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A Precision Analysis of Menkes Disease by Using Bioinformatics Tools

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ABSTRACT:

MNK is caused by two related genes, ATP7A and ATP7B. The goal of this research is to create a new MNK risk prediction prototype and evaluate the incorporation of a family's medical history, psychographic, clinical, and genomic data to improve predictive model performance. We present mutations in the ATP7A gene, transferrin saturation, serum ferritin concentration, and demographic data, all of which were collected from different journals. In this review, a conditional characterization of copper deficiency and serious and fatal consequences can occur over time. A genetic change in the ATP7A gene causes mild Menkes disease and cortex horn disorder, and a medical history is established, as well as an analysis of the drug molecules used to treat Menkes disease.

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I. INTRODUCTION:

MNK is an X-linked gene mutation problem that occurs with copper deficiency. Human diseases are caused by two related genes, ATP7A and ATP7B. Wedge-shaped calcium deposits in the occipital bone, coarse hair, and loose skin and joints are all symptoms. Men were more likely to get this disease than females. This disorder is characterised by brain and cognitive abnormalities. Menkes disorder is characterised by the effects of the body's copper levels(1). Clinical signs include thinning, kinky hair, failure to gain weight and grow at the normal rate, and deterioration of the central nervous system. Weak muscle tone, sagging facial features, seizures, developmental delay, and intellectual disability are some of the other signs and symptoms. Menkes disease strikes kids in early adulthood, and most of them do not live to be three years old. Some people with copper poisoning may benefit from early treatment.

Copper is used by the body as a transcription factor for enzyme functions that act as catalysts. When copper-dependent enzyme inhibitors that control hair, brain, bones, liver, and arteries don't work properly, it's called a copper deficiency, and serious and fatal consequences can occur over time. Genetic changes in the ATP7A gene because mild Menkes disease and cortex horn disorder(2), which have fewer serious symptoms. There is no specific treatment for Menkes disease, but if started within the first 28 days of life, early treatment with parenteral copper histidinate (CuHis) can enhance the effects and reduce neurological problems.

CAUSES:

Mutations in the ATP7A gene cause this disease.Copper levels in the brain and liver are unusually low in Menkes disease patients, while copper levels in the intestines and kidneys are excessive(3). Copper-dependent enzymes' activity is reduced when copper is not present as a key component in their structure and function.

If a man with an X-linked disorder can reproduce, the defective gene will be passed on to all of his daughters who are carriers. Because males always pass on their Y chromosome rather than their X chromosome to their sons, a male cannot pass an X-linked gene to his sons(4). Males are affected by X-linked genetic problems, which are induced by a non-functioning X chromosome gene. Females who have a genetic defect on one of their X chromosomes are carriers of the disorder. Carrier females rarely show symptoms because they have two X chromosomes, one of which contains the non-working gene(5). Males, on the other hand, inherit only one X chromosome from their mothers.

SIGNS AND SYMPTOMS:

The baby may also seem yellow, which is caused by hyperbilirubinemia. Hypothermia can also happen in the newborn period. Other symptoms of Menkes disease include failure to thrive, seizures, lack of muscle development, poor head control, reduced muscle tone, sagging cheeks, abnormal sternum and rib cage development, low body temperature in the newborn period, and intellectual disability in older children. The hair appears to be unusually kinky, colourless or silvery, and brittle(6). The grey matter of the brain can suffer from extensive neuronal degeneration. Fractures can occur as a result of weakened bones (osteoporosis). Due to neurodegenerative effects, blood clots in the brain and osteoporosis are common.

MECHANISM:

The ATP7A gene is capable of transporting copper across cell membranes. Except for the liver, it can be found all over the body. The ATP7A regulates the uptake of copper from food in the small intestine. The protein moves between the Golgi apparatus and the cell membrane in other cells to keep copper levels in the cell stable. The protein is ordinarily observed in the Golgi apparatus, which is responsible for protein modification, such as enzyme modification. The ATP7A protein provides copper to important enzymes in the Golgi apparatus. Table 1 explains the importance of bone and the nervous system for bone structure and function(5,6). Copper is required for the proper function of one of the enzymes(6).This enzyme is in charge of cross-linking tropocollagen into strong collagen fibrils. Some of the acknowledged symptoms of this disease are caused by defective collagen (T1). When copper layers get to be excessively high, the protein travels to the cell membrane and removes the obscene amount of copper. Deletions and insertions in the ATP7A gene cause segments of the gene to be deleted, which causes copper deficiency in certain enzymes.

DIAGNOSIS:

A physical examination is the first step in diagnosing Menkes disease. To make an accurate diagnosis, plasma catecholamine analysis is best for newborns and genetic testing can help diagnose the disorder(7). Menkes disease is diagnosed when the hair becomes brittle, tangled, sparse, steely, or kinky after several months. The diagnosis is supported by blood tests that show low levels of serum copper and ceruloplasmin. Measurement of plasma catecholamine levels is a new clinical medical technique that could help with frequent babies before depletion causes brain damage(8). This could form the basis for future Menkes disease newborn scanning. Molecular genetic testing for ATP7A gene mutations could also be an effective population-based new born screening method(9). Carrier testing and prenatal diagnosis are applied once a specific ATP7A gene variant has been identified in an affected family member. T- 2 illustrates the chemical compounds used to design drug molecules. An evaluation tool for early identification has been proposed using the ratio of homovanillic acid to vanillylmandelic acid in urine.

T-1 :(ClinicalFeatures)

Author	**Lecturer Review**
Menkes	• He identified six cuproenzymes, five of which he believes are responsible for the disorder's symptoms. • For the depigmentation of hair and skin pallor. • Monoamine oxidase for kinky hair. Hypothermia cytochrome c oxidase. • Hypothermia oxidase of cytochrome skeletal demineralization ascorbate oxidase. The cuproenzyme dopamine-beta-hydroxylase is also a cuproenzyme, but it's unclear what role it plays in the phenotype of kinky hair disease. •
Bray	• He recognised the babies as having spastic dementia, seizures, and thinning hair. Amino acids in the blood and urine were both within normal limits.
French and Sherard	This condition could indicate a problem with lipid metabolism. • Microscopically, pilitorti, monilethrix, and trichorrhexisnodosa were found among the sparse, whitish, lacklustre, kinky hair. • Growth has slowed.

	• Micrognathia and a high-arched palate are two characteristics of micrognathia. • Mental development deteriorates Seizures, both focal and generalised, begin.
Danks	• He observed toluidine-blue-metachromasia of fibroblasts
Wesenberg	• The pilitorti are not visible in the foetal hair.
Goka	• Copper concentrations in cultured fibroblasts are over 5 times higher than in normal fibroblasts.
Williams	• Menkes disease's cellular pathology
Osaka	• It's possible that the hair isn't abnormal, thatserum copper identification. Congenital hypocupraemia" is a better fit.
Chan	• Copper egress from Menkes disease fibroblasts is abnormal.
Haas	• X-linked recessive inheritance, severe psychomotor retardation with seizures, low serum copper and ceruloplasmin levels, and a block in gut copper absorption were all symptoms of Menkes disease.
Tonnesen	• Copper and ceruloplasmin levels in the serum were unusually low. Cu uptake and retention, on the other hand, were significantly higher in the range seen in classic Menkes patients.
Godwin-Austen	• It was discovered that copper absorption from the distal intestine was impaired, resulting in high copper levels in the rectal mucosa.
Proud	• The clinical characteristics of four affected people from three generations of a family who had an unusual variant of Menkessyndrome. These patients had a normal head circumference, moderate to severe mental retardation that began when they were 3 to 4 years old.
Kaler	• This gene is an A-to-T modify near the 3-prime end of the MNK coding sequence at the +3 position of the splice donor site, resulting in abnormal splicing.
Wakai	• Menkes syndrome and the occipital horn syndrom are induced by mutations in the ATP7A gene, phenotypic overlap is to be expected.
Gerard-Blanluet	• They explained that a 'occipital horn' is a wedge-shaped calcification that forms within the trapezius and sternocleidomastoid muscles' tendinous insertions at their attachment to the occipital bone.
Jankov	• Copper accumulation studies on cultured fibroblasts confirmed the diagnosis of Menkes disease, which was discovered at autopsy. • The onset of fatal complications in Menkes disease at such a young age had never been seen before.
Smpokou	• Menkes disease clinical features that have been reported.Hypotonia, myopathicfacies, and severe global developmental delay were among the symptoms. • Cerebrovascular tortuosity and brain or cerebellar atrophy were present in all of them.

Biochemical Features:

Copper deficiency causes connective tissue changes in animals. This process is copper-dependent. The dramatic hair changes are most likely the result of keratin disulfide bond formation problems(10). Fibroblasts had significantly higher copper content and a faster rate of copper incorporation than Menkes cells, with an accumulation of metallothionein or a metallothionein-like protein(11,12).

A mutation in a gene on the X chromosome that controls the synthesis of a putative zinc-binding protein called ZBP causes Menkes disease(13,14). Ionic zinc causes the metallothionein to be synthesised in the liver or intestine, which is where the zinc is bound. Metallothionein has a 100,000-fold higher affinity for copper than zinc(15)(16).Increase in ionic zinc, which is known to induce metallothionein synthesis.

Mapping:

MNK is most likely to be found in the Xq12-q13.3 region. Researchers created a cosmid coting spanning 150 kb from a nearby CpG island to the X chromosome breakpoint(17,18).A female with MNK symptoms was diagnosed with a de novo balanced translocation 46, X, t(X;13) (q13.3; q14.3). Low serum copper and ceruloplasmin levels, as well as increased copper uptake in cultured fibroblasts, confirmed the diagnosis(19). The translocation had disrupted the function of the ATP7A gene, either structurally or functionally through silencing

Molecular Genetics:

The MNK protein is found in the trans-Golgi network (TGN). According to studies with copper-resistant Chinese hamster ovary cells (CHO), is a protein that alternates

Between the TGN and the plasma membrane. MNK contains specific localization signals, as do a number of other Golgi-resident proteins(20). The MNK proteins transmembrane

T-2 (Drug Used for MNK Disease)

DRUG NAME	GROUP	BRAND NAME	CHEMICAL FORMULA	DRUG BANK ACCESSION NUMBER	DRUG BANK LINK
Copper histidine	Investigational	Aminofit	C12H16CuN6O4	-	https://pubchem.ncbi.nlm.nih.gov
Copper	Approved, Investigational	Vitsafol-one	Cu	DBO9130	https://go.drugbank.com
Droxidopa	Approved, Investigational	Northera	C9H11NO5	DB09130	https://go.drugbankcom .
Levodopa	Approved	Duodopa	C9H11NO4	DB01235	https://go.drugbank.com
Carbidopa	Approved	Duopa	C10H14N2O4	DB00190	https://go.drugbank.com
Safinamide	Approved, Investigational	Xadago	C17H19FN2O2	DB06654	https://go.drugbank.com
Disulfiram	Approved	Antabuse	C10H20N2S4	DB00822	https://go.drugbank.com
Cupric sulfate	Approved	Tandem Plus	CuO4S	DBO6778	https://go.drugbank.com
Allopurinol	Approved	Aloprim	C5H4N4O	DB00437	https://go.drugbank.com
Penicillamine	Approved	Cuprimine	C5H11NO2S	DB00859	https://go.drugbank.com
Trientine	Approved, Investigational	Syprine	C6H18N4	DB06824	https://go.drugbank.com)
Cimetidine	Approved, Investigational	Tagamet	C10H16N6S	DB00501	https://go.drugbank.com
Nifedipine	Approved	Procardia	C17H18N2O6	DB01115	https://go.drugbank.com
Ibuprofen	Approved	Addaprin	C13H18O2	DB01050	https://go.drugbank.com
Naproxen	Approved	Naprelan	C14H14O3	DB00788	https://go.drugbank.com
Pyridoxal phosphate	Approved, Investigational	EnBrace HR	C8H10NO6P	DB00114	https://go.drugbank.com

domain 3 was sufficient for Golgi complex localization. As a result, the exon 10 protein sequence may be responsible for this differential localization. The MNK protein was the exon 10 protein sequence may be responsible for this differential localization. The MNK protein was mapped to the TGN using immunogold electron microscopy(20). MNK was redistributed to the cytoplasm and plasma membrane in CHO cells when the extracellular copper concentration was increased.

II. Conclusion:

Menkes disorder is a condition characterised by the effects of the body's copper levels. We present mutations in the ATP7A gene, transferrin saturation, serum ferritin concentration, and demographic data, all of which were collected from different journals. In this review, a conditional characterization of copper deficiency and serious and fatal consequences can occur over time. A genetic change in the ATP7A gene causes mild Menkes disease and cortex horn disorder, and a medical history is established, as well as an analysis of the drug molecules used to treat Menkes disease.

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