, V. Norci, K. Hayasaka, UJ. Kang, S. Das, WB. Dobyns: Expansion of the first PolyA tract of ARX causes infantile spasms and status dystonicus. Neurology 69, 427-33 (2007)

40. MM. Troester, T. Trachtenberg, V. Narayanan: A novel mutation of the ARX gene in a male with nonsyndromic mental retardation. J Child Neurol 22, 744-8 (2007)

41. S. Ohtahara, T. Ispida, E. Oka, Y. Yamatogi, H. Inoue, S. Kanda: On the specific age-dependent epileptic syndrome: the early-infantile epileptic encephalopathy with suppression bursts. No Ho Hattatsu 8, 270-280 (1976)

42. S. Ohtahara, Y. Yamatogi: Ohtahara syndrome: with special reference to its developmental aspects for differentiating from early myoclonic encephalopathy. Epilepsy Res 70 (Suppl 1), S58-67 (2006)

43. H. Saitsu, M. Kato, T. Mizuguchi, K. Hamada, H. Osaka, J. Tohyama, K. Uruno, S. Kumada, K. Nishiyama, A. Nishimura, I. Okada, Y. Yoshimura, S. Hirai, T. Kumada, K. Hayasaka, A. Fukuda, K. Ogata, N. Matsumoto: De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet 40, 782-8 (2008)

44. L. Fusco, C. Pachatz, M. Di Capua, F. Vigevano: Video/EEG aspects of early-infantile epileptic encephalopathy with suppression-bursts (Ohtahara syndrome). Brain Dev 23, 708-14 (2001)

45. D. Friedman, AD. Rothner, M. Estes, R. Cruse, G. Erenberg., E. Wyllie: Characterisation of seizures in an hospitalised population of persons with neurofibromatosis. Epilepsia 30, 670-671 (1989)

46. S. Wallace: Epilepsy in children. Chapman and Hall, London. (2005)

47. A. Lux, J. Osborne: A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. Epilepsia 45, 1416-28 (2004)

48. A. Lux, J. Osborne: The influence of etiology upon ictal semiology, treatment decisions and long-term outcome in infantile spasms and West syndrome. Epilepsy Res 70S, S77-S86 (2006)

49. I. Desguerre, R. Nabbout, O. Dulac: The management of infantile spasms. Arch Dis Child 93, 462-463 (2008)

50. Commission of Classification and Terminology of the International League Against Epilepsy Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 30, 389-399 (1989)

51. AL. Lux: Is hypsarrhythmia a form of non-convulsive status epilepticus in infants? Acta Neurol Scand 115 (Suppl 186), 37-44 (2007)

52. L. Pavone, F. Mollica, G. Incorpora, G. Pampiglione: Infantile spasms syndrome in monozygotic twins. Arch Dis Child 55, 870–872 (1980)

53. K. Hemminki, X. Li, S.E. Johansson, K. Sundquist, J. Sundquist: Familial risks for epilepsy among siblings based on hospitalisation in Sweden. Neuroepidemiology 27, 67-73 (2006) .

54. M. Ruggieri, I. Pascual-Castroviejo, C. Di Rocco: Neurocutaneous Disorders. Phakomatoses and Hamartoneoplastic Syndromes. Springer Velag, New York/Wien (2008)

55. MG. Price, JW. Yoo, DL. Burgess, F. Deng, RA. Hrachovy, JD Jr Frost, JL. Noebels: A triplet repeat expansion genetic mouse model of infantile spasms syndrome, Arx (GCG)10+7, with interneuronopathy, spasms in infancy, persistent seizures, and adult cognitive and behavioral impairment. J Neurosci 29, 8752-63 (2009).

56. E. Marsh, C. Fulp, E. Gomez, I. Nasrallah, J. Minarcik, J. Sudi, SL. Christian, G. Mancini, P. Labosky, W. Dobyns, A. Brooks-Kayal, JA. Golden: Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. Brain 132,1563-76 (2009)

57. MW. Partington, JC. Mulley, GR. Sutherland, A. Hockey, A. Thode, G. Turner: X-linked mental retardation with dystonic movements of the hands. Am J Med Genet 30, 251-262 (1988)

58. S. Rujirabanjerd, K. Tongsippunyoo, T. Sripo, P. Limprasert: Mutation screening of the Aristaless-related homeobox (ARX) gene in Thai pediatric patients with delayed development: first report from Thailand. Eur J Med Genet 50, 346-54 (2007)

59. WB. Dobyns, E. Berry-Kravis, NJ. Havernick, KR. Holden, D. Viskochil: X-linked lissencephaly with absent corpus callosum and ambiguous genitalia. Am J Med Genet 86, 331-337 (1999)

60. AJ. Barkovich, TK. Koch, CL. Carrol: The spectrum of lissencephaly: Report of ten patients analyzed by magnetic resonance imaging. Ann Neurol 30,139–146 (1991).

61. WB. Dobyns, CL. Truwit: Lissencephaly and other malformations of cortical development: 1995 update. Neuropediatrics 26, 132–147 (1995)

62. V. Des Portes, JM. Pinard, P. Billuart, MC. Vinet, A. Koulakoff, A. Carrie, A. Gelot, E. Dupuis, J. Motte, Y. Berwald-Netter, M. Catala, A. Kahn, C. Beldjord, J. Chelly: A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell 92,51-61 (1998).

63. WB. Dobyns, RJ. Levenker: Lissencephaly: the clinical and molecular genetic basis of diffuse malformations of neuronal migration. In: Barth PG (ed.) Disorders of neuronal migration. Eds: Mac Keith Press - International Review of Child Neurology, London:, (2003)

64. R. Guerrini, WB. Dobyns, AJ. Barkovich: Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options”**.** Trends Neurosci 31, 154-62 (2008).

65. VK. Proud, C. Levine, NJ. Carpenter: New X-linked syndrome with seizures, acquired micrencephaly, and agenesis of the corpus callosum. Am J Med Genet 43, 458-466 (1992)

66. Y. Shinozaki, M. Osawa, H. Sakuma, H. Komaki, E. Nakagawa, K. Sugai, M. Sasaki, Y. Goto: Expansion of the first polyalanine tract of the ARX gene in a boy presenting with generalized dystonia in the absence of infantile spasms. Brain Dev 31, 469-72 (2009).

67. BB. Little, KA. Knoll, VR. Klein, KB. Heller: Hereditary cranium bifidum and symmetric parietal foramina are the same entity. Am J Med Genet 35, 453-458 (1990)

68. O. Reish, T. Fullston, M. Regev, E. Heyman, J. Gecz: A novel de novo 27 bp duplication of the ARX gene, resulting from postzygotic mosaicism and leading to three severely affected males in two generations. Am J Med Genet A 149A, 1655-60 (2009)

69. MK. Demos, T. Fullston, MW. Partington, J. Gécz, WT. Gibson: Clinical study of two brothers with a novel 33 bp duplication in the ARX gene. Am J Med Genet A 149A, 1482-6 (2009)

Key Words*:* ARX; Aristaless gene; Interneuronopathies; West Syndrome; XLAG, Review

Send correspondence to: Martino Ruggieri, Institute of Neurological Science, National Research Council, Via Paolo Gaifami, 18, 95125, Catania, Italy, Tel: 39 095 7338107, Fax: 39 095 7338110, E-mail: m.ruggieri@isn.cnr.it

http://www.bioscience.org/current/vol2E.htm