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Review Article

Clinical and Genetic Variant Profile of Asian Charcot-Marie Tooth Patients: A Systematic Review

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Abstract

Background: Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy by high clinical and genetic heterogeneity. Although many studies reported from East Asian countries, data from West/South Asia remain limited. The current study aimed to summarize available epidemiological, clinical and genetic data of CMT patients in Asia.

Methods: We searched PubMed, Scopus, Web of Sciences, Nature, Google Scholar, Science Direct, and Willey for relevant published articles between 2003 until Feb 2023, according to PRISMA guidelines. Articles were screened for epidemiological, clinical and genetic information. Inclusion required published mutation frequency or genetic variant in CMT patients. The Q-Genie tool and Newcastle-Ottawa (NOS) were used to evaluate the quality of genetics and observational studies, respectively.

Results: Out of 320, 32 screened articles met the inclusion criteria. Most studies were reported from China (n = 12), Japan (n=7), and Korea (n=6). The axonal CMT was the frequent type (50%), followed by demyelinating (28%) and intermediate (9%) types. Autosomal dominant (AD) inheritance was observed in 62% of genetically confirmed cases. Frequently mutated genes were *GDAP1*, *MPZ*, and *JGB1*, which have been found mostly in the East Asia.

Conclusion: This systematic review reports substantial knowledge gap in West/South Asian CMT research. The review emphasized the urgent need to use comprehensively of next-generation sequencing (NGS) to uncover new mutations and improve diagnostics in West/South Asian. Future region-specific cohort studies and registries can be essential to identify frequent variants and fill the diagnostic gaps.

Keywords: Asian; Charcot-Marie-tooth disease; Clinical; Epidemiology; Genetics

Introduction

Charcot-Marie-Tooth disease (CMT), alternatively referred to as hereditary motor and sensory neuropathy, encompasses a diverse range of inherited neuropathies. This group of neuropathies is categorized by the gradual deterioration of muscles and weakness in the distal regions, along with diminished sensation in the same areas. Additionally, individuals with CMT may experience foot deformities and exhibit reduced reflexes in tendons (1,2). CMT can be inherited through dif-

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ferent modes, including autosomal dominant (AD), autosomal recessive (AR), and X-linked inheritance. However, sporadic cases, which occur without a clear hereditary pattern, have also been widely documented (3). CMT is commonly classified into three types based on their electrophysiological properties, namely demyelinating (CMT1), axonal (CMT2), and intermediate Int-CMT or (ICMT) (4). CMT1 is characterized by a significantly slow motor nerve conduction velocity (MNCV) (< 38 m/s) in the upper limbs. Nerve biopsies of individuals with CMT1 typically reveal segmental de- and remyelination, along with the formation of onion bulbs. These onion bulb formations indicate abnormal changes in the myelin sheath surrounding the nerve fibers. In CMT2, the MNCV is either normal or slightly reduced (> 38 m/s) in the upper limbs. Histopathological analysis of nerve samples from CMT2 patients reveals signs of axonal impairment, including axonal loss and the presence of regeneration clusters. ICMT is identified by MNCV ranging between 25 and 45 m/s in the upper limbs. In ICMT, there are features that present a combination of both demyelination and axonal degeneration (3,5). CMT is a complex genetic condition with a wide range of associated genes. To date, researchers have identified over 100 genes that play a role in the development of CMT. However, a significant majority of genetically diagnosed cases, more than 90%, can be attributed to mutations in just four genes, namely *PMP22*, *GJB1*, *MFN2*, and *MPZ* (6).

The prevalence of CMT in Asia varies across different regions and populations. Unfortunately, there is limited comprehensive data available specifically for the prevalence of CMT in Asia as a whole. However, studies conducted in some Asian countries provided epidemiological insights. Prevalence rates may differ among various ethnic groups within a country as well. Additionally, the prevalence of CMT can vary within different subtypes of the disease (CMT1, CMT2, etc.). It can be influenced by factors such as genetic variations, environmental factors, and population demographics. Further research and studies are necessary to obtain a more comprehensive understanding of the prevalence of CMT in Asia and its specific variations among different countries and populations within the continent.

Methods

The present study is a systematic review conducted following PRISMA 2020 guidelines. We followed a structured methodology to ensure transparency and reproducibility as below. Furthermore, as the current study is based solely on previously published data, the ethical approval was not required.

Search strategy

The literature search was comprehensively conducted across six databases: PubMed, Scopus, Science Direct, Willey, Web of Sciences, and Google Scholar. The search covered publications from January 2003 to February 2023 through a combination of Medical Subject Headings (MeSH) and free-text terms including "Charcot-Marie-Tooth disease" OR "CMT" OR "hereditary motor and sensory neuropathy" AND "Asia" OR "the name of each country located in Asia continent". References of included studies were also screened manually to identify additional eligible articles. Original studies involving Asian patients diagnosed with CMT in which the frequency or types of genetic variants were reported and included relevant clinical or demographic data; were included. Exclusion criteria were reviews, editorials, case reports, animal or in vitro studies, and studies lacking genetic information or appropriate data. In addition, studies in English language were reported to warrant to consistency and quality of our review.

Selection criteria

Two group members (S.K. and Z.K.) selected the papers independently and discussed with N.A.M. to solve the disagreements. Studies met the following criteria included in the systematic review: 1) comparative studies with/without a control group, and 2) studies reported the frequency of mutations in Asia. Excluded from our study

were: 1) conference abstracts, comments, letters, animal studies, reviews, case reports, and in vitro studies; 2) duplicate publications; and 3) studies that lacked sufficient data for calculating the desired parameters.

Selection of studies

Reviewers independently screened all titles, abstracts, and full-text articles. All these articles were physically downloaded and imported into an Excel file by one author and analyzed the articles before submitting them to the second author to cross-check the accuracy. Any disagreements between the authors were solved by consensus and discussion.

Data extraction process and assessment of methodological quality

One researcher extracted data from the studies included in this review. A second researcher checked the accuracy of the extraction process. Any discrepancy was resolved through discussion and consensus, ensuring approval at each step of the finalization process. Data extracted from eligible studies including study design, country, sample size, CMT subtype, inheritance pattern, age of onset, genetic testing method, and reported gene mutations.

Quality assessment was performed using Q-Genie for genetic studies (7) and the Newcastle-Ottawa Scale (NOS) for observational studies (8). Q-Genie evaluates 11 domains related to study design, statistical methods, and interpretation of findings, while NOS assesses selection, comparability, and outcome reporting (7,8). We reported scores as high, moderate or low based on validated thresholds. Studies, which scored high and moderate, were included in the current review.

However, in the present study, a meta-analysis was not performed because of significant heterogeneity in genetic testing methods. A narrative synthesis was used to sum regional gene frequencies, CMT subtypes, inheritance patterns, and clinical observations.

Results

An initial 320 records were identified. We removed 246 articles after screening for titles and abstracts. The remaining 74 records were considered for the full review, after which we removed 20 records for reasons of missing key data, the letter to the editor, or review articles and 22 articles were removed after assessing by qualitative tools (Fig. 1). Finally, 32 articles from China (n=12), Japan (n=7), Korea (n=6), Vietnam (n=1), Iran (n=2), Lebanon (n=1), Taiwan (n=1), Pakistan (n=1), and India (n=1) fulfilled our selection criteria and were included in the review.

Epidemiology and Clinical Expression of CMT

This review of 32 studies on CMT found that the axonal CMT type in Asia was about 50% (n=16/32) of the studies, followed by the demyelinating type in approximately 28% (n=9/32) and the intermediate form in about 0.09% (n=3/32). The mean age of onset was 16 ± 5 yr that most studies were from China, Japan and Korea. However, there were limited studies to explain clearly the prevalence of CMT in other regions in Asia, including West/South Asian countries like India, Iran, Pakistan, and Lebanon.

Previous studies reported the demyelinating CMT type in China at 47-75% (5,9,10), followed by the axonal type at 29-65% (5,9) and the intermediate form at 18% (5). In Japan, the axonal CMT type was between 30-60%, and the demyelinating CMT type was between 28% and 54% (11,12). In Vietnam, the demyelinating, axonal, and intermediate CMT types were reported in 51.6%, 38.7%, and 9.7%, respectively (13).

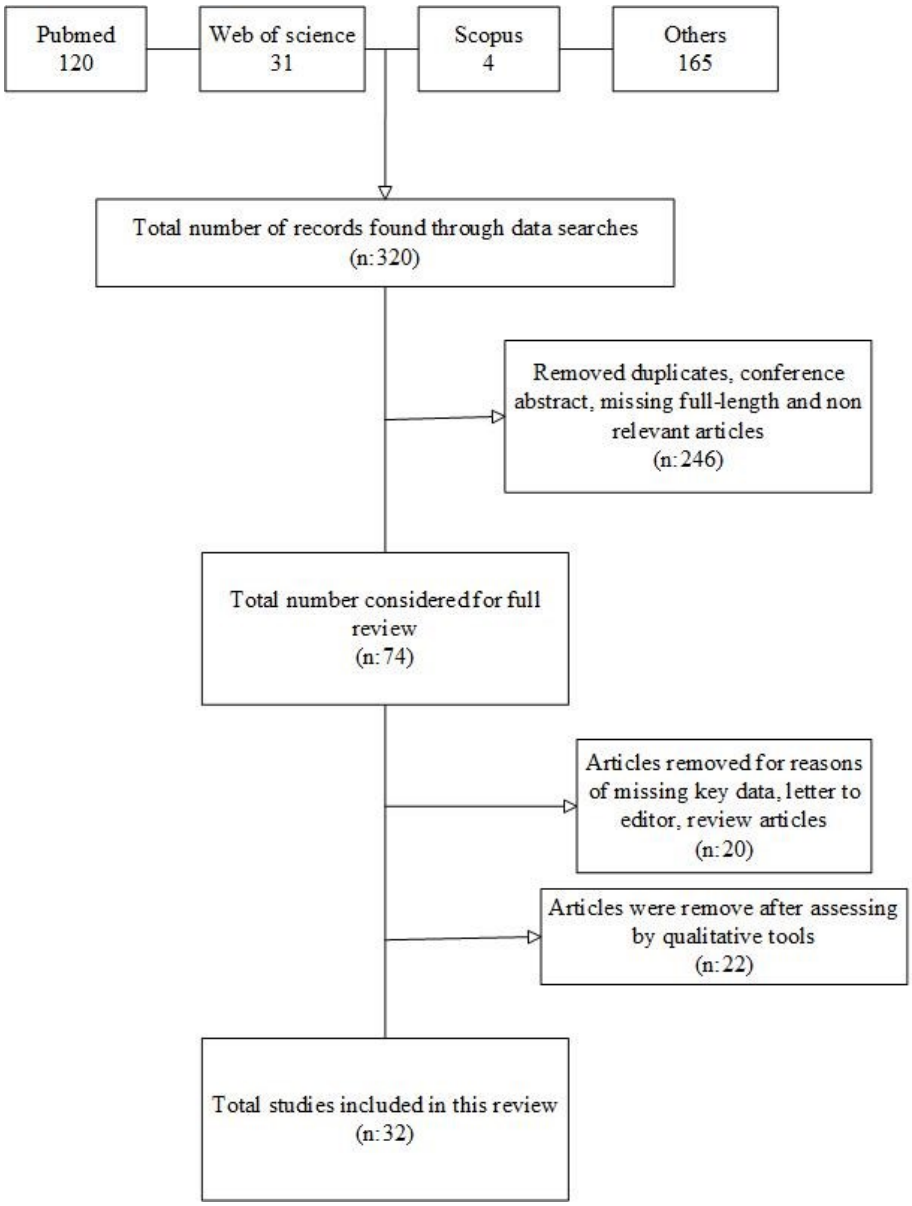

Fig. 1: Flow chart of studies selection

The disease started mostly in the first two decades of life, but later onset cases were also reported. Starting symptoms included muscle weakness, atrophy, gait disturbance, pes cavus, and absent deep reflexes (14–17); while only few cases reported scoliosis, claw hand, impaired hearing, numbness and episodic pain, hyperlexia, and flat feet as the less common starting symptoms in CMT patients (4,12,15,18,19). In India, unique symptoms were reported, such as impaired vision, hearing (5,20), facial palsy (20), impaired cognition (2,20), seizures, pyramidal signs, slow tongue movements, and psychosis. A study from Korea focused on mutations in several aminoacyl-tRNA synthetase (*ARS*) genes, a high frequency of hand muscle atrophy was observed in patients with *GARS1* variants (4). In addition, one study from Iran, focusing on the membrane metalloendopeptidase (*MME*) gene reported impaired temperature and pain sensation in extremities as one of the symptoms of CMT (16) not observed frequently in the most of studies.

The prevalence of CMT in Asia is limited due to the lack of detailed studies and the lack of precise classification of different types (2,21,22).

Variants with High Frequency

Several techniques have been used to identify the causative genes associated with CMT over time. Next generation sequencing (NGS) and whole exome sequencing (WES) were the most common methods used to identify causative genes in CMT. The results showed the frequency of mutations in multiple genes in Asia, including *PMP22, GJB1, MFN2, NDRG1, RAB7, SORD, MORC2, MPZ, GDAP1, CX32, SH3TC2, PRX, FGD4, BCL2, NEFL, GARS1, KIF1B, FIG4, MME,* and *IGHMBP*. Supplementary Table 1 showed all information related to the previous studies in detail and the detail of the novel mutations in different regions in Asia.

In China, several studies have reported novel mutations in many genes such as *RAB7* that has been associated with CMT2B and a novel mutation p. Asn161Ile in the potential mutational hotspot region (23). *SORD* is another gene showing three novel variants, likely pathogenic, including p.P244L, p.A259V, and p.L284P, together with p.A253Qfs* 27 frame shift) (19). *MORC2* also is associated with the high rate of mutations among Chinese population, revealing novel variants in CMT2 in the N-terminal ATPase module (18). *GDAP1* gene has been evaluated the frequency of several studies in China, showing three novel variants, including p.L26R, p.S169fs, and c.694 + 1G>A (3,14). Furthermore, *NDRG1* c.595-2A>G) relatively showed high frequency of mutations among CMT1A patients in the South-East China (5). *GJB1* has been reported as one of the common genes in different types of CMT, particularly with the new identification of a missense mutation c.605T>A) in *GJB1*, associated with CMTX (24). Table 1 showed the novel variants of other genes in CMT in detail.

In Korea, some genes have been reported as the genes with high frequency of mutations, with the extracellular 2 *(*EC2) domain of *GJB1* protein identified as the hot spot mutation domain in 44% of Koreans beside nine mutations were not previously reported (25). Charcot-Marie-Tooth disease type 4H (CMT4H) is an autosomal recessive demyelinating subtype of peripheral neuropathies caused by mutations in the *FGD4* gene. Exon sequencing revealed novel compound heterozygous mutations in *FGD4* as the underlying cause in cases p. Arg468Gln and c.1512-2A>C in *FC73*, p. Met345Thr and c.2043+1G>A p. Trp663Trpfs*30) in *FC646*) (26).

In Japan, the frequency of mutations in some genes *MPZ, MFN2, GJB1*, and *GDAP1*) have been higher than other genes in CMT. Three myelin-related protein gene abnormalities, *PMP22* duplication, *MPZ* mutations, and *CX32* mutations, resulted in a wide variety of demyelinating and axonal features and substitutional mutations (12,17,27). Other novel variants in various genes among Japanese have been presented in Table 1.

Table 1: Genetic characteristics included in this study

ID	Country	Prevalence	CMT type	Disease genes	Variants	Quality score	References
1	Lebanon	13	CMT1A AD)	*PMP22*	1.5-Mb duplication at 17p11.2	High	(31)
			CMT4F AR)	*PRX*	c.586C > T p. Arg196*		
			CMT4H AR)	*FGD4*	c.1698G > A p. Met566Ile		
2	Japan	7.90	CMT2	*MFN2*	c.154G >A, c.326A>G, c.389C>T, c.658G>A	High	(12)
3	Taiwan	0.57	CMT2 AR)	*BCL2*	c.269C>T; ch11:62469965G>A	High	(28)
4	Korea	14.80	CMTX1 AD, AR)	*GJB1*	c.283G>A, c.47A>G, c.112G>T, c.139G>A, c.157T>C, c.328G>A, c.414C>G	High	(32)

Table 1: Continued…

5	China	66.70	CMT1 sporadic)	*NDRG1*	c.595-2A>G	High	(5)
			CMT1X X-linked)	*GJB1*	c.T617A p.V206E)		
			CMT2A AD)	*MFN2*	c.G284C p.R95T)		
6	India	87	CMT2A AD)	*MFN2*	c. 605G>A/p. Gly202Asp/Het	High	(20)
			CMT4C AD/AR)	*SH3TC2*	c. 1105C>T/p. Arg369Cys/Het		
			CMT4H AR)	*FGD4*	c. 1062_1063insT/p		
7	Japan	30.00	CMT	*GJB1, MFN2, MPZ*	NR	High	(21)
8	China	1.63	CMT2K AR, AD)	*GDAP1*	c.122G>A, c.603delT, c.112C>T, c.643G>A, c.113A>G	Moderate	(3)
9	China	2.78	CMT2K AR)	*GDAP1*	c.T77G Het), c.505_511del Het), c.694+1G>A Hom)	Moderate	(14)
10	Korea	NR	CMT2 Dominant), CMT1 Dominant), CMT2 Isolated), respectively	*MPZ*	c.352G>A, c.449-1G>T, c.706A>G	High	(33)
			CMT1 De novo), CMT1 X-linked Dominant)	*GJB1*	c.408T>C , c.502T>C		
			CMT2 Isolated)	*NEFL*	c.1001T>C		
			CMT1 Dominant)	*PMP22*	c.318delT		
11	Japan	NR	CMT	*SLC12A6*	c.865G>A, c.1731_1733del, c.2036A>C	Moderate	(2)
12	China	12.60	CMT4 AR) CMT1	*SH3TC2*	c.2872_2872del, c.3710C>T and c.2782C>T	High	(34)
13	Korea	1.22	CMT2D	*GARS1*	c.2171C>A	High	(4)
			CMTDID	*AARS1*	c.1168C>T		
			CMT2W	*HARS1*	c.1147A>G		
			CMT	*WARS1*	c.751G>A, c.1067A>T		
			CMTDIC	*YARS1*	c.497A>G		
14	China	1.40	CMT2 AD, SF)	*MORC2*	c.1397A>G, c.260C>T, c.754C>T, c.1220G>A	High	(18)
15	China-Japan	1, 6.5	CMT2 sporadic)	*SORD*	c.757 del G, c.757 del GM c.776 C>T, c.731 C>T, c.851 T>C	Moderate	(19)
16	China	2.10	CMT1	*GJB1*	c.−16-12_−16-2delGGTGTTTTGCA	High	(9)
			CMT2	*MFN2*	c.295G>A, c.1835C>T		
			CMT1, 2	*MPZ*	c.301T>G, c.379T>C		
			CMT2	*IGHMBP2*	c.1814G>A, c.2215delA		
17	China	2.37	CMT2K AR, AD)	*GDAP1*	p.H256R	Moderate	(35)
18	China	NR	CMT2B	*RAB7*	p. Asn161Ile	Moderate	(23)
19	China	62.50	CMT1A-duplication Isolated)	*MPZ*	c.449-1G>T	High	(10)
			CMT1A-duplication X-linked dominant, Isolated)	*Cx32*	c.622G>A, c.643C>T		

Table 1: Continued…

20	Japan	~25 of de-myelinating CMT	Axonal CMT, Demyelinating CMT	*MPZ*	c.235-1G4C, c.278G4C, c.410G4C	Moderate	(36)
			Axonal CMT, Demyelinating CMT	*GJB1*	c.124A4C, c.247_256del10		
			Axonal CMT	*MFN2*	c.310C4T, c.476C4T, c.2171T4C		
			Demyelinating CMT	*PRX*	c.875-906del32; c.915-923dup9; c.924A4T; c.927T4G		
			Axonal CMT	*GDAP*	c.740C4A) + c.845G4A)		
21	Japan	45.30	CMT1 AD, sporadic)	*MPZ*	p. His81Asp, p. Ser111Tyr, p. Val142Asp	Moderate	(27)
22	China	NR	CMTX1	*GJB1*	c.605T>A	High	(24)
23	Korea	5.30	CMTX Domi-nant)	*CX32 EC2 domain)*	c.454delG, c.458T>G, c.536-537insACTG	High	(25)
24	China	NR	CMT1 AR)	*SH3TC2*	c.283C>G, c.3143T>C, c.3313G>A	High	(15)
25	Japan	NR	CMT1	*PMP22*	Duplication of PMP22 gene	High	(17)
				MPZ	Asp35Tyr, Ile62Phe, Ser63del		
				Cx32	Ser26Leu, Thr55Ala, Gln57His		
26	Vietname	41.90	CMT1E	*PMP22*	c.281delG	High	(13)
			CMT1F	*NEFL*	c.64C > A		
27	Korea	0.70	CMT4H AR)	*FC73 novel compound heter-ozygous muta-tions in FGD4)*	c.1512-2A>C	High	(26)
			CMT4H AR)	*FC646 novel compound heter-ozygous muta-tions in FGD4)*	c.2043+1G>A		
28	Korea	0.7 of 1,143	CMT2K AD)	*GDAP1*	p. R120W	Moderate	(37)
			CMT2K AD)	*GDAP1*	p. Q218E		
			CMTRIA AR)	*GDAP1*	H256R+H256		
29	China	NR	CMT	*MPZ*	c.389A>G	High	(22)
30	Pakistan	NR	CMT4C	*SH3TC2*	c.2599C>T, c.3650G>A	Moderate	(29)
			CMT4G	*HK1*	c.19C>T		
			CMT2A2B	*MFN2*	c.334G>A		
31	Iran	60.86	CMT1C	*LITAF*	c.271C>T	Moderate	(30)
			CMT4D AR)	*NDRG1*	c.205+1delG		
			CMT2A1	*KIF1B*	c.2455A>C		
			CMT4J AR)	*FIG4*	c.1728A>G		
32	Iran	NR	CMT2 AR)	*MME*	c.1564C>T	Moderate	(16)

In Vietnam, the most frequent causative gene alteration was *PMP22* (29%), followed by *MFN2* (6.5%) with two de novo variants, *NEFL* (c.64C > A p.P22T). Additionally, frameshift mutation was observed in *PMP22* c.281delG (p.94Afs*17) (13).

There are few articles to clearly identify the common variants of CMT in other countries. A

study conducted in Taiwan identified two heterozygous missense variants in *BSCL2*, and five pathogenic homozygous mutations in *SH3TC2, HK1*, and *REEP1* (28). In India, 62 variants were identified, harboring novel mutations associated with genes like *MFN2, SH3TC2, WNK1*, and *GDAP1* (20). In Pakistan, five pathogenic homozygous mutations were identified (29). Two studies from Iran found novel mutations in *LITAF, NDRG1, KIF1B, FIGF,* and *MME* genes, and a nonsense mutation in *MME* gene (16,30). In Lebanon, a common study with France reported some genes and variants, with a prevalence of CMT at about 13% (31). *SH3TC2* has been reported as a common related-CMT gene across Asia continent (5,9,21,29–31); however, more studies are needed to clarify mutations and related-CMT variants in other countries.

Discussion

This systematic review provides an extensive overview of the genetic and clinical aspects of Charcot-Marie-Tooth throughout Asia 32 studies (from 10 countries over the last two decades), highlighting a significant gap of knowledge in genotype profiles of CMT patients, particularly in West and South Asian countries. The globally estimated prevalence of CMT is around 17.69 per 2500 individuals making the disease as the most common neuropathy (38). However, our study indicated that the CMT regional prevalence rate is underreported or absent in Asia- particularly in South and West of the continent. East Asian countries such as China, Japan and South Korea have contributed the majority of data. Many Asian countries have not conducted population-based research or national registration due to the limited infrastructure, access to health care systems, availability of genetic tests, and genetic consulting for inherited neuropathies.

Clinical patterns and subtype distribution

Our systematic review found that axonal CMT is the most common subtype (50%) followed by demyelinating (28%) and intermediate (9%) CMTs. This observation was in contrast to large-scale studies in which CMT1 demyelinating form reported as the most common type (6,38,39).

The observed predominate of CMT2 in Asia may reflect true genetic differences or underdiagnosis of CMT1. Demyelinating variants are more common in Africa (58.3%) (6). This closeness between studies implies that the clinical manifestations of CMT retain some consistency across a variety of populations, even in the face of varying genetic backgrounds. CMT patients typically experience symptoms between the first and second decade of life. While the main clinical features such as primarily distal muscle weakness (3,5,17,19,20,24,25), were consistent with other reports, several unique symptoms like poor vision, hearing, facial palsy, impaired cognition, seizures, pyramidal signs, delayed ton, and psychosis were more prevalent in South Asia (20). In addition, despite slow progress of CMT the rapid progress has been observed (3,19,26). These findings highlight the broader neurological symptoms neglected in routine clinical assessments and suggest considering regional diagnostic protocols.

Most instances and families showed dominant form of CMT (n=20/32), followed by recessive inheritance (n=15/32), and then X-linked CMT (n=6).

However, it is crucial to consider under-reported cases in Asia (3,9,11,30) and highlight genes with high frequency in different regions, such as *GDAP1, MPZ,* and *GJB1*.

Asian genetic landscape of CMT

GDAP1

Mutations in *GDAP1* ganglioside-induced differentiation-associated protein (1) were among the most frequently reported in Asian-based studies (11/32), despite studies which found its low frequency rate in Asia (11,35,37,40). Novel variants were identified in several studies in China, Japan, India and Iran. Mutations in *GDAP1* typically causes AR or AD CMT2K. Chen et al shown mutations of this gene are loss of function and its dysfunction may lead into mitochondrial impairing which usually pathologically affect muscle and nervous tissues (5). H256R variant was the most

frequent in *GDAP1* associated-CMT. Common features of Chinese patients harboring H256R were early age of initial symptoms and moderate severity and axonal subtype (3). In India and Iran, novel mutations such as P66R and P144L and c.802_803delTG have also been reported (20,30). In Europe mutation in this gene accounts for 7-14% of CMT (41–43). In West Asia because of the consanguinity, the higher rates of *GDAP1* mutations are anticipated.

MPZ

MPZ (Myelin protein zero) contributes to onset of demyelinated (CMT1B) and axonal (CMT2I/J) subtypes (44). In our review, 10 studies, especially from Japan and China, found MPZ mutations. Intriguingly, Hattori et al from Japan found many variants among siblings in families, causing distinctive subgroups with a demyelinating or axonal phenotype. Neural deafness and pupillary abnormality in axonal patients were observed, indicating a common mechanism causes axonal phenotype and mentioned symptoms (17). In Chinese cohorts, novel variants (like K130R causing different subtypes of CMT and T34N causing CMT1) were observed with AD inheritance (5,22). Song et al from China found one mutation in *MPZ* and two mutations in *CX32* in Chinese CMT1 patients, indicating no ethnic difference in the distribution of the mutation (10). Choi from South Korea suggested that the *MPZ* mutation rate was similar to those reported in other ethnic non-duplicated CMT groups (33). CMT phenotypes caused by *MPZ* variants varies from severe pediatric onset to mild adult onset (27). However, the lack of data in West Asian countries prevents more accurate reporting of CMT frequency in West/South Asian regions.

GJB1

Another common gene *GJB1 (*gap junction beta-1), associated with CMTX, was reported in many studies (n=9/32). CMTX is identified as the second-most common form of hereditary motor and sensory neuropathy and accounts for up to 15% of all CMT cases worldwide that is usually caused by mutations in GJB1 gene (5). Studies in the current review did not mentioned difference of frequency between Asian countries and Europe and mutated *GJB1* is frequently reported in Asia, for instance this gene was involved in of CMT cases 9- 23% in China (45,46). Additional novel mutations reported in studies from China (c.605 T>A, c.-16-8_-14del), South Korea (c.22A>C), Vietnam (c.43C > T), and Japan (c.397delT) (13,32,47). Our findings confirm the similarity between *GJB1* mutations in Asians and non-Asians; while, novel reported variants highlight the significance of local database establishment and functional validations.

PMP22

PMP22 (peripheral myelin protein 22) duplication is the most prevalent cause of CMT1; however, some studies from East Asia suggested less involvement of this gene in CMT cases continent (48,49). This observation proposed the potential region-specific variation or diagnostic bias.

Emerging CMT genes

Our review bring light to escalating importance of novel gene variants causing CMT in Asia (Fig. 2). Numerous reported genes from Asia are rarely mentioned globally. For instance, novel mutations of *SH3TC2* commonly associated with AR CMT4 and *FGD4* associated with CMT4H were reported in India, Pakistan and China (15,20,29,34), Lebanon, and Korea (20,26,31). A systematic review from Africa highlights *LMNA, GDAP1*, and *SH3TC2* as being prominent emerging genes, with a significant shift towards AR inheritance in 91.2% of instances (6). This review and the recent study on CMT in Africa highlight the genetic heterogeneity of CMT and the need for developing comprehensive genetic testing instead of traditional four-gene panel.

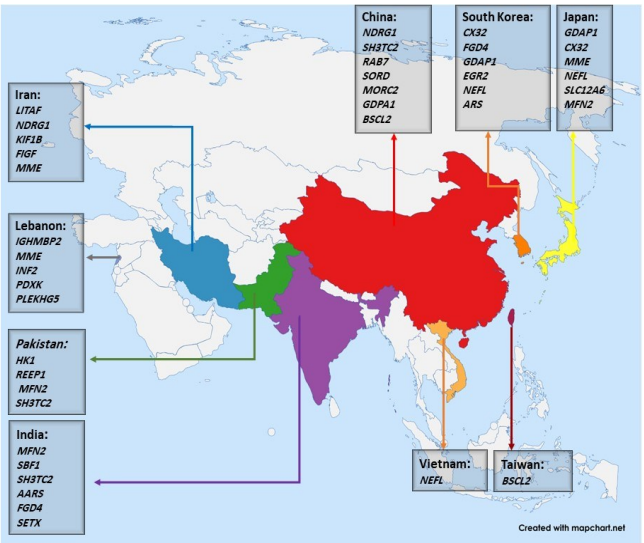

Fig. 2: Novel genes reported in respective Asian countries

Regional comparison

This review outlines a wide inconsistency in CMT research in Asia, with most work concentrated in East Asia (China, Japan, and South Korea) leaving scarce data from West and South Asia India, (Pakistan, Iran and Lebanon). CMT2 dominates in East Asia, with repeated mutations in the genes *GDAP1, MPZ, GJB1*, and *MFN2*. Infrequent *GDAP1* mutations were specifically noted among Chinese and Korean patients, indicating regional specificity (3,14,35–37). In contrast, West and South Asian populations have a higher frequency of AR-CMT in line with common consanguinity and *SH3TC2, MME,* and *NDRG1* mutations (5,16,20,29,30,34). More generalized clinical manifestations, including facial palsy and intellectual impairment, were more commonly reported in these populations. In addition, East Asia is assisted by greater use of advanced genetic screening methods like NGS, while limited resources in West/South Asia could result in underdiagnosis. Greater genetic facilities and Asian databases are essential to more balanced, comprehensive CMT studies across Asia.

Limitations

This is the first systematic review focused specifically on the clinical and genetic landscape of CMT in Asian populations, yet there are a number of limitations that need to be noted. First, there were heterogeneous methods of genetic testing, with older literature using targeted Sanger sequencing whereas studies that are more recent used wider NGS or WES panels. This produced substantial bias, and for this reason, we chose not to undertake a meta-analysis. Second, the vast majority of studies had no functional assays or control group, limiting the potential for confirming pathogenicity of variants. Third, prevalence data are still unavailable for most Asian countries, making it impossible to make solid epidemiological inferences and perhaps underestimating the true burden of CMT in the region. To overcome these obstacles in future, researchers should focus on: establishing national registries centers throughout Asia; developing designed genetic test based on specific- genetic of a nation; establishing region-specific data bases; and conducting collaborative cohort studies on CMT epidemiology and genetics in Asia.

Conclusion

CMT is not rare, and is probably underreported in Asia, especially in West/South Asian countries and briefly describes the current clinical and genetic profile. The genetic epidemiology of CMT in these Asian regions could lead to new discov-

eries important to the global research effort for therapeutic perspectives and invite researchers from West/South Asian countries to start new research of CMT with aim to provide and report more comprehensive profile of CMT in these Asian countries. The increasing access to NGS technologies offers to Asian scientists a perfect opportunity to fully describe relevant or novel variants in known genes, and also to discover novel CMT-associated genes that may improve our understanding and care of this condition in Asia, especially in West/South Asian countries that there are not comprehensive and precise profile of them.

Journalism Ethics considerations

Ethical issues Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc. have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Hsu YH, Lin KP, Guo YC, et al (2019). Mutation spectrum of Charcot-Marie-Tooth disease among the Han Chinese in Taiwan. *Ann Clin Transl Neurol*, 6 (6): 1090–1101.
2. Ando M, Higuchi Y, Yuan J, et al (2022). Novel heterozygous variants of SLC12A6 in Japanese families with Charcot-Marie-Tooth disease. *Ann Clin Transl Neurol*, 9 (7): 902–11.
3. Pakhrin PS, Xie Y, Hu Z, et al (2018). Genotype–phenotype correlation and frequency of distribution in a cohort of Chinese Charcot-Marie-Tooth patients associated with GDAP1 mutations. *J Neurol*, 265 (3): 637–46.
4. Nam DE, Park JH, Park CE, et al (2022). Variants of aminoacyl-tRNA synthetase genes in Charcot-Marie-Tooth disease: A Korean cohort study. *J Peripher Nerv Syst,* 27 (1): 38–49.
5. Chen X, Zhang Y, Li J, Huang L, Wu Z (2019). Genetic spectrum and clinical profiles in a southeast Chinese cohort of Charcot-Marie-Tooth disease. *Clin Genet,* 96 (5): 439-448.
6. Yalcouyé A, Diarra S, Traoré F, et al 2022). Current profile of Charcot-Marie-Tooth disease in Africa: A systematic review. *J Peripher Nerv Syst,* 27 (2): 100-112.
7. Sohani ZN, Meyre D, de Souza RJ, et al (2015). Assessing the quality of published genetic association studies in meta-analyses: the quality of genetic studies Q-Genie) tool. *BMC Genet,* 16: 50.
8. Lo CKL, Mertz D, Loeb M (2014). Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol,* 14: 45.
9. Xie Y, Hu Z, Li X, et al (2021). Genotype and phenotype distribution of 435 patients with Charcot-Marie-Tooth disease from central south China. *Eur J Neurol,* 28 (11): 3774-3783.
10. Song S, Zhang Y, Chen B, et al (2006). Mutation frequency for Charcot-Marie-Tooth disease type 1 in the Chinese population is similar to that in the global ethnic patients. *Genet Med,* 8 (8): 532–5.
11. Yoshimura A, Yuan JH, Hashiguchi A, et al (2017). Clinical and mutational spectrum of Japanese patients with Charcot-Marie-Tooth disease caused by GDAP1 variants. *Clin Genet,* 92 (3): 274–80.
12. Ando M, Higuchi Y, Yoshimura A, et al (2017). Clinical and genetic diversities of Charcot-Marie-Tooth disease with MFN2 mutations in a large case study. *J Peripher Nerv Syst,* 22 (3): 191-199.
13. Nguyen-Le T, Pham TT, Tran HQ, et al (2022). Genotype–phenotype characteristics of Vietnamese patients diagnosed with Charcot-Marie-Tooth disease. *Brain Behav,* 12 (9): e2744.
14. Chen C, Li J, Dong H, Liu G, Bai G, Wu Z (2020). Identification and functional characterization of novel GDAP1 variants in Chinese patients with Charcot-Marie-Tooth disease. *Ann Clin Transl Neurol,* 7 (12): 2381–92.

15. Zhao X, Jiang MM, Yan YZ, et al (2018). Screening for SH3TC2, PMP2, and BSCL2 variants in a cohort of Chinese patients with Charcot-Marie-Tooth. *Chin Med J (Engl),* 131 (2): 151–5.
16. Jamiri Z, Khosravi R, Heidari MM, et al (2022). A nonsense mutation in MME gene associates with autosomal recessive late-onset Charcot-Marie-Tooth disease. *Mol Genet Genomic Med,* 10 (5): e1913.
17. Hattori N, Yamamoto M, Yoshihara T, et al (2003). Demyelinating and axonal features of Charcot-Marie-Tooth disease with mutations of myelin-related proteins PMP22, MPZ and Cx32): a clinicopathological study of 205 Japanese patients. *Brain,* 126 (Pt 1): 134–51.
18. Duan X, Liu X, Wang G, et al (2021). Characterization of genotype-phenotype correlation with MORC2 mutated axonal Charcot-Marie-Tooth disease in a cohort of Chinese patients. *Orphanet J Rare Dis,* 16 (1): 244.
19. Liu X, He J, Yilihamu M, et al (2021). Clinical and genetic features of biallelic mutations in SORD in a series of Chinese patients with Charcot-Marie-Tooth and distal hereditary motor neuropathy. *Front Neurol,* 12: 733926.
20. Sharma S, Govindaraj P, Chickabasaviah YT, et al (2022). Genetic spectrum of inherited neuropathies in India. *Ann Indian Acad Neurol,* 25 (3): 407–16.
21. Yoshimura A, Yuan JH, Hashiguchi A, et al (2019). Genetic profile and onset features of 1005 patients with Charcot-Marie-Tooth disease in Japan. *J Neurol Neurosurg Psychiatry,* 90 (2): 195–202.
22. Hao X, Li C, Lv Y, et al (2022). MPZ gene variant site in Chinese patients with Charcot-Marie-Tooth disease. *Mol Genet Genomic Med,* 10 (4): e1890.
23. Wang X, Han C, Liu W, et al (2014). A novel RAB7 mutation in a Chinese family with Charcot-Marie-Tooth type 2B disease. *Gene,* 534 (2): 431–4.
24. Liu Y, Xue J, Li Z, et al (2020). A novel GJB1 mutation associated with X-linked Charcot-Marie-Tooth disease in a large Chinese family pedigree. *Mol Genet Genomic Med,* 8 (3): e1127.
25. Kim Y, Choi KG, Park KD, et al (2012). X-linked dominant Charcot-Marie-Tooth disease with connexin 32 Cx32) mutations in Koreans. *Clin Genet,* 81 (2): 142–9.
26. Hyun YS, Lee J, Kim HJ, et al (2015). Charcot-Marie-Tooth disease type 4H resulting from compound heterozygous mutations in FGD4 from nonconsanguineous Korean families. *Ann Hum Genet,* 79 (6): 460–9.
27. Taniguchi T, Ando M, Okamoto Y, et al (2021). Genetic spectrum of Charcot-Marie-Tooth disease associated with myelin protein zero gene variants in Japan. *Clin Genet,* 99 (3): 359–75.
28. Lin Y, Chen Y, Wang J, Huang Z, Wu Y (2016). Clinical and molecular characterization of BSCL2 mutations in a Taiwanese cohort with hereditary neuropathy. *PLoS One,* 11 (1): e0147677.
29. Kanwal S, Choi YJ, Lim SO, et al (2021). Novel homozygous mutations in Pakistani families with Charcot-Marie-Tooth disease. *BMC Med Genomics,* 14 (1): 174.
30. Bakhshandeh M, Ghorbani A (2023). Mutational spectrum and clinical symptoms of Iranian patients with Charcot-Marie-Tooth disease: a study of 23 patients. *J Iran Med Counc,* 6 (3): 488–503.
31. Megarbane A, Bizzari S, Deepthi A, et al (2022). A 20-year clinical and genetic neuromuscular cohort analysis in Lebanon: an international effort. *J Neuromuscul Dis,* 9 (1): 193–210.
32. Hong YB, Park JM, Yu JS, et al (2017). Clinical characterization and genetic analysis of Korean patients with X-linked Charcot-Marie-Tooth disease type 1. *J Peripher Nerv Syst,* 22 (3): 172–81.
33. Choi BO, Lee MS, Shin SH, et al (2004). Mutational analysis of PMP22, MPZ, GJB1, EGR2 and NEFL in Korean Charcot-Marie-Tooth neuropathy patients. *Hum Mutat,* 24 (2): 185–6.
34. Sun B, He ZQ, Li YR, et al (2022). Screening for SH3TC2 variants in Charcot-Marie-Tooth disease in a cohort of Chinese patients. *Acta Neurol Belg,* 122 (5): 1169–75.
35. Fu J, Dai S, Lu Y, et al (2017). Similar clinical, pathological, and genetic features in Chinese patients with autosomal recessive and dominant Charcot-Marie-Tooth disease type 2K. *Neuromuscul Disord,* 27 (8): 760–5.
36. Abe A, Numakura C, Kijima K, et al (2011). Molecular diagnosis and clinical onset of Charcot-Marie-Tooth disease in Japan. *J Hum Genet,* 56 (5): 364–8.

37. Kim HS, Kim HJ, Nam SH, et al (2021). Clinical and neuroimaging features in Charcot-Marie-Tooth patients with GDAP1 mutations. *J Clin Neurol,* 17 (1): 52–62.
38. Ma M, Li Y, Dai S, et al (2023). A meta-analysis on the prevalence of Charcot-Marie-Tooth disease and related inherited peripheral neuropathies. *J Neurol,* 270 (5): 2468–82.
39. Pisciotta C, Bertini A, Tramacere I, et al (2023). Clinical spectrum and frequency of Charcot-Marie-Tooth disease in Italy: data from the National CMT Registry. *Eur J Neurol,* 30 (8): 2461–70.
40. Manzoor U, Ali A, Ali SL, et al (2023). Mutational screening of GDAP1 in dysphonia associated with Charcot-Marie-Tooth disease: clinical insights and phenotypic effects. *J Genet Eng Biotechnol,* 21 (1): 119.
41. Auranen M, Ylikallio E, Toppila J, et al (2013). Dominant GDAP1 founder mutation is a common cause of axonal Charcot-Marie-Tooth disease in Finland. *Neurogenetics,* 14 (2): 123–32.
42. Crimella C, Tonelli A, Airoldi G, et al (2010). The GST domain of GDAP1 is a frequent target of mutations in the dominant form of axonal Charcot-Marie-Tooth type 2K. *J Med Genet,* 47 (10): 712–6.
43. Zimoń M, Battaloğlu E, Parman Y, et al (2015). Unraveling the genetic landscape of autosomal recessive Charcot-Marie-Tooth neuropathies using a homozygosity mapping approach. *Neurogenetics,* 16 (1): 33–42.
44. Lee JH, Kim JH, Park JS, Shin JH, Jung WS (2022). Clinical genetics of Charcot-Marie-Tooth disease. *J Clin Med,* 11 (5): 1284–93.
45. Shu XM, Tian MQ, Li J, Peng LY, Yu XH (2015). X-linked hereditary motor sensory neuropathy type 1 CMTX1) in a three-generation Gelao Chinese family. *Neuropediatrics,* 46 (6): 424–7.
46. Sun B, Chen Z, Ling L, Yang F, Huang X (2017). Clinical and genetic spectra of Charcot-Marie-Tooth disease in Chinese Han patients. *J Peripher Nerv Syst,* 22 (1): 13–8.
47. Sakaguchi H, Yamashita S, Miura A, et al (2011). A novel GJB1 frameshift mutation produces a transient CNS symptom of X-linked Charcot-Marie-Tooth disease. *J Neurol,* 258 (2): 284–90.
48. Wang R, He J, Li JJ, et al (2015). Clinical and genetic spectra in a series of Chinese patients with Charcot-Marie-Tooth disease. *Clin Chim Acta,* 451 (Pt 2): 263–70.
49. Nakagawa M (2011). A commentary on molecular diagnosis and clinical onset of Charcot-Marie-Tooth disease in Japan. *J Hum Genet,* 56 (5): 341–2.