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Short Communication

The Milder Allelic Form, Occipital Horn Syndrome, in Contrast to the More Severe Form, Menkes Disease, is caused by Very Small Amounts of Normal ATP7A Transcript

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INTRODUCTION

The gene ATP7A encodes for the copper-transporting ATPase ATP7A, important for regulating copper [Cu (I)] level in the cells. In the small intestine, the ATP7A protein helps controlling the absorption of Cu (I) from food. The ATP7A gene contains 23 exons. Pathogenic variants in the gene, ATP7A, results in two different copper-deficiency disorder, occipital horn syndrome (OHS; OMIM #304150) and the more severe form, Menkes disease (MD; OMIM #309400).

MD is far the most common form, but the milder form, OHS, had been observed in approximately 5% of the cases. OHS has been observed in several patients with splice site mutations in ATP7A. Based on a previous observation of a splice site variant in ATP7A, leading to skipping of exon 10 in a patient with OHS (IVS10+3A>T), it has been proposed that OHS could be a result of functional activity of the splice-variant encoded by an ATP7A transcript missing exon 10. As the splice variant without exon 10 preserves the correct reading frame, it was reasonable to believe that this variant encodes an ATP7A protein variant with some functional activity. Previously, it also has been verified that exon 10 encoded a signal important for Golgi localization, and as a result of this the splice variant encodes an ATP7A protein, which was found located in the endoplasmic reticulum.

In our paper, "Occipital horn syndrome as a result of splice site mutations in ATP7A", we demonstrated, in contrast to what was previously thought, that the ATP7A protein product encoded by a transcript missing exon 10 is not functional. We demonstrated that this protein variant was not able to rescue a yeast-strain deficient in the gene, which encodes the homologous copper-pump, ccc2. Furthermore, MD patients with splice site variants leading to skipping of exon 10 had abundant amounts of this alterative ATP7A transcript, making it unlikely that it could be responsible for the OHS phenotype.

Furthermore, we have observed a splice variant leading to skipping of exon 15 in a patient with OHS (IVS15+4A>C) who had an unusual mild phenotype, long survival and a high intellectual function. We did testing to determine if a splice variant without exon 15, could encode for any functional protein. Also a transcript without exon 15 preserves the reading frame

Similar to the protein product encoded by a transcript without exon 10, we demonstrated that the protein product, which was encoded by a transcript without exon 15 was not functional.

Although the two splice variants, IVS10+3A>T and IVS15+4A>C, predominantly leading to transcripts without exon 10 or exon 15, respectively, small amounts of normal ATP7A transcript were still present. In comparison to the amount of normal ATP7A transcript in these OHS patients to the amount of normal ATP7A transcript in MD patients due to other ATP7A splice site mutations or exon deletions, we demonstrated that the OHS patients have at least 3% normal ATP7A transcript compared to controls. In contrast, patients with MD have less than 1% normal ATP7A transcript compared to controls. Thus while the splice site variants do not seem to be responsible for the milder OHS phenotype, very small amounts of normal ATP7A transcript do.

This conclusion is in agreement with our previously studies demonstrating that very small amount of wild type transcript permits the milder form OHS in contrast to the more severe form MD.

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REFERENCES

1. Menkes JH, Alter M, Steigleder GK, Weakley DR, Sung JH. A sex-linked recessive disorder with retardation of growth, peculiar hair and focal cerebral and cerebellar degeneration. Pediatrics. 1962;29:764–779.
2. Kodama H, Murata Y. Molecular genetics and pathophysiology of Menkes disease. Pediatr Int. 1999;41:430–435.
3. Das S, Levinson B, Vulpe C, Whitney S, Gitschier J, Packman S. Similar splicing mutations of the Menkes/mottled copper-transporting ATPase gene in occipital horn syndrome and the blotchy mouse. Am J Hum Genet. 1995;56:570–576.

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4. Møller LB, Mogensen M, Horn N. Molecular diagnosis of Menkes disease: genotype-phenotype correlation. Biochimie. 2009;91:1273–1277.
5. De Paepe A, Loeys B, Devrient K, Fryns JP. Occipital horn syndrome in a 2 year old boy. Clin Dysmorphol. 1999;8:179–183.
6. Skjørringe T, Tümer Z, Møller LB. Splice site mutations in the ATP7A gene. PLoS One. 2011;6:e18599.
7. Møller LB, Hicks JD, Holmes CS, et al. Diagnosis of copper transport disorders. Curr Protoc Hum Genet. 2011;Chapter 17:Unit17.9.
8. Dierick HA, Ambrosini L, Spencer J, Glover TW, Mercer JFB. Molecular structure of the Menkes disease gene (ATP7A) Genomics. 1995;28:462–469.
9. Desmet FO, Hamroun D, Lalande M, Collod-Beroud G, Claustres M, Béroud C. Human Splicing Finder: an online bioinformatics tool to predict splicing signals. Nuclei Acids Res. 2009;37:e67.
10. Mount SM. A catalogue of splice junction sequences. Nuclei Acids Res. 1982;10:459–472.