ARX: A Small Gene with a Crucial Role in X-Linked Intellectual Disability

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Received June 24, 2019; Accepted July 03, 2019; Published April 07, 2020

ABSTRACT

Intellectual disability is the most common neurodevelopmental defect in the world. This disorder affects 1-3% of the general population. X-linked intellectual disability (XLID) is the frequent form of intellectual disability which includes a heterogeneous group of inherited disorders emerging as various degrees of intellectual disabilities. Phenotypically, XLID is subdivided into syndromic (S-XLID) and non-syndromic (NS-XLID) forms; where two-thirds of the XLID cases are thought to be non-syndromic. Among the non-syndromic form, the aristaless-related homeobox gene (ARX) is one of the ideal candidates to be evaluated in NS-XLID, since its mutations are responsible for about 9.5% of XLID cases. Based on the previous literature, mutations in the ARX gene influence the critical processes associated with brain development. Our bioinformatics results showed that the ARX is a highly conserved protein with a substantial role in an important developmental pathway; and its deficiency can cause irreversible defects, mainly in the brain, that leads to the development of XLID. Moreover, we addressed the structural properties of the ARX protein to decipher the important role of the ARX gene in the integrity of normal brain development.

Keywords: ARX, X-linked intellectual disability, Protein structure, Wnt/β-catenin signaling

INTRODUCTION

Intellectual disability (ID) is the most frequent neurodevelopmental disorder in the world characterized by an intelligence quotient (IQ) below 70 [1]. The prevalence of ID is approximately 2-3% in the general population [2-8]. ID or associated phenotypes resulted from a monogenic defect are subdivided into 4 categories according to the mode of inheritance, autosomal dominant ID, autosomal recessive ID, X-linked ID and mitochondrial ID [9-13]. Mutations in X-linked genes account for 5-10% of all types of ID and are the most likely causes of ID in males [14].

ARX GENE: STRUCTURE AND FUNCTION

The Aristaless-related homeobox gene (ARX) is located on the Xp22.13. It consists of 5 exons (Figure 1) and is transcribed into 2.8 kb mRNA. The structure of the ARX protein consists of several different compartments, including [15-18]: 1) A highly conserved homeobox domain (repressor domain) that spans the amino acids from 328 to 387. This domain directly binds to DNA [19]; 2) C-terminal OAR or aristaless domain (activator domain) which spans the amino acids from 530 to 543 of protein (Figure 1) [20]; 3) Octapeptid domain which is a receptor site beside the N-terminal of the ARX protein for some enhancer proteins that contribute to ARX functional activity adjustments [21]; 4) Four polyalanine tracts which are located between hundredth-degree amino acids and 115, 144 and 155, 278 and 281, also 432 and 440, that each one has 16, 12, 7 and 9 residues, respectively [22-24]. It was determined that the ARX gene is evolutionary conserved in different species and according to Figure 2; it has a high local similarity to its target binding sites. Also, the sequence alignment of this protein with other species (Figure 3) confirms that the functional domains of ARX protein are highly conserved, thus it has been predicted that mutations of this gene can be highly pathogenic [25-35].

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Figure 1. Schematic representation of the ARX gene and its exons. The protein domains and important functional regions of ARX including octapeptide domain (OP), nuclear localization signals (NLS), poly-alanine expansion repeats (PA), Acidic domain (Acidic), prd-like homeodomain (prd-like HD) and Aristaless domain/C-peptide (AR) are depicted [36].

Figure 2. A) Quaternary structure assembly of the hetero-tetrameric ARX protein. B) Four subunits of 4 distinct polymer entities.

Figure 3. The phylogenetic tree of ARX protein (The comparison between Homo sapiens ARX protein and 10 other species).

**ARX AND THE FREQUENCY OF ITS MUTATIONS**

According to European XLID consortium, mutations of ARX gene has been found in 9.5% of families with X-linked intellectual disability and 7.5% of large families with 2 or more affected males from multi-generations that are related with each other through an obligate carrier female [21,36-38].

**ARX-ASSOCIATED PHENOTYPES**

ARX incapacitate mutations through exons and introns and subsequently different domains, are associated with a wide spectrum of phenotypes ranging from severe developmental abnormalities of the brain to syndromic forms of XLID. Early infantile epileptic encephalopathy-type1 (OMIM#308350); Lissencephaly-type2 (OMIM#300215); Hydranencephaly with abnormal genitalia (OMIM#300215);
Proud Syndrome (OMIM#300004); Partington Syndrome (OMIM#300510); X-linked Mental retardation and ARX-related (OMIM#300419) are the known various syndromic phenotypes associated with ARX mutations [39-43]. Nonetheless, how different mutations in this single transcription factor can produce different phenotypes is not completely understood.

During the recent theory of Il-Taeg Cho et al. [44], the ARX gene has interaction with different cofactors/transcription factors and regulates single target genes in different cell types. According to Il-Taeg Cho’s study, by using the proteomics method, it was determined that the Wnt/β-catenin signaling pathway includes three components such as B-cell CLL/lymphoma 9 (BCL9), β-catenin (CTNNB1) and leucine-rich repeat flightless interacting protein 2 (LRRFIP2). They showed that ARX positively controls Wnt/β-catenin signaling and that the C-terminal domain of ARX interacts with the armadillo repeats of β-catenin to move forward Wnt/β-catenin signaling. Furthermore, they understood that P300 and BCL9 also interact with ARX to adjust Wnt/β-catenin signaling. These data offer new insights into how ARX can exclusively regulate cortical neurogenesis and link the role of ARX with Wnt/β-catenin signaling [44] (Figure 4).

**Figure 4.** ARX functions through specific interactions with β-catenin, BCL9 and P300 proteins, which constitute a transcriptional activator complex downstream of WNT/β-catenin signaling pathway.

**BIOINFORMATICS ANALYSIS**

To study the molecular features, the structure of the ARX gene, bioinformatics analysis was performed using the ExPASy tool and SWISS-MODEL server, respectively. The phylogeny tree of ARX protein was also drawn using the software.

As illustrated in Figure 3, it was determined that the ARX gene is evolutionarily conserved in different species. Moreover, the sequence alignment of this protein with other spices confirms that the functional domains of ARX protein are highly conserved, and therefore it has been predicted that the mutations of this gene can be highly pathogenic.

**WEB RESOURCES**

The URLs for data offered here are as follows:


SWISS-MODEL server (http://swissmodel.expasy.org)

Phylogeny software (http://phylogeny.lirmm.fr)

Expasy software (http://www.expasy.org/)

Ensembl Genome Browser (http://www.ensembl.org)

**REFERENCES**


