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

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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 and155, 278 and281, 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 evolutionarily 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 the mutations of this gene can be highly pathogenic [25-35].

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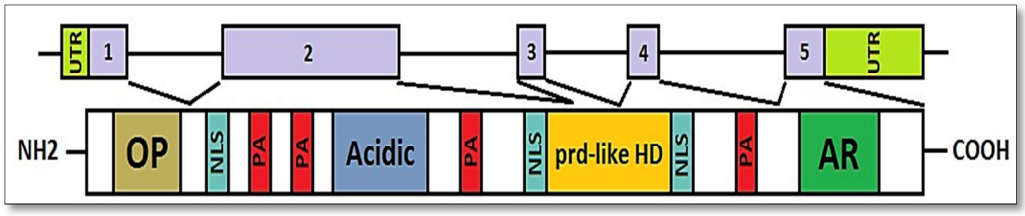

Figure 1. Schematic representation of the ARX gene and its exons. The protein domains and important functional regions of ARX including octapeptide domain (OP), nuclear localization signals (NLS), poly-alanine expansion repeats (PA), Acidic domain (Acidic), prd-like homeodomain (prd-like HD) and Aristaless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

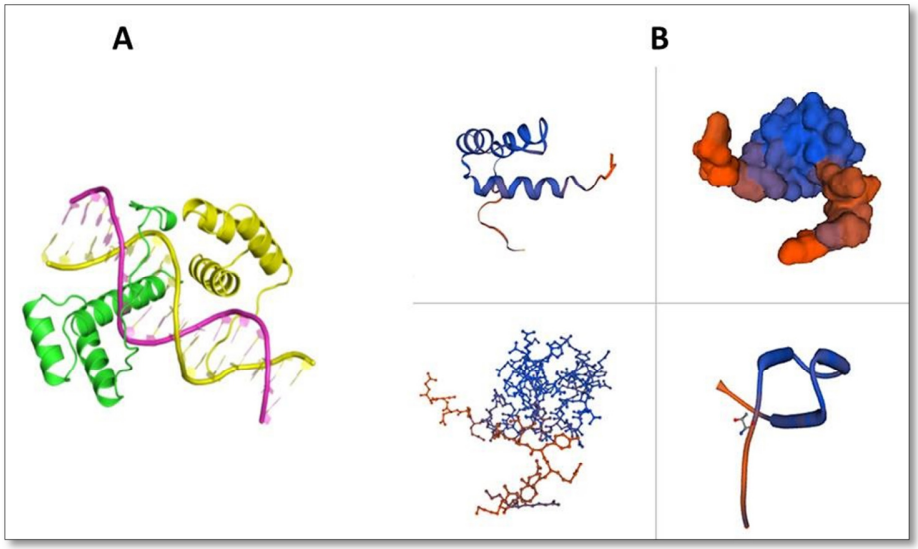

Figure 2. A) Quaternary structure assembly of the hetero-tetrameric ARX protein. **B)** Four subunits of 4 distinct polymer entities.

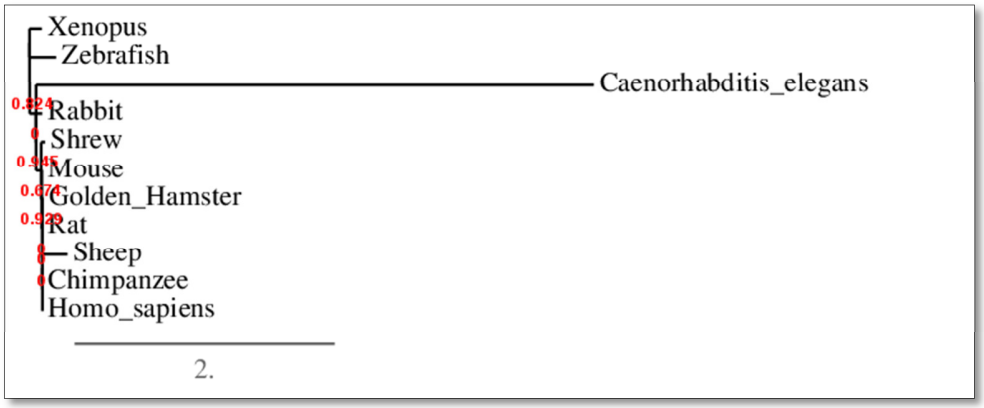

Figure 3. The phylogenetic tree of ARX protein (The comparison between *Homo sapiens* ARX protein and 10 other species).

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# 309510); 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)**.

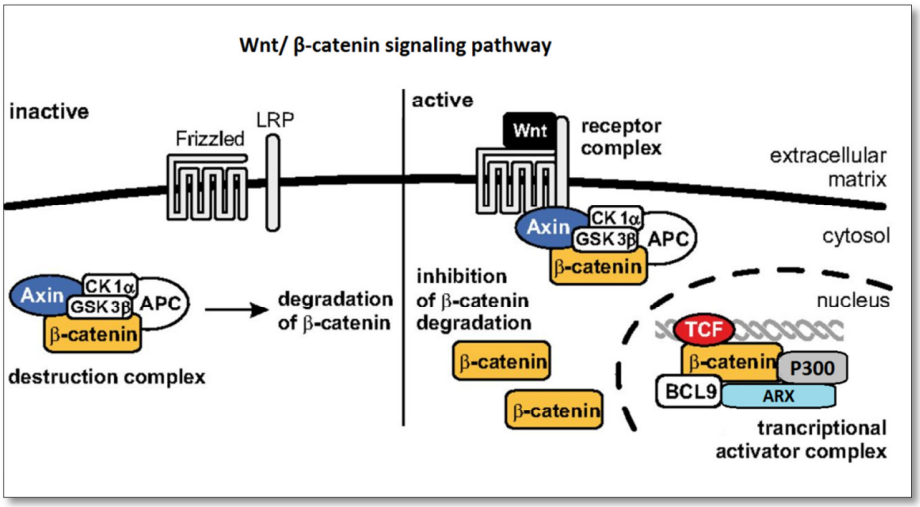

Figure 4. ARX functions through specific interactions with β-catenin, BCL9 and P300 proteins, which constitute a transcriptional activator complex downstream of WNT/β-catenin signaling pathway.

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:

NCBI database (http://www.ncbi.nlm.nih.gov)

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

1. Ropers HH, Hamel BC (2005) X-linked mental retardation. Nat Rev Genet 6: 46-57.
2. Leonard H, Wen X (2002) The epidemiology of mental retardation: Challenges and opportunities in the new millennium. Ment Retard Dev Disabil Res Rev 8: 117-134.
3. WHO (2005) Atlas: child and adolescent mental health resources: Global concerns, implications for the future. World Health Organization.
4. Durkin M, Khan NZ, Davidson LL, Huq S, Munir S, et al. (2000) Prenatal and postnatal risk factors for mental retardation among children in Bangladesh. Am J Epidemiol 152: 1024-1033.
5. Durkin MS, Hasan Z, Hasan K (1998) Prevalence and correlates of mental retardation among children in Karachi, Pakistan. Am J Epidemiol 147: 281-288.

6. Durkin M (2002) The epidemiology of developmental disabilities in low-income countries. Ment Retard Dev Disabil Res Rev 8: 206-211.
7. Costeff H, Cohen BE, Weller L (1972) Parental consanguinity among Israeli mental retardates. Acta Pediatr Scand 61: 452-458.
8. Bashi J (1977) Effects of inbreeding on cognitive performance. Nature 266: 440.
9. Thompson BL, Levitt P, Stanwood GD (2009) Prenatal exposure to drugs: effects on brain development and implications for policy and education. Nat Rev Neurosci 10: 303-312.
10. Chaney RH, Givens CA, Watkins GP, Eyman RK (1986) Birth injury as the cause of mental retardation. Obstet Gynecol 67: 771-775.
11. King BH, Dykens E. (1997) Mental retardation: A review of the past 10 years. Part II. J Am Acad Child Adolesc Psychiatry 36: 1664-1671.
12. Piton A, Redin C, Mandel JL (2013) XLID-causing mutations and associated genes challenged in light of data from large-scale human exome sequencing. Am J Hum Genet 93: 368-383.
13. Raymond FL, Tarpey P (2006) The genetics of mental retardation. Hum Mol Genet 15: 110-R116.
14. Bassani S, Zapata J, Gerosa L, Moretto E, Murru L, et al. (2013) The neurobiology of X-linked intellectual disability. Neuroscientist 19: 541-552.
15. Bienvenu T, Poirier K, Friocourt G, Bahi N, Beaumont D, et al. (2002) ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. Hum Mol Genet 11: 981-991.
16. Chiurazzi P, Tabolacci E, Neri G (2004) X-linked mental retardation (XLMR): From clinical conditions to cloned genes. Crit Rev Clin Lab Sci 41: 117-158.
17. Ohira R, Zhang HY, Guo W, Dipple K, Shih SL, et al. (2002) Human ARX gene: Genomic characterization and expression. Mol Genet Metab 77: 179-188.
18. Poirier K, Van Esch H, Friocourt G, Saillour Y, Bahi N, et al. (2004) Neuroanatomical distribution of ARX in brain and its localisation in GABAergic neurons. Brain Res Mol Brain Res 122: 35-46.
19. Kato M, Dobyns WB (2004) X-linked lissencephaly with abnormal genitalia as a tangential migration disorder causing intractable epilepsy: Proposal for a new term, "interneuronopathy". J Child Neurol 19: 392-397.
20. Friocourt G, Poirier K, Rakic S, Parnavelas JG, Chelly J (2006) The role of ARX in cortical development. Eur J Neurosci 23: 869-876.
21. Wigle J, Eisenstat D (2008) Homeobox genes in vertebrate forebrain development and disease. Clin Genet 73: 212-226.
22. Strømme P, Mangelsdorf ME, Shaw MA, Lower KM, Lewis SM, et al. (2002) Mutations in the human ortholog of Arista-less cause X-linked mental retardation and epilepsy. Nat Genet 30: 441-445.
23. Kitamura K, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, et al. (2002) Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. Nat Genet 32: 359-369.
24. Kato M, Das S, Petras K, Kitamura K, Morohashi K, et al. (2004) Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Hum Mutat 23: 147-159.
25. Turner G, Partington M, Kerr B, Mangelsdorf M, Gecz J (2002) Variable expression of mental retardation, autism, seizures and dystonic hand movements in two families with an identical ARX gene mutation. Am J Med Genet 112: 405-411.
26. Frints SGM, Froyen G, Marynen P, Willekens D, Legius E, Fryns JP (2002) Re-evaluation of MRX36 family after discovery of an ARX gene mutation reveals mild neurological features of Partington syndrome. Am J Med Genet 112: 427-428.
27. Grønskov K, Hjalgrim H, Nielsen IM, Brøndum-Nielsen K (2004) Screening of the ARX gene in 682 retarded males. Eur J Hum Genet 12: 701-705.
28. Reish O, Fullston T, Regev M, Heyman E, Gecz J. (2009) A novel de novo 27 bp duplication of the ARX gene, resulting from post-zygotic mosaicism and leading to three severely affected males in two generations. Am J Med Genet A 149: 1655-1660.
29. Shinozaki Y, Osawa M, Sakuma H, Komaki H, Nakagawa E, et al. (2009) 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: 469-472.
30. Nasrallah MP, Cho G, Simonet JC, Putt ME, Kitamura K, et al. (2011) Differential effects of a polyalanine tract expansion in Arx on neural development and gene expression. Hum Mol Genet 21: 1090-1098.
31. McKenzie O, Ponte I, Mangelsdorf M, Finnis M, Colasante G, et al. (2007) Arista-less 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: 236-247.

32. Cho G, Nasrallah MLP, Lim Y, Golden JA (2012) Distinct DNA binding and transcriptional repression characteristics related to different ARX mutations. Neurogenetics 13: 23-29.

33. Lin W, Ye W, Cai L, Meng X, Ke G, et al. (2009) The roles of multiple importins for nuclear import of murine arista-less related homeobox protein. J Biol Chem 284: 20428-20439.

34. Shoubridge C, Tan MH, Fullston T, Cloosterman D, Coman D, et al. (2010) Mutations in the nuclear localization sequence of the Arista-less related homeobox; sequestration of mutant ARX with IPO13 disrupts normal subcellular distribution of the transcription factor and retards cell division. Pathogenetics 3: 1.

35. Dereeper A, Guignon V, Blanc G, Audic S, Buffet S, et al. (2008) Phylogeny. fr: robust phylogenetic analysis for the non-specialist. Nucleic Acids Res 36: W465-W469.

36. Takahashi T, Fukuyama Y. (2008) Biology of seizures susceptibility in development brain. 2008: John Libbey Eurotext.

37. Cossée M, Faivre L, Philippe C, Hichri H, Martin AdS, et al. (2011) ARX polyalanine expansions are highly implicated in familial cases of mental retardation with infantile epilepsy and/or hand dystonia. Am J Med Genet A 155: 98-105.

38. De Brouwer AP, Yntema HG, Kleefstra T, Lugtenberg D, Oudakker AR, et al. (2007) Mutation frequencies of X-linked mental retardation genes in families from the EuroMRX consortium. Hum Mutat 28: 207-208.

39. Poirier K, Lacombe D, Gilbert-Dussardier B, Raynaud M, Desportes V, et al. (2006) Screening of ARX in mental retardation families: Consequences for the strategy of molecular diagnosis. Neurogenetics 7: 39-46.

40. Shoubridge C, Fullston T, Gecz J (2010) ARX spectrum disorders: Making inroads into the molecular pathology. Hum Mutat 31: 889-900.

41. Mandel JL, Chelly J. (2004) Monogenic X-linked mental retardation: Is it as frequent as currently estimated? The paradox of the ARX (Arista-less X) mutations. Eur J Hum Genet 12: 689-693.

42. Bienvenu T, Poirier K, Friocourt G, Bahi N, Beaumont D, et al. (2002) ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. Hum Mol Genet 11: 981-991.

43. Abedini SS, Kahrizi K, Behjati F, Banihashemi S, Ghasemi Firoozabadi S, et al. (2012) Mutational screening of ARX gene in Iranian families with X-linked intellectual disability. Arch Iran Med 15: 361-365.

44. Cho IT, Lim Y, Golden JA, Cho G. (2017) Arista-less related homeobox (ARX) interacts with beta-catenin, BCL9 and P300 to regulate canonical Wnt signaling. PLoS One 12: e0170282.