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Review Article

Molar incisor hypomineralization: A review and prevalence in Japan

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ABSTRACT

Molar incisor hypomineralization (MIH) is defined as hypomineralization of systemic origin of one to four first permanent molars, and incisors are also frequently affected. This disorder is a serious concern in pediatric dentistry. Teeth affected by MIH have many dental problems, such as hypersensitivity, poor aesthetics, and rapid progression of dental caries. The prevalence of MIH ranges from 2.8% to 21% among studies with more than 1000 subjects in different countries and age groups. The etiology of MIH is unclear, but genetic and environmental factors have been proposed. This review describes the prevalence, etiology, and clinical management of MIH. A detailed description of MIH prevalence in Japan is also provided.

1. Introduction

In recent years, site-specific hypoplastic enamel disorders such as molar incisor hypomineralization (MIH) and hypomineralized second primary molars (HSPMs) have become serious concerns in pediatric dentistry [1]. MIH is a hypomineralized defect of one to four first permanent molars, and it occasionally involves permanent incisors (Fig. 1) [2]. A high rate of need for treatment for MIH-affected molars has been reported among patients in areas with a generally low prevalence of caries [3–5]. The increased number of caries is due to hypomineralized enamel, which has fewer distinct prism edges and crystals and more pronounced interprismatic space, and the immature permanent tooth has a higher ratio of carbonated apatite than hydroxyapatite [6]. As a result, MIH enamel is more porous and weaker than normal enamel [7].

MIH often appears as differently colored opacities in the affected teeth, which sometimes undergo post-eruptive breakdown due to weak enamel [8]. The European Academy of Pediatric Dentistry guidelines are often used to diagnose MIH and include the following criteria: clearly demarcated opacity in the occlusal and buccal surfaces of the crowns, white or yellow-to-brown discolorations, MIH defects of at least 1 mm in diameter, the presence of hypersensitivity, the presence of atypical restorations, and the need for extraction of permanent teeth [9,10]. Clinical management of MIH is difficult due to the rapid development of dental caries, limited cooperation of children, and repeated breakdown of restorations [11]. MIH can affect both aesthetics and cariogenic susceptibility and is considered a global dental problem [12].

This review describes the prevalence, proposed etiology, and clinical management of MIH. Furthermore, a detailed description of MIH prevalence in Japan is provided.

2. Prevalence of MIH

Today, abundant data on the prevalence of MIH are available. The prevalence of MIH has been shown to range from 2.8% to 44% in different studies [13]. Among studies with more than 1000 subjects, the prevalence of MIH ranges from 2.8% to 21%. Overall, the prevalence of MIH varies by country, region, and age group studied [14].

Examination for MIH should be done at the age of 8 years, because at this age, all first molars and most incisors have erupted. Furthermore, the first molars are in relatively good condition at this point [8]. Of course, post-eruptive breakdown occurring before 8 years of age needs attention in clinical practice. Understanding the true prevalence of MIH requires a uniform calibration procedure, and the number of subjects included needs to be large enough to be representative of the studied population [10]. Table 1 shows

Abbreviations: MIH, molar incisor hypomineralization; HSPM, hypomineralized second primary molar; CPP-ACP, casein phosphopeptide-amorphous calcium phosphate; GIC, glass ionomer cement; S-PRG, surface pre-reacted glass ionomer; PMC, preformed metal crown.

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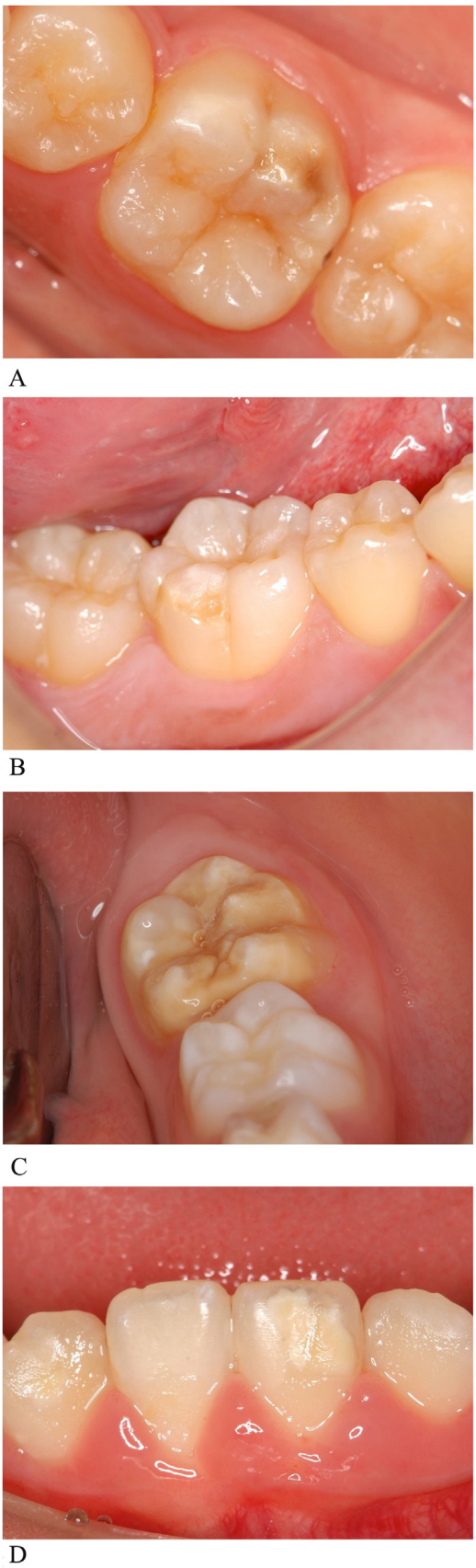

Fig. 1. A presentation of MIH.
A: A dark opacity of tooth discoloration in a lower right first permanent molar. B: An enamel defect. An infected lower left first permanent molar. C: An enamel and dentin defect in a lower left first permanent molar. D: A white opacity of tooth discoloration in the lower left incisor.

the prevalence of MIH in 28 studies that included more than 1000 subjects.

3. Etiology of MIH

MIH was initially described as an idiopathic defect [15]. Most studies suggest that a combination of factors may affect ameloblasts, resulting in abnormal enamel formation leading to MIH [13]. Ameloblasts can be adversely affected in both the prenatal and postnatal periods of tooth development by other antecedents, such as low birth weight, maternal illness or psychological stress during pregnancy, delivery complications, dioxins in the mother's milk during breastfeeding, and smoking and alcohol use during pregnancy, as well as asthma, pneumonia, respiratory infections, otitis media, tonsillitis, chickenpox, and early use of amoxicillin in those with MIH [16–18]. Crombie et al. reported that moderate evidence supported the link between MIH and exposure to polychlorinated biphenyl/dioxin, and only weak evidence supported the role of nutrition, birth and neonatal conditions, and acute or chronic childhood illness and associated treatments [19,20]. Evidence implicating fluoride or breastfeeding as a risk factor for MIH is also considered weak [19]. Although correlations between several potential factors and MIH have been reported, most papers provide a low level of evidence for associations of any specific factor with MIH, and it is not possible to identify causal factors [21]. In the latest article published by Lee et al., they found that smoking during pregnancy and pediatric respiratory infection within three years after birth were associated with a higher prevalence of MIH, and the use of supplements (vitamins, folic acid, iron) during pregnancy was associated with a low prevalence of MIH [22]. Although the etiology of MIH is still unknown, it appears that a combination of environmental, genetic, and epigenetic factors contributes to this disorder [14,23].

4. Clinical management of MIH

Clinical management of MIH is difficult. The most commonly reported clinical problems for patients with MIH include post-eruptive enamel breakdown leading to dentin exposure, hypersensitivity, lack of effect of local anesthesia, aesthetic problems in anterior teeth, rapid progression to caries, and behavioral problems during treatment due to dental fear and anxiety related to the pain experienced by patients during multiple treatment appointments [8,24].

Optimal dental care is needed to minimize the post-eruptive breakdown of enamel and any damage due to caries to improve the health of MIH-affected teeth. In mild cases, preventive remineralization therapy is undertaken to prevent further breakdown and secondary caries. The fundamental approach for MIH-affected teeth is daily home care with toothpaste containing at least 1000 ppm of fluoride [10,25]. If tooth sensitivity is an issue, desensitizing toothpaste with 1000 ppm of fluoride is available. Daily use of the oral care product casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) is reported to harden the surface of the teeth and reduce tooth sensitivity [26]. Defective enamel rods in MIH molars develop into a more geometric, mature, and mineralized prism with CPP-ACP supplementation [27]. Professional application of topical fluoride can enhance remineralization of enamel and resistance to demineralization by providing a reservoir of fluoride ions for redeposition as fluorapatite during remineralization [28]. A fluoride varnish is considered a preventive product for MIH-affected teeth, resulting in surface hardening of demineralized enamel [10]. Fissure sealant is also an essential procedure to protect MIH-affected permanent molars from breakdown of. Glass ionomer cement (GIC) sealant is an obvious choice for teeth that are not fully erupted

Table 1
Prevalence of MIH in studies with more than 1000 subjects.

	Study	Published year	Location	Enlisted patients	Age (y, range or mean)	Number of subjects	% MIH
1	Dietrich et al. [60]	2003	Dresden, Germany	Schools	10–17	2408	5.6
2	Jasulaityte et al. [61]	2007	Kaunas, Lithuania	Schools	7–9	1277	14.9
3	Preusser et al. [62]	2007	Giessen, Germany	Schools	6–12	1022	5.9
4	Kemoli [63]	2008	Machakos, Kenya	Schools	6–8	3591	13.7
5	Cho et al. [64]	2008	Hong Kong, China	School dental clinic	11–14	2635	2.8
6	Lygidakins et al. [65]	2008	Athens, Greece	Dental clinics	5.5–12	3518	10.2
7	Kukleva et al. [66]	2008	Plovdiv, Bulgaria	Schools	7–14	2960	3.6
8	Zawaideh et al. [67]	2011	Amman, Irbid and Al-Karak, Jordan	Schools	7–9	3241	17.6
9	Biondi et al. [68]	2011	Buenos Aires, Argentina	Dental clinics	11	1098	15.9
10	Parikh et al. [69]	2012	Gujarat, India	Schools and dental clinics	8–12	1366	9.2
11	Balmer et al. [70]	2012	Hull, York and North Yorkshire, Newcastle, and Bradford, UK	Schools	12	3233	15.9
12	Condò et al. [71]	2012	Rome, Italy	Dental clinics	4–15	1500	7.3
13	Sönmez et al. [72]	2013	Ankara, Turkey	Schools	7–12	4049	7.7
14	Souza et al. [73]	2013	Araraquara, Brazil	Schools	7–12	1151	12.3
15	Mittal et al. [74]	2014	Chandigarh, India	Schools	6–9	1792	6.3
16	Petrou et al. [75]	2014	Greifswald, Germany	Schools	8–9	2395	10.1
17	Ng et al. [76]	2014	Singapore	Schools	7.7	1083	12.5
18	Sakurai and Shintani [45]	2014	Chiba, Japan	Schools	6–12	1753	11.9
19	Kühnisch et al. [51]	2015	Munich, Germany	Hospitals	10	1048	13.6
20	Kevrekidou et al. [77]	2015	Thessaloniki (three cities), Greece	Schools	8–14	2335	21
21	Krishnan et al. [78]	2015	Tamilnadu, India	Schools	9–14	4989	7.3
22	Oyedele et al. [79]	2015	Ile-Ife, Nigeria	Schools	8–16	2107	12.7
23	Yannam et al. [80]	2016	Chennai, India	Schools	8–12	2864	9.7
24	Tourino et al. [81]	2016	Urban and rural areas of Lavras, Brazil	Schools	8–9	1181	20.4
25	Koruyucu et al. [82]	2018	Istanbul, Turkey	Schools	8–11	1511	14.2
26	Saitoh et al. [46]	2018	Japan (the whole country)	Dental clinics and university	7–9	4496	19.8
27	Kılınç et al. [83]	2019	Izmir, Turkey	University	9–10	1237	11.5
28	Amend et al. [84]	2020	Urban and rural areas of Hesse state, Germany	Schools	6–12	2103	13.5

because GIC sealant is easy to apply and provides long-term fluoride release, chemical bonding, and hydrophilicity for conditions with inadequate moisture control [29]. Because retention of GIC sealant is poor due to its weak mechanical properties, this sealant needs to be reapplied or replaced with a resin-based fissure sealant when the tooth has fully erupted and moisture control is adequate [10].

Recently, an ion-releasing glass filler and a surface pre-reacted glass ionomer (S-PRG) filler were introduced as bioactive materials shown to prevent tooth demineralization and encourage remineralization, serve as acid buffers, and have antibacterial effects in in vitro studies [30–33]. Material containing S-PRG is now available with a sealant (Beautisealant, Shofu Inc., Kyoto, Japan). Many studies have used S-PRG materials to prevent demineralization and promote remineralization of enamel [34–36]. A further study of MIH-affected teeth with S-PRG materials is expected in the near future.

Microabrasion is effective in addressing the aesthetic concerns associated with incisors affected by mild MIH. Microabrasion involves the removal of a small amount of surface enamel (<100 μm) and erosion using 18% hydrochloric or 37.5% phosphoric acid with an abrasive paste [37]. Home application of CPP-ACP after microabrasion was found to improve remineralization of the treated enamel surface [38]. However, this microabrasion is limited to the superficial layer (shallow defects) of hypomineralized enamel.

Resin infiltration has been shown to be beneficial in the aesthetic management of MIH incisors. Icon® resin infiltration (DMG America, Englewood, NJ, USA) is commercially available for aesthetic restoration of MIH-affected incisors. This material removes the surface of hypomineralized enamel spots using 15% hydrochloric acid etchant, which allows for resin penetration [39,40]. However, because Icon has shown erratic penetration [41], this technique requires further investigation [42].

Resin composite restoration and veneers provide good results for large enamel defects. These methods can also achieve a more satisfactory aesthetic result [5]. However, these invasive treatments may not be effective for immature incisors, which have a large pulp size and unstable gingival contours.

MIH-affected molars are fragile, and caries may develop quickly in these molars. The foremost aim should be relief of associated pain followed by the best individualized management regimen [5]. The MIH-affected hypersensitive tooth is difficult to anesthetize even with an increase in the local anesthetic dose, which may be related to chronic pulp inflammation [24]. The additional use of nitrous oxide and oxygen inhalation analgesia may relieve anxiety, reduce dental pain during restorative treatment, and reduce behavior management problems in patients [11]. When treating MIH-affected teeth, the cavity design should involve removal of not just discolored enamel, but all porous enamel until resistance is felt. The rationale for this approach is that defective enamel remnants compromise the results [24]. The choice of the materials depends on the severity of the defect and the cooperation of the child. Adhesive materials are selected due to the atypical cavity outlines following removal of hypomineralized enamel [43]. GIC or resin-modified GIC restorations can be used as an intermediate approach for MIH-affected teeth. As mentioned above, an advantage of these materials is use of the GIC sealant. The most frequent treatment of MIH-affected teeth includes a resin composite, followed by GIC or resin-modified GIC restorations. The resin composite has shown long-term stability compared with other restorative materials in MIH-affected teeth [10]. Bond strengths of resin composite to affected-MIH enamel, however, are significantly lower than bond strengths to sound enamel for both single-bottle total-etch and self-etching primer adhesives [11]. A recent report showed that

Table 2
Distribution of MIH-affected children based on the number of hypomineralized first permanent molars and incisors in Yachiyo City, Chiba Prefecture, Japan (Sakurai and Shintani [45]).

		Affected molars				
		1M	2M	2M	4M	Total
Affected incisors	0I	75	29	9	6	119
	1I	19	6	4	2	31
	2I	22	6	1	3	32
	3I	5	4	2	1	12
	4I	3	2	2	1	8
	5I	2	3	0	0	5
	6I	0	0	0	1	1
	7I	0	0	1	0	1
	8I	0	0	0	0	0
	Total	126	50	19	14	209

the composite's strength was not significantly different when using self-etch compared with etch-and-rinse adhesives [44]. The resin composite for hypomineralized enamel is susceptible to wear and marginal fractures. Therefore, long-term maintenance is required. In moderate to severely damaged MIH-affected molars, full coverage restorations with a preformed metal crown (PMC) are the treatment of choice in a grown-up. PMCs have high long-term survival rates and can prevent further post-eruptive enamel breakdown, control tooth sensitivity, and establish correct interproximal and occlusal contacts; they require little tooth preparation and can be done in a single visit [11]. Although all dental students in Japan undergo education about primary and permanent PMCs in the school curriculum, there is generally little clinical training of dental residents in its use. A few dentists, including pediatric dentistry specialists, use PMCs. Because orthodontists are an unusual choice for extraction of severe MIH-affected molars, later orthodontic treatment may be complicated [11]. In all cases, specialized dental care is essential for improving MIH-affected teeth.

5. Studies of MIH in Japan

Sakurai and Shintani conducted an epidemiological study of school children to clarify the prevalence and severity of MIH in Yachiyo City, Chiba Prefecture, Japan [45]. A clinical examination for MIH was performed in 1753 elementary school children aged 6–12 years. The prevalence of MIH was 11.9%. Only slight opacity or discolored regions were observed in 76.6% of children with MIH. However, 49 children (23.4%) had a wide range of affected tooth surfaces or enamel defects and were classified as having severe MIH. Table 2 shows the distribution of MIH-affected children based on the number of hypomineralized first permanent molars and incisors. This report is the first MIH study in Japan. Sakurai and Shintani also carried out an etiological survey of all subjects. A self-administered questionnaire was obtained from parents and included items on prenatal factors related to pregnancy, such as hospitalization history and systemic disease. The results showed no significant differences among categories. Saitoh et al. also reported the prevalence of MIH and showed regional differences throughout Japan [46]. A total of 4496 children aged 7–9 years were evaluated in that study. The overall prevalence of MIH was 19.8% (892/4496). However, these studies have some limitations. For calibration of this study, the criteria index with 35 clinical photographs was prepared. A dedicated specialist who knows how to use the criteria index would be required to examine patients in more than 370 local clinics to cover the whole of Japan. Random sampling from each area (community-based design) would be ideal. However, such a study is not feasible when considering the need for cooperation from local communities/schools throughout Japan. Therefore, the study by Saitoh et al. used a clinic- and hospital-based study design. Thus, the true prevalence of MIH may be slightly lower than this study reported. In this study, MIH frequency decreased significantly with increasing age: 22.2% in 7-year-old children, 19.9% in 8-year-old children, and 17.0% in 9-year-old children ($p < 0.001$). Hypomineralized teeth carry a propensity for development of dental caries over time without appropriate prevention [47]. Although hypomineralized enamel would be masked by dental caries, the possibility of annual decrease in MIH prevalence rates cannot be excluded [48].

Several studies examined whether vitamin D deficiency was associated with MIH, HSPM, and dental caries [49,50]. Kühnisch et al. suggested that increases in serum 25-hydroxyvitamin D concentrations were correlated with less MIH and dental caries in a 10-year-old group of children [51]. Nørrisgaard et al. reported that high-dose vitamin D supplementation during pregnancy was associated with approximately 50% reduced odds of enamel defects in the offspring [52]. Reed et al. showed that, at 12 weeks of gestation, the 25-hydroxyvitamin D concentrations were significantly lower for children with enamel hypoplasia in the primary teeth [53]. Endogenous vitamin D3 is synthesized in the skin through exposure to ultraviolet B radiation from sunlight, and exogenous vitamin D3 is obtained from dietary sources. Vitamin D3 undergoes hydroxylation in the liver, producing 25-hydroxyvitamin D, which is the active form of vitamin D [54]. Lee et al. showed that children with more than three hours of daily outdoor activities had a lower prevalence of MIH than those with zero hours of outdoor activity [22]. Saitoh et al. investigated MIH prevalence rates throughout Japan by evaluating eight regions from the northeast to southwest, because Japan is a very long country in the northeast to southwest direction [46], and the daylight hours are longer and ultraviolet B radiation is greater in the southwestern part than in the northeastern part of Japan. However, MIH had a low prevalence in northeastern areas and a high prevalence in southwestern areas of Japan (Fig. 2); thus, a negative correlation was observed, but that study did not estimate the time of outdoor activities. When a person living in a high-temperature area goes out, the time of outdoor activities may be shorter than in a comfortable-temperature area. Osteoporosis also occurs more frequently in southwestern areas than in northeastern areas of Japan. Patients with osteoporosis have low serum 25-hydroxyvitamin D concentrations [55,56]. Vitamin D intake, mainly from fish and fish products, is much higher in northeastern areas than in southwestern areas of Japan [57]. Nutrient intake from fish may explain the regional differences observed in the prevalence of MIH in Japan. However, van der Tas et al. reported that 25-hydroxyvitamin D concentrations in prenatal and postnatal periods were not associated with the presence of HPSMs or with MIH in 6-year-old children [58]. Although vitamin D may be an important factor in the occurrence of MIH, HSPM, and dental caries, additional studies are required.

6. The future prospects of MIH

A combination of factors may affect the occurrence of MIH and result in abnormal enamel formation. Although MIH was initially described as an idiopathic defect [15], it has recently been proposed that it is a genetic condition [5,21,59]. A possible association has been observed between MIH and variations in the *AMBN*, *ENAM*, *TUFT1*, *TFIP11*, and *SCUBE1* genes [24]. In a monozygotic twin pair study, there was greater agreement in the occurrence of MIH than in dizygotic twins, which suggests a genetic factor in the disease. However, one study indicated that environmental factors are also associated with the occurrence of MIH [23]. HSPM and MIH share a similar clinical presentation, structural properties, and

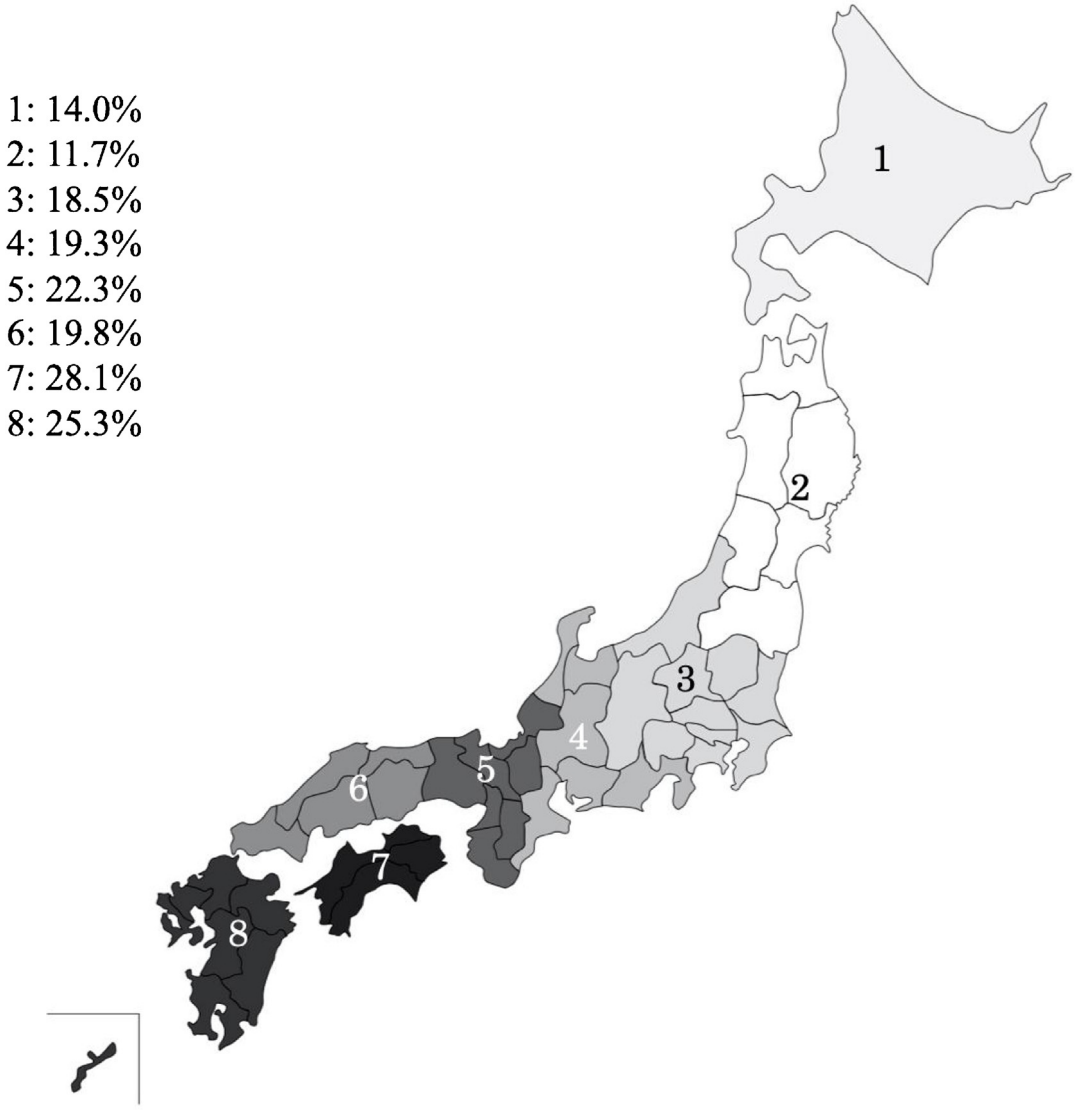

Fig. 2. MIH prevalence rates throughout Japan.
MIH has a low prevalence in northeastern areas and a high prevalence in southwestern areas of Japan (Saitoh et al. [46]).

putative etiology. In HSPM, a genetic concordance study showed weak evidence of higher concordance in monozygotic twins than in dizygotic twins [1]. Further prospective studies of biological principles, as well as genetic and epigenetic (environmental factors) studies, are needed.

Conflict of interest

The authors declare no conflict of interest.

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