2-O-B1-2 Oral Sessions

GCG repeat expansion in *ARX* gene inhibits *ARX* protein translation through the ectopic formation of RNA G-quadruplex

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Aristaless-related homeobox (*ARX*) is a crucial gene involved in the development of interneurons in the fetal brain. The *ARX* gene mutations are a significant contributor to X-Linked intellectual disability (XLID) including epilepsy. We investigated that the pathological mechanism of *ARX*-associated XLID in the most frequent polyalanine expansion mutation [c.334ins(GCG)7], termed GCG17. Biophysical analyses in circular dichroism (CD) spectra and thioflavin T assay revealed that GCG17 formed a parallel RNA G-quadruplex (G4RNA) exhibiting the stereotypical potassium specificity *in vitro*, but a control GCG10 and GCG10+GCA7 repeat RNA did not. Consistent with the results, the GCG17 stably expressing cells decreased the polyalanine expression compared to that of GCG10 and GCG10+GCA7 cells without changing these mRNA levels. G4RNAs are secondary structures proposed to function as negative regulators of post-transcriptional mRNA translation. Further, a mouse model of *ARX*-associated XLID shows the decrease of *ARX* protein translation. Taken together, inhibition of *ARX* protein translation by GCG17-derived ectopic G4RNA formation may cause *ARX*-associated XLID.