J Genet Resour 2026; 12(1): 94-106 *Homepage: http://sc.journals.umz.ac.ir/*
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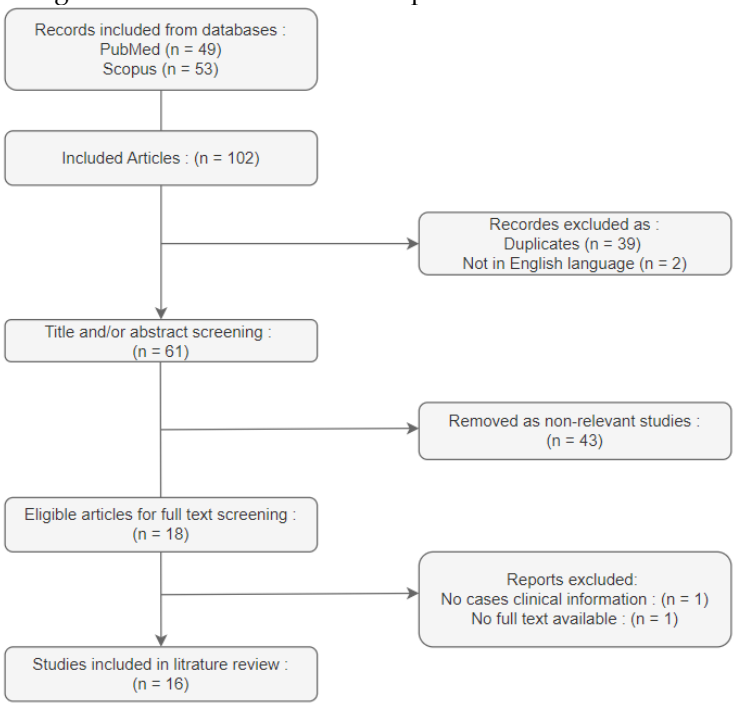
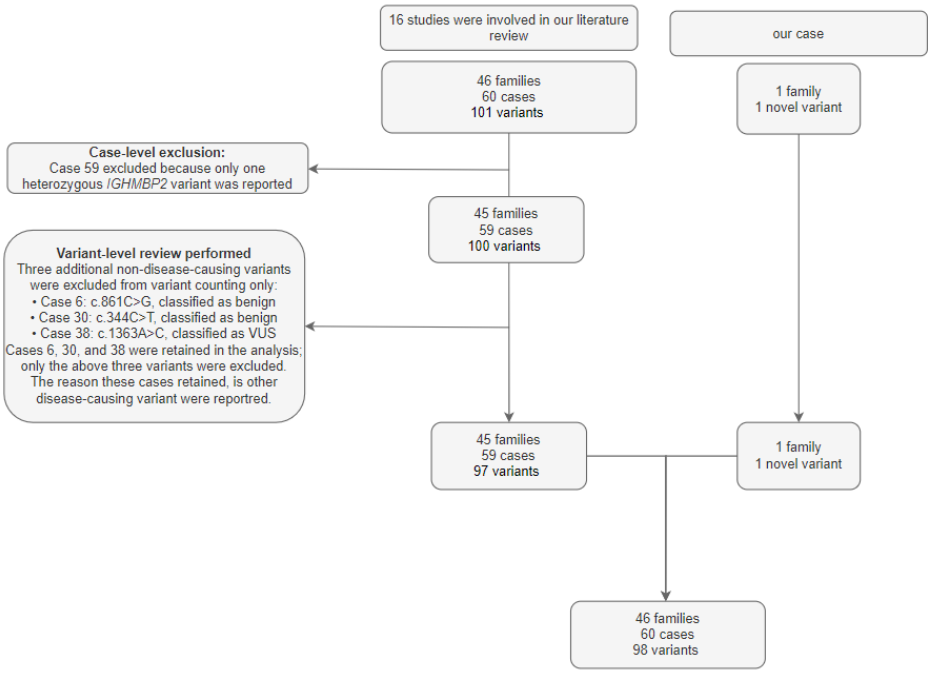
Supplement 1. The flow diagram for the literature review process from different literature databases.



Supplement 2. The flowchart above shows the process used to count variants during the literature review.



Supplement 3. Statistical analysis of coverage in exome sequencing

Average Coverage	% Target bp Covered					
(X)	0X	≥1X	≥ 2X	≥ 10X	≥ 20X	≥ 50X
107.00	1.60	98.40	98.00	98.00	96.00	77.00

Supplement 4. Literature review search strategy in PubMed and Scopus database

Query	Count
Scopus	
(TITLE-ABS-KEY (ighmbp2 gene) AND TITLE-ABS-KEY (charcot marie tooth disease) OR TITLE-ABS-KEY (cmt2s))	53
PubMed	
("IGHMBP2 protein, human" [Supplementary Concept] OR "IGHMBP2"[Title/Abstract]) AND ("Charcot-Marie-Tooth Disease"[Mesh] OR "CMT2S"[Title/Abstract])	49

Supplement 5. ACMG criteria applied for the *IGHMBP2* variant c.509T>C (p.Leu170Pro)

Criteria met	Justification
PM2	The variant was absent from population databases, including gnomAD, supporting rarity in the general population.
PP3_moderate	Multiple in silico prediction tools supported a deleterious effect of the variant, including SIFT, PolyPhen-2, CADD, AlphaMissense, REVEL, DANN, and MutationTaster. In addition, structural prediction analyses suggested that the variant may affect protein stability and structure. Therefore, PP3 was applied at moderate strength.
PP1_supporting	The variant showed segregation with the disease phenotype in the family. Because the number of informative meioses was limited, PP1 was conservatively applied at supporting strength rather than moderate strength. First family: N_1 = 1 (proband V-1) * ¾ (unaffected sibling V-2) * ¾ (unaffected sibling V-3) = 9/16 Second Family: N_2 = ¼ (affected individual V-4) Combined segregation probability: $N_{combined} = N_1 * N_2 \rightarrow N_{combined} = 9/16 * ¼ = 9/64 = 0.1406$ According to Jarvik & Browning (2016), for evidence from more than one family: **PP1 Supporting:** $N_{combined} \leq 1/4$ **PP1 Moderate:** $N_{combined} \leq 1/8$ **PP1 Strong:** $N_{combined} \leq 1/16$ Since $N_{combined}$ = 0.1406 is below 1/4 but above 1/8, the segregation data support application of PP1 at the supporting strength (PP1_Supporting).
PP2_supporting	Missense variation is an established disease mechanism for *IGHMBP2*-related disorders, and pathogenic missense variants are enriched among reported non-VUS missense variants in this gene. According to the VarSome gene-level assessment, 77 of 94 non-VUS missense variants in *IGHMBP2* are classified as pathogenic, corresponding to 81.9%, which exceeds the suggested threshold of 80.8%. Therefore, PP2 was applied at supporting strength.

Supplement 6. PP2_supporting evidence for the *IGHMBP2* variant c.509T>C (p.Leu170Pro) based on VarSome assessment

Supplement 7. Summary of Genetic Variants Reported in Previous Studies

Row Number	Family	Case	Ethnicity	Gender	Age of onset	Age at the examination	cDNA change	Location	Zygosity	Protein Alteration	Mutation Type	ACMG from Franklin database	Refs
1	1	1	Iranian	Female	2y	9y	c.509T>C	Exon 4	Homozygous	p.(Leu170Pro)	Missense	VUS	This study
2	2	2	Turkish	Male	2y	7y	c.2568_2569delAG	Exon 13	Homozygous	p.(Gly857Alafs*27)	Frameshift	LP	Yavas *et al.*, 2025
3		3	Turkish	Male	4y	7y	c.2568_2569delAG	Exon 13	Homozygous	p.(Gly857Alafs*27)	Frameshift	LP	Yavas *et al.*, 2025
4	3	4	Georgian	Male	18m	12y	c.181G>C	Exon 2	Compound heterozygous	p.(Gly61Arg)	Missense	LP	Tkemaladze *et al.*,, 2025
5							c.613T>C	Exon 5		p.(Ser205Pro)	Missense	VUS	
6		5	Georgian	Male	NA	7y	c.181G>C	Exon 2	Compound heterozygous	p.(Gly61Arg)	Missense	LP	Tkemaladze *et al.*,, 2025
7							c.613T>C	Exon 5		p.(Ser205Pro)	Missense	VUS	
8	4	6	Pakistani	Female	10y	28y	c.1363A>C	Exon 9	Homozygous	p.(Thr455Pro)	Missense	VUS	Tkemaladze *et al.*,, 2025
9							c.1591C>A	Exon 11	Homozygous	p.(Pro531Thr)	Missense	LP	
10	5	7	Vietnamese	Male	2y	13y	c.1235+3A>G	Intron 8	Compound heterozygous	p.(Ala355Leufs*10)	Splicing	LP	Tran *et al.*,, 2024
11							c.2362C>T	Exon 13		p.(Arg788*)	Nonsense	P	
12	6	8	Vietnamese	Male	4m	3y	c.1235+3A>G	Intron 8	Compound heterozygous	p.(Ala355Leufs*10)	Splicing	LP	Tran *et al.*,, 2024
13							c.1334A>C	Exon 9		p.(His445Pro)	Missense	LP	
14	7	9	Chinese	Male	8m	6y	c.743T>A	Exon 6	Compound heterozygous	p.(Val248Glu)	Missense	VUS	Liu *et al.*,, 2024
15							c.1235+3A>G	Intron 8		p.(Ala355Leufs*10)	Splicing	LP	
16		10	Chinese	Female	8m	12y	c.743T>A	Exon 6	Compound heterozygous	p.(Val248Glu)	Missense	VUS	Liu *et al.*,, 2024
17							c.1235+3A>G	Intron 8		p.(Ala355Leufs*10)	Splicing	LP	
18	8	11	Chinese	Female	4m	9y	c.1489G>A	Exon 10	Compound heterozygous	p.(Gly497Arg)	Missense	LP	Liu *et al.*,, 2024
19							c.1694_1696delATG	Exon 12		p.(Asp565del)	In-frame	LP	
20	9	12	Chinese	Male	2y	1.3y	c.2362C>T	Exon 13	Compound heterozygous	p.(Arg788*)	Nonsense	P	Liu *et al.*,, 2024
21							c.2509A>T	Exon 13		p.(Arg837*)	Nonsense	LP	
22	10	13	Chinese	Male	3m	3y	c.2598_2599delGA	Exon 13	Compound heterozygous	p.(Lys868Serfs*16)	Frameshift	P	Liu *et al.*,, 2024
23							c.1256C>A	Exon 9		p.(Ser419*)	Nonsense	LP	
24	11	14	Chinese	Male	5y	25y	c.791G>A	Exon 6	Compound heterozygous	p.(Arg264His)	Missense	P	Liu *et al.*,, 2024
25							c.884A>G	Exon 6		p.(Asp295Gly)	Missense	LP	
26	12	15	Chinese	Female	3y	4y	c.272T>C	Exon 3	Compound heterozygous	p.(Leu91Pro)	Missense	VUS	Lei *et al.*,, 2022
27							c.1924T>C	Exon 13		p.(Tyr642His)	Missense	VUS	
28	13	16	Chinese	Female	7y	38y	c.575T>A	Exon 5	Compound heterozygous	p.(Leu192Gln)	Missense	VUS	Lei *et al.*,, 2022
29							c.1814G>A	Exon 13		p.(Arg605Gln)	Missense	VUS	

Continues of Supplement 7

Row Number	Family	Case	Ethnicity	Gender	Age of onset	Age at the examination	cDNA change	Location	Zygosity	Protein Alteration	Mutation Type	ACMG from Franklin database	Ref
30	14	17	Chinese	Female	3m	8y	c.989T>C	Exon 7	Compound heterozygous	p.(Leu330Pro)	Missense	VUS	Lei *et al.*,, 2022
31							c.1196G>A	Exon 8		p.(Gly399Asp)	Missense	VUS	
32		18	Chinese	Male	1y	3y	c.989T>C	Exon 7	Compound heterozygous	p.(Leu330Pro)	Missense	VUS	Lei *et al.*,, 2022
33							c.1196G>A	Exon 8		p.(Gly399Asp)	Missense	VUS	
34	15	19	Chinese	Female	3m	4y	c.2215delA	Exon 13	Compound heterozygous	p.(Ser739Alafs*23)	Frameshift	LP	Lei *et al.*,, 2022
35							c.2784+1G>A	Intron 14		?	Splicing	LP	
36	16	20	Not stated	Female	3m	9y	c.1730T>C	Exon 12	Compound heterozygous	p.(Leu577Pro)	Missense	P	Cassini *et al.*,, 2019
37							c.1235+894C>A	Intron 8		introudce new pseudo exon	Intronic	LP	
38	17	21	Turkish	Female	1y	9y	c.2568_2569delAG	Exon 13	Homozygous	p.(Gly857Alafs*27)	Frameshift	LP	İpek *et al.*,, 2025
39	18	22	Pakistani	Male	NA	20y	c.1591C>A	Exon 11	Homozygous	p.(Pro531Thr)	Missense	LP	Ahmed *et al.*,, 2024
40	19	23	Pakistani	Female	NA	NA	c.1591C>A	Exon 11	Homozygous	p.(Pro531Thr)	Missense	LP	Ahmed *et al.*,, 2024
41		24	Pakistani	Male	NA	7y	c.1591C>A	Exon 11	Homozygous	p.(Pro531Thr)	Missense	LP	Ahmed *et al.*,, 2024
42	20	25	Indian	Female	NA	5y	c.1198G>A	Exon 8	Homozygous	p.(Asp400Asn)	Missense	LP	Chandrasekharan *et al.*,, 2022
43	21	26	Indian	Female	NA	10y	c.1198G>A	Exon 8	Homozygous	p.(Asp400Asn)	Missense	LP	Chandrasekharan *et al.*,, 2022
44	22	27	Caucasian	Male	<1y	11y	c.1156T>C	Exon 8	Compound heterozygous	p.(Trp386Arg)	Missense	LP	Kulshrestha *et al.*,, 2018
45							c.2747G>A	Exon 14		p.(Cys916Arg)	Missense	VUS	
46	23	28	Iranian	Female	1	30y	c.1325A>G	Exon 9	Homozygous	p.(Tyr442Cys)	Missense	VUS	Tomaselli *et al.*,, 2018
47	24	29	Japanese	Female	4y	22y	c.1034C>A	Exon 7	Compound heterozygous	p.(Ala345Glu)	Missense	VUS	Yuan *et al.*,, 2017
48							c.1783C>T	Exon 13		p.(Arg595Trp)	Missense	VUS	
49	25	30	Chinese	Male	13y	22y	c.344C>T	Exon 3	Compound heterozygous	p.(Thr115Met)	Missense	B	Yuan *et al.*,, 2017
50							c.1195G>A	Exon 8		p.(Gly399Ser)	Missense	VUS	
51							c.1060+5G>C	Intron 7		?	Splicing	VUS	
52	26	31	Chinese	Male	childhood	66y	c.2759A>G	Exon 14	Homozygous	p.(Tyr920Cys)	Missense	VUS	Yuan *et al.*,, 2017
53	27	32	Chinese	Male	7y	49y	c.1235+3A>G	Intron 8	Homozygous	p.(Ala355Leufs*10)	Splicing	LP	Liu *et al.*,, 2017
54		33	Chinese	Male	8y	62y	c.1235+3A>G	Intron 8	Homozygous	p.(Ala355Leufs*10)	Splicing	LP	Liu *et al.*,, 2017
55		34	Chinese	Male	20y	66y	c.1235+3A>G	Intron 8	Homozygous	p.(Ala355Leufs*10)	Splicing	LP	Liu *et al.*,, 2017
56	28	35	Chinese	Female	9m	2y	c.1737C>A	Exon 12	Compound heterozygous	p.(Phe579Leu)	Missense	LP	Liu *et al.*,, 2017
57							c.2597_2598delAG	Exon 13		p.(Lys868Serfs*16)	Frameshift	P	

Continues of Supplement 7

Row Number	Family	Case	Ethnicity	Gender	Age of onset	Age at the examination	cDNA change	Location	Zygosity	Protein Alteration	Mutation Type	ACMG from Franklin database	Ref
58	29	36	Chinese	Male	18m	7y	c.1489G>A	Exon 10	Compound heterozygous	p.(Gly497Arg)	Missense	LP	Liu *et al.*,, 2017
59							c.2356delG	Exon 13		p.(Ala786Profs*45)	Frameshift	P	
60	30	37	Chinese	Female	40d	5y	c.1061-2A>G	Intron 7	Compound heterozygous	p.(Ala355Leufs*10)	Splicing	P	Liu *et al.*,, 2017
61							c.1909C>T	Exon 13		p.(Arg637Cys)	Missense	LP	
62	31	38	Pakistani	Male	6m	6y	c.2T>C	Exon 1	Homozygous	p.(Met1?)	Startloss	LP	Pedurupillay *et al.*,, 2016
63							c.861C>G	Exon 6	Homozygous	p.(Ser287Arg)	Missense	B	
64	32	39	Norwegian	Male	4m	4.5y	c.983_987delAAGAA	Exon 7	Compound heterozygous	p.(Lys328Thrfs*46)	Frameshift	P	Pedurupillay *et al.*,, 2016
65							c.1478C>T	Exon 10		p.(Thr493Ile)	Missense	P	
66		40	Norwegian	Female	1m	11m	c.983_987delAAGAA	Exon 7	Compound heterozygous	p.(Lys328Thrfs*46)	Frameshift	P	Pedurupillay *et al.*,, 2016
67							c.1478C>T	Exon 10		p.(Thr493Ile)	Missense	P	
68	33	41	Kurdish	Female	13m	6y	c.449+1G>T	Intron 3	Homozygous	p.(Lys150Asnfs*0)	Splicing	P	Pedurupillay *et al.*,, 2016
69	34	42	Lebanese	Male	6m	34y	c.449+1G>T	Intron 3	Homozygous	p.(Lys150Asnfs*0)	Splicing	P	Schottmann *et al.*,, 2015
70		43	Lebanese	Female	2y	22y	c.449+1G>T	Intron 3	Homozygous	p.(Lys150Asnfs*0)	Splicing	P	Schottmann *et al.*,, 2015
71	35	44	English	Male	2y	18y	c.2784+1G>T	Intron 14	Homozygous	p.(Gly871Aspfs*6)	Splicing	P	Schottmann *et al.*,, 2015
72		45	English	Female	3y6m	14y	c.2784+1G>T	Intron 14	Homozygous	p.(Gly871Aspfs*6)	Splicing	P	Schottmann *et al.*,, 2015
73	36	46	Turkish	Female	6y	37y	c.138T>A	Exon 2	Compound heterozygous	p.(Cys46*)	Nonsense	P	Schottmann *et al.*,, 2015
74							c.2911_2912delAG	Exon 15		p.(Arg971Glufs*4)	Frameshift	LP	
75	37	47	English	Female	7y	43y	c.138T>A	Exon 2	Compound heterozygous	p.(Cys46*)	Nonsense	P	Cottenie *et al.*,, 2014
76							c.2911_2912delAG	Exon 15		p.(Arg971Glufs*4)	Frameshift	LP	
77		48	English	Female	6y	40y	c.138T>A	Exon 2	Compound heterozygous	p.(Cys46*)	Nonsense	P	Cottenie *et al.*,, 2014
78							c.2911_2912delAG	Exon 15		p.(Arg971Glufs*4)	Frameshift	LP	
79	38	49	English	Male	5y	23y	c.138T>A	Exon 2	Compound heterozygous	p.(Cys46*)	Nonsense	P	Cottenie *et al.*,, 2014
80							c.2911_2912delAG	Exon 15		p.(Arg971Glufs*4)	Frameshift	LP	
81	39	50	Serbian	Male	2y	14y	c.138T>A	Exon 2	Compound heterozygous	p.(Cys46*)	Nonsense	P	Cottenie *et al.*,, 2014
82							c.604T>G	Exon 5		p.(Phe202Val)	Missense	LP	
83		51	Serbian	Female	2y	15y	c.138T>A	Exon 2	Compound heterozygous	p.(Cys46*)	Nonsense	P	Cottenie *et al.*,, 2014
84							c.604T>G	Exon 5		p.(Phe202Val)	Missense	LP	

Continues of Supplement 7

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85	40	52	Pakistani	Female	7y	20y	c.1591C>A	Exon 11	Compound heterozygous	p.(Pro531Thr)	Missense	LP	Cottenie *et al.*,, 2014
86							c.1738G>A	Exon 12		p.(Val580Ile)	Missense	P	
87	41	53	Vietnamese	Female	3y	39y	c.1813C>T	Exon 13	Compound heterozygous	p.(Arg605*)	Nonsense	P	Cottenie *et al.*,, 2014
88							c.2770C>T	Exon 14		p.(His924Tyr)	Missense	VUS	
89	42	54	English	Male	4y	15y	c.238A>G	Exon 2	Compound heterozygous	p.(Ser80Gly)	Missense	VUS	Cottenie *et al.*,, 2014
90							c.1488C>A	Exon 10		p.(Cys496*)	Nonsense	P	
91	43	55	American	Female	6y	10y	c.1156T>C	Exon 8	Compound heterozygous	p.(Trp386Arg)	Missense	LP	Cottenie *et al.*,, 2014
92							c.2911_2912delAG	Exon 15		p.(Arg971Glufs*4)	Frameshift	LP	
93	44	56	Polish	Female	4y	28y	c.2968_2980del	Exon 15	Homozygous	p.(990_994del)	Frameshift	VUS	Cottenie *et al.*,, 2014
94	45	57	Italian	Female	1y	12y	c.1118T>G	Exon 8	Compound heterozygous	p.(Val373Gly)	Missense	VUS	Cottenie *et al.*,, 2014
95							c.1582G>A	Exon 11		p.(Ala528Thr)	Missense	LP	
96		58	Italian	Male	1y	6y	c.1118T>G	Exon 8	Compound heterozygous	p.(Val373Gly)	Missense	VUS	Cottenie *et al.*,, 2014
97							c.1582G>A	Exon 11		p.(Ala528Thr)	Missense	LP	
98	46	59	Korean	Male	5y	41y	c.734A>G	Exon 6	Heterozygous	p.(Asn245Ser)	Missense	VUS	Cottenie *et al.*,, 2014
99	47	60	English	Male	7y	20y	c.1813C>T	Exon 13	Compound heterozygous	p.(Arg605*)	Nonsense	P	Cottenie *et al.*,, 2014
100							Deletion	-		?	Deletion	?	
101		61	English	Male	10y	18y	c.1813C>T	Exon 13	Compound heterozygous	p.(Arg605*)	Nonsense	P	Cottenie *et al.*,, 2014
102							Deletion	-		?	Deletion	?	

Legend: P = Pathogenic; LP = Likely pathogenic; VUS = Variant uncertain significance; LB= Likely benign; B= Benign; NA= Not available; Y= Year; M= Month; D= Day