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An Empirical Study of Charcot-Marie-Tooth Disorder Using Bioinformatics Tools.

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ABSTRACT:
The typical kind of inherited neuropathy is Charcot-Marie-Tooth (CMT). It is of autosomal predominant descent, but there are also X-linked and autosomal recessive subtypes. CMT is characterised by a wide range of inheritance patterns as well as a large number of genes, reflecting the disorder's heterogeneity. The diagnostic context, biochemical awareness, and medicinal research of these CMT subtypes are highlighted in this review. The typical kind of inherited neuropathy is Charcot-Marie-Tooth (CMT). It is of autosomal predominant descent, but there are also X-linked and autosomal recessive subtypes. CMT is characterised by a wide range of inheritance patterns as well as a large number of genes, reflecting the disorder's heterogeneity. The diagnostic context, biochemical awareness, and medicinal research of these CMT subtypes are highlighted in this review. This report demonstrates the gaps in epidemiologic studies' understanding of CMT that still exist in the human world. Research analyses are of questionable performance and employ various approaches, making it possible to draw a firm conclusion. More research into the features of CMT in different countries and indigenous groups is required. The most prevalent genetic mutations have gotten a lot of attention in terms of disease-modifying therapy (PMP22, GJB1, MPZ, and MFN2).

KEYWORDS: *Charcot-Marie-Tooth disease; congenital disease; gene; autosomal*

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I. Introduction:

CMT disease is an inherited nerve problem. CMT causes nerve damage. It is also called an inherited peripheral nerve disorder. CMT can be passed down through the generations in three different ways: X-linked, Autosomal Dominant, and Autosomal Recessive(1). It happens when genes affecting the nerves of the feet, legs, hands, and arms are mutated. CMT is caused by a hereditary genetic mutation. This disease is actually caused by a mutation of the gene that provides information about the protein connexin-32.

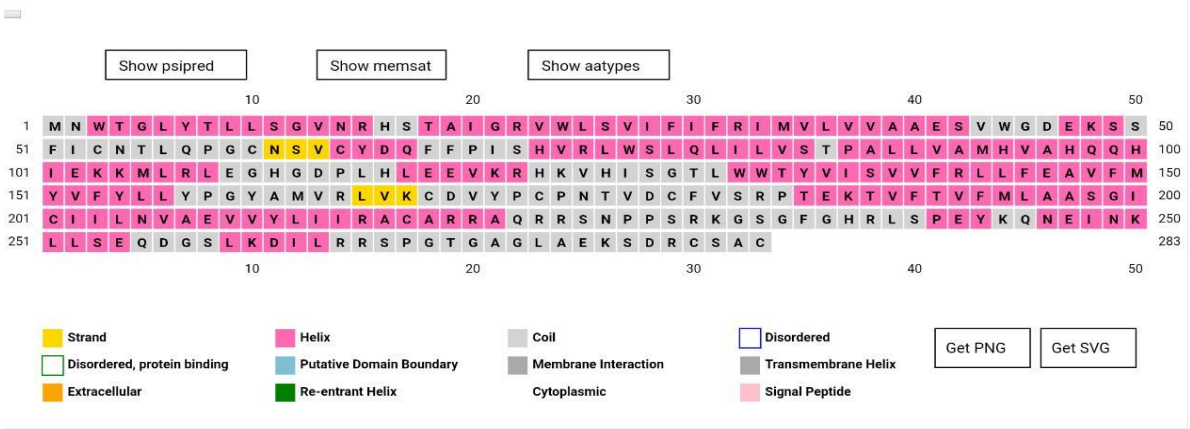

Figure 1(a)

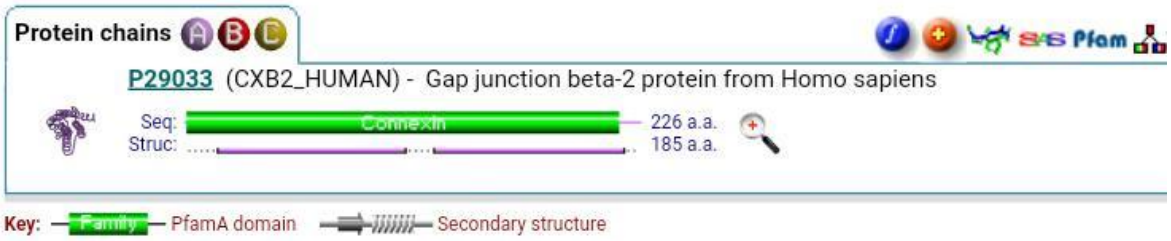

Figure 1(b)

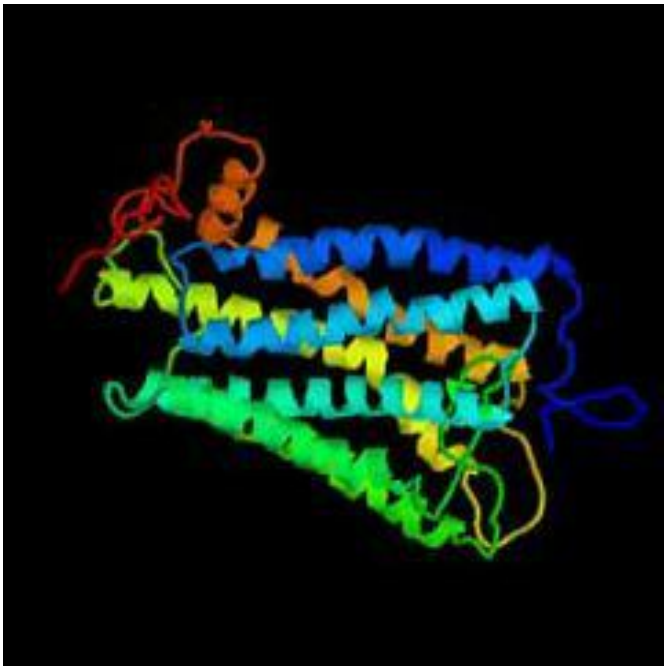

Figure 1(c)

The newly discovered point mutations in the MFN2 gene broaden the clinical spectrum beyond CMT2 and intermediate CMT, possibly including CMT1 and dHMN phenotypes(2). Different conformational changes of the MPZ protein, (Fig1a) which affect the functional tetramers, are likely to be the cause of different missense mutations in the MPZ gene. Over 90 genetic variations have been linked to the development or progression of these neuropathies so far. They've been linked to a number of molecular path mechanisms related to protein synthesis and post-translational processing.(Fig1b and 1c) Four genes (PMP22, MPZ, GJB1, and MFN2) account for cases of CMT.

CHARACTERISTICS OF THE DISEASE:

The symptoms of the disease normally start at an age between 5 and 15. The starting symptoms of the disease usually begin in the legs and feet. They also affect the hands and arms of the person. The features of this disease and early signs of this disease are clumsiness and falling down(3). The following are the characteristics of the disease:

- Muscle weakness
- Muscle contractions that are rhythmic and have a smaller size.
- Decreased Sensation
- Hammer toes
- Slow reaction
- Balance Disorder
- Abnormality in walking
- Flaccid muscles
- High arches
- Tremor
- Curled legs
- Hearing loss

- Areflexia
- Scoliosis

There are several types of CMT disease, each of which is distinguished by its effects on nerve cells and inheritance pattern(4). Myelin is a characteristic of Type 1. Abnormalities in the fibres or axons characterise Type-2.

REASON OF THE DISEASE:

CMT is a congenital disease. The meaning of this word is that this disease is present from birth but does not show symptoms during birth and during childhood. They show their symptoms in their teenage years or in their older years. This could be due to various methods of measurement or founder effects. Different inheritance patterns as well as different electrophysiological classes reflect genetic heterogeneity(5). The main reason for this disease is mutated genes from one or both of the parents. The CMT-causing genes can cause problems with different parts of the peripheral nerves. CMT disease is caused by mutations in the genes that affect the nervous system (Table 1) of the feet, legs, hands, arms, etc(5,6). Nerves can be damaged by mutation. Other mutations damage the protective coating of the nerve called the myelin sheath. The gene which is responsible for this mutation is GJB1.

PROBLEMS OF THE DISEASE*:*

The intensity of CMT disease varies from person to person.

- Difficulties in walking
- Injure areas of the body that experience decreased sensation.
- Sometimes the brain does not send a signal to the body's foot muscles to contract.
- Difficulties in breathing
- A range of voluntary movements
- It effects swallowing.

***CLINICAL FEATURES*:**

Advances in genetic therapy are having an impact on the field of CMT. Gene transfer treatment is being tested with CMT1X and CMT4C for mutations that cause loss of function. Future advanced treatments for CMT may be possible thanks to molecular therapeutic potential.The patients presented with pain in the lower extremities between 18 and 61 years of age. The symptoms evolved over decades into continuous foot pain, and many individuals also had distal upper limb paraesthesias. Physical examination of most patients showed evidence of peripheral neuropathy, with decreased vibration sense and loss of deep tendon reflexes. However, some patients only complained of disturbed sleep due to the pain(7,8). Tandem walking becomes difficult with age(9,10). Nerve conduction studies were normal at the outset but showed decreased sensory and motor nerve amplitudes later in the disease course in some patients, suggestive of an axonal neuropathy; surely nerve biopsy was not performed(11,12).

Table 1: **The CMT affected individuals typically has**

The CMT affect	symptoms
INHERITANCE	Autosomal recessive
SKELETAL	Feet and Pes cavus
NEUROLOGIC	The Peripheral Nervous System: • Distal climbing muscle weakness • Foot drop • Steppage gait • Ankle reflexes are absent. • Hyperreflexia in the knee • Hyperreflexia in the upper limbs • Loss of myelinated fibres on nerve biopsy • Thin myelin sheaths • Rare axonal regeneration • Sensorineural deafnes

MAPPING:

The difficulty of wringing being tested in clinical trials by improved biomarkers and natural history data(13–15). Different observers explained (Table 2) the linkage and effect of the mutation of CMT.

Table 2 (**Review of literature**)

Observer	Year	Function
Kennerson et aL	2001	The CMTDIB locus was found to be within a 16.8-cM region flanked by the markers D19S586 and D19S546 after haplotype analysis with 14 additional markers.
Speer et al.	2002	The minimum candidate interval for CMTDI1 has been reduced to 9 cM, which is spanned by markers D19S586 and D19S432.
Zhu et al.	2003)	Additional members of the family were subjected to haplotype analysis and clinical evaluation.
Speer et al., 2002	2002	D19S558 and D19S432 flank the candidate region for the CMTDI1 gene by a 6-cM interval. On the basis of neural expression and microarray analysis of Schwann cell differentiation in vivo, positional candidate genes for screening were chosen
Bergoffen et al	2015	The mutation, discovered through whole-exome sequencing, was found to be associated with the disorder in the family. NAGLU enzyme activity was significantly lower in patient leukocytes (36–54 percent of controls), indicating that the mutation had a negative effect.
Bergoffen et al	2015	A point mutation in connexin-32 was discovered in an affected person from one of eight CMTX families. a point mutation in connexin-32 in an affected person from eight CMTX families.
Tabaraud et al	2004	Tabaraud et al discovered prominent demyelination as the cause of X-Linked CMT disease.
Omoei et al	2002	Studied four known mutations in the connexin-32 gene. That is Lys60 to phe, Val139 to meet, Lys60 to phe, Val139 to meet, Arg215 to trp, and Ala220 to ter.
Ikegami et al.	1998	Began more than 130 different mutations of the GJB1 gene, including coding and noncoding regions. Has been reported in patients with X-Linked CMT.

MOLECULAR GENETICS**:**

Clinic populations have been used to estimate the prevalence of various CMT genetic variants, but data on the prevalence in the general public is deficient. The gene involvement, clinical features, and the occurrence of CMT are analysed in Table 3. And drug design are analysed in Table 4. Point mutations in the mitofusin 2 gene have only been found in CMT2(16–18). A genetic variation in the myelin protein zero gene creates CMT, but the mechanism is still a mystery(19). The adhesion in the spiral wraps of the Schwann cell's myelin sheath is mediated by the myelin protein zero. X-linked Mutations in the cx32 gene, which encodes a peptide bond that forms gap junctions in a hexameric array, cause Charcot-Marie Tooth disease (CMTX)(20–22).

Table 3 :(Clinical Features)

Gene Involved	Clinical Features	The Occurrence of CMT
PMP22	Autosomal dominant and most common demyelinating	60.5%
GJB1	Split hand syndrome, X-linked and white matter changes	16.7%
MPZ	Tonic pupils and autosomal dominant	9.4%
MFN2	CMT2 autosomal dominant and optic atrophy	4.4%
HDAC6	Correct axonal transport defects by increasing acetylated alpha-tubulin.	4.4%
NT-3	In Tr-J mice, NT-3 improved axonal regeneration and myelination. It has also been shown to be effective in patients with CMT1A. Because of its short half-life and scarcity.	2%
stem cells,	Neurotrophic factors secreted by stem cells promote axonal growth and remyelination..	9.4%
Neuregulin-1 ,Type III	Tumor necrosis factor-converting enzyme inhibits Nrg1 type III, and TACE inhibits myelination as a result.	5%

Table 4: DRUG DATA AVAILABLE FOR CMT DISORDER:

DRUG NAME	GROUP	BRAND NAME	CHEMICAL FORMULA	DRUG BANK ACCESSION NO	DRUG LINK
Ubidecarenone	Approved, Investigational, Nutraceutical	____	$C_{59}H_{90}O_4$	DB09270	https://go.drugbank.com/drugs/DB09270
Biotin	Approved, Investigational, Nutraceutical	Concept Ob, Infuvite, Infuvite Pediatric, Irospan 24/6 Kit	$C_{10}H_{16}N_2O_3S$	DB00121	https://go.drugbank.com/drugs/DB00121
Ascorbic acid	Approved, Nutraceutical	Infuvite Pediatric, Moviprep, Mvc-fluoride	$C_6H_8O_6$	DB00126	https://go.drugbank.com/drugs/DB00126
Efmitermant alfa	Investigational	_____	_____	DB16686	https://go.drugbank.com/drugs/DB16686
PXT 3003	Investigational	_____	$C_{21}H_{27}N_3O_2$	DB16745	https://go.drugbank.com/drugs/DB16745
Mexiletine	Approved, Investigational	_____	$C_{11}H_{17}NO$	DB00379	https://go.drugbank.com/drugs/DB00379
Baclofen	Approved	Fleqsuvy, Gablofen, Kemstro	$C_{10}H_{12}CINO_2$	DB00181	https://go.drugbank.com/drugs/DB00181
Naltrexone	Approved, Investigational, Vet approved	Contrave, Embeda, Vivitrol	$C_{20}H_{23}NO_4$	DB00704	https://go.drugbank.com/drugs/DB00704
Sorbitol	Approved	Cystosol	$C_6H_{14}O_6$	DB01638	https://go.drugbank.com/drugs/DB01638
PXT 3003	Investigational	_____	$C_{21}H_{27}N_3O_2$	DB16745	https://go.drugbank.com/drugs/DB16745
Oxycodone	Approved, Illicit, Investigational	Endocet, Endodan Reformulated May 2009, Nalocet	$C_{18}H_{21}NO_4$	DB00497	https://go.drugbank.com/drugs/DB00497
Loxoprofen	Approved	_____	$C_{15}H_{18}O_3$	DB09212	https://go.drugbank.com/drugs/DB09212
Quinidine	Approved, Investigational	Nuedexta	$C_{20}H_{24}N_2O_2$	DB00908	https://go.drugbank.com/drugs/DB00908
Benzydamine	Approved	Pharixia, Tantum	$C_{19}H_{23}N_3O$	DB09084	https://go.drugbank.com/drugs/DB09084
Doxepin	Approved, Investigational	Prudoxin, Silenor, Sinequan	$C_{19}H_{21}NO$	DB01142	https://go.drugbank.com/drugs/DB01142
Carbamazepine	Approved, Investigational	Carbatrol, Carnexiv, Epitol	$C_{15}H_{12}N_2O$	DB00564	https://go.drugbank.com/drugs/DB00564
gamma-Aminobutyric acid	Approved, Investigational	_____	$C_4H_9NO_2$	DB02530	https://go.drugbank.com/drugs/DB02530

II. Conclusion:

With a prevalence of 1 in 1214, Charcot-Marie-Tooth disease is the most common inherited peripheral nervous system disorder. In the general population, CMT1 and CMT2 are equally common. The MFN2 gene has been linked to two new phenotypes, but more research is needed to confirm these MFN2 mutations. PMP22 duplication and mutations in Cx32, MPZ, and MFN2 are found in 19.6%, 4.8%, 1.1%, and 3.2% of people, respectively.

Finding a robust therapy that works across the various subtypes of CMT has its limitations. The difficulty of wringing a clear effect size with very slow disease progression as a control also makes it difficult to translate molecular studies to clinical trials. Future most-modifying treatments for CMT may be possible thanks to advances in molecular therapeutic potential.

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