Archives of Dermatological Research (2019) 311:735–740
https://doi.org/10.1007/s00403-019-01966-1

REVIEW

Genetic disposition to primary hyperhidrosis: a review of literature

M. A. Henning[1] · O. B. Pedersen[2] · G. B. Jemec[1]

Received: 2 May 2019 / Accepted: 15 June 2019 / Published online: 21 August 2019

Abstract

Primary hyperhidrosis is a condition characterized by excessive sweating. The estimated prevalence is between 0.6 and 4.4%, and it can have economic, psychological, and social consequences for affected individuals. Family and genetic studies have suggested a genetic component in the inheritance of the disease. In this review, we summarize the current literature on genetic disposition to primary hyperhidrosis. We Identified 20 studies on Pubmed and Embase in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Probands reported a positive family history in 5.7–65% of cases, and the inheritance appeared to be either autosomal dominant or recessive. Individuals with palmoplantar phenotypes and a positive family history had a younger age of onset. Genetic linkage and genome-wide association studies have identified loci on chromosome 2, 14, and 16. However, the evidence is heterogeneous and limited. It seems that primary hyperhidrosis is polygenically inherited, and considering the impairment, further data to understand the genetic etiology of the disease are needed.

Keywords Causality · Genetics · Primary hyperhidrosis · Pedigree · Sweating

Introduction

Primary hyperhidrosis is a condition characterized by excessive sweating above the physiological need, often in the axillae, palms, and soles [19, 25]. It can have severe implications for the affected individual, including social isolation, reduced work ability, and increased feeling of depression and anxiety [1, 14, 35]. The prevalence is between 0.6% and 4.4% [1, 25, 28, 35], and most studies show equal rates between men and women [28, 35, 38]. The condition is however underreported [35]. Primary hyperhidrosis is believed to be related to a dysfunction in the nervous system [33]. The onset is usually at early age [15, 27, 30], and symptoms are aggravated by emotional and thermal stimuli [1, 26, 27, 30]. Several studies have reported a positive family history and identified loci for hyperhidrosis [4, 11, 18]. However, the evidence is limited and heterogeneous, and the etiology remains unknown. In this review, we summarize the current literature on the genetics of primary hyperhidrosis.

Method

We used Pubmed and Embase to identify relevant literature from their inception until March 13, 2019 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. See Online Appendix for details.

Inclusion criteria were (1) clinical studies describing the genetics of primary hyperhidrosis. Exclusion criteria were (1) review studies (2) case reports (3) letters and correspondences, and (4) commentaries. However, an exception was made for a study published by Chen et al. [4] because it presents novel and relevant findings for the current review.

The initial database search yielded 689 studies. Another nine studies were identified in reference lists. All 698 study abstracts and, or titles were reviewed and 42 studies were assessed in full length. We excluded 22 studies because of irrelevant study aim. Twenty studies were included and data

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00403-019-01966-1) contains supplementary material, which is available to authorized users.

✉ M. A. Henning
maahe@regionsjaelland.dk

[1] Department of Dermatology, Faculty of Health and Medical Sciences, Zealand University Hospital, University of Copenhagen, Sygehusvej 5, 4000 Roskilde, Denmark

[2] Department of Clinical Immunology, Naestved Hospital, Ringstedgade 77B, 4700 Næstved, Denmark

on author, method, limitations, publication, results, study population characteristics, and year were extracted. See Fig. 1.

Results

The reviewed studies comprised of one Genome Wide Association study (GWAS), one case–control study, two classical family studies, two retrospectively accessed case series based on hospital records, three cross sectional cohort studies accessing self-reported family history of disease by questionnaire or interviews, three genetic linkage family studies, and eight prospectively accessed hospital based case series including self-reported family history of disease. Between 5.7 and 65% of subjects with primary hyperhidrosis reported a positive family history [1, 4–6, 15, 17, 18, 21–23, 25–30, 32, 38]. Most studies included subjects with average or mean ages between 18 and 35 years, with the severe phenotype in the axilla, palms, and soles. However, method differences may elucidate the diverse rates of reported familial hyperhidrosis.

Most family and genetic linkage studies indicated that primary axillar, palmar, and plantar hyperhidrosis is inherited in an autosomal dominant manner [4, 9, 18, 22]. An American family study from 2002 included 49 individuals with severe primary axillar and palmoplantar hyperhidrosis and a history of thoracoscopic sympathectomy [32]. Each subject answered a questionnaire and underwent examination. Altogether 65% reported a positive family history of hyperhidrosis and the estimated disease penetrance was 0.25. In addition, 20 matched controls with thoracic outlet

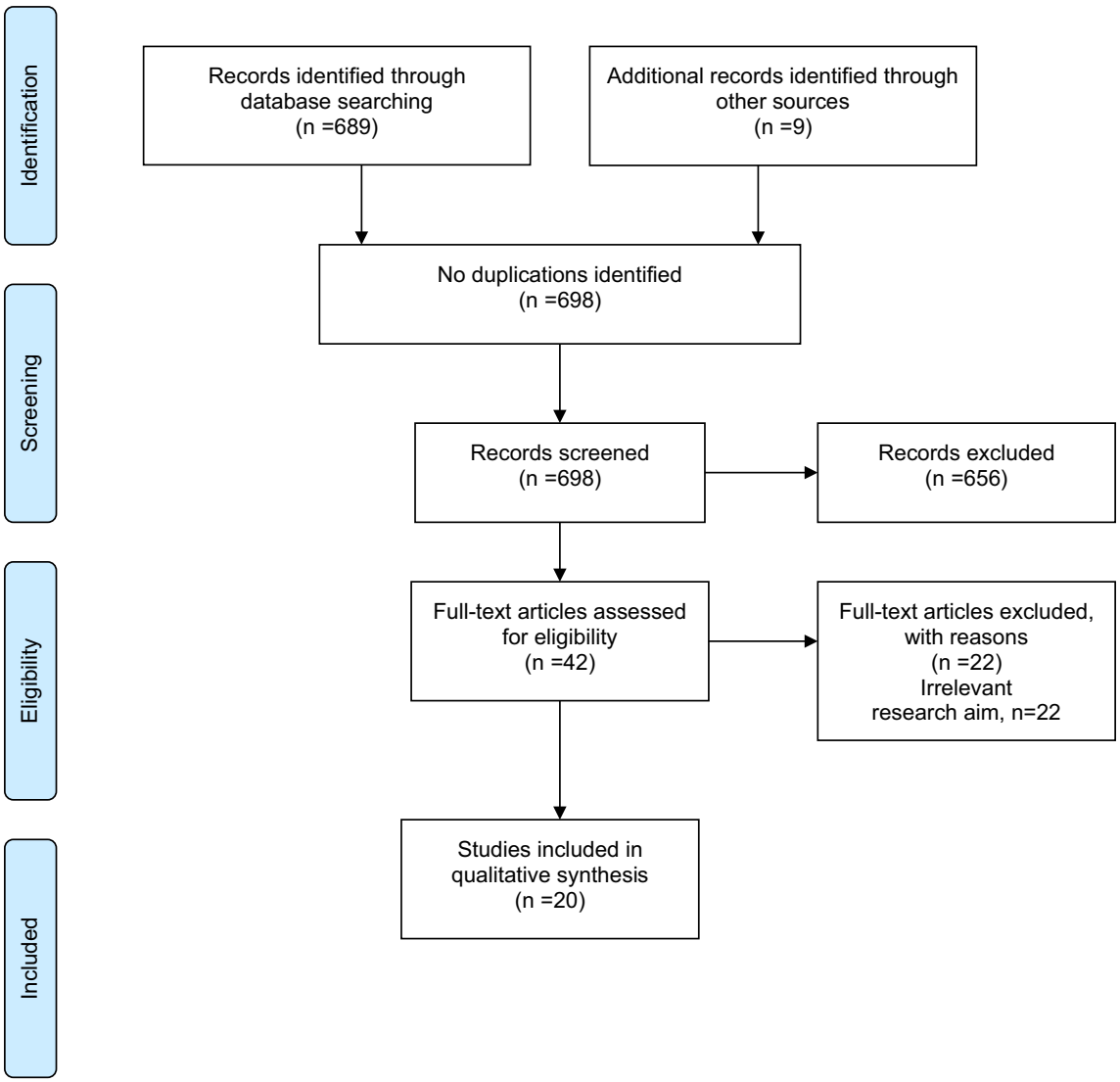

Fig. 1 Diagram depicting the study selection process

syndrome were included, and none had family members with hyperhidrosis. Another American family study from 2003 identified 21 subjects with severe palmar hyperhidrosis that had applied for botox treatment [22]. Iodine–starch test and observation confirmed the diagnosis and subjects answered a questionnaire. Altogether 62% had a family history of hyperhidrosis, with no difference between sex, and pedigree charts indicated an autosomal dominant inheritance. However, in six families the disease did not affect each generation, owing to either reduced disease penetrance or autosomal recessive inheritance. Moreover, mitochondrial transmission was improbably because the disease not exclusively affected females, and mothers not always passed it on to their offspring. X-linked inheritance also remained unlikely as sons of affected fathers had the disease. For details on recurrence risk of primary hyperhidrosis, see Table 1.

Three genetic linkage family studies on hyperhidrosis have been done. In one of these, both probands and family members were interviewed [4, 9, 18]. A Japanese genome-wide linkage study analyzed 82 subjects from 11 families with primary palmar hyperhidrosis [18]. Three families had linkage to loci on chromosome 14q11.2-q13. An Italian genetic linkage study examined with microsatellites the same loci on chromosome 14q and the candidate gene Aaquaporin-5 (AQP5) in a female proband with primary axillar and palmoplantar hyperhidrosis and her family [9]. The results showed autosomal dominant inheritance but no linkage to the suggested loci. In a similar Chinese genetic linkage study on 21 family members with autosomal dominant inherited primary focal hyperhidrosis the same method with microsatellites excluded association to loci on chromosome 14q11.2-q13 [4]. However, in the genome-wide single-nucleotide polymorphism (SNP) linkage analysis, the researchers found a region on chromosome 2q22.1–q31.1 containing 72 genes. Sequencing of the three candidate genes DYNC1I2, DLX1, and PDK1 did not identify a causative mutation. For details on the Hornberger's criteria, see Table 2.

A German case–control study enrolled 345 outpatients with primary focal hyperhidrosis and 154 healthy controls [15]. Thirty-seven percent of hyperhidrosis outpatients reported having family members with hyperhidrosis. Two Chinese cross-sectional studies assessed 32,152 and 67,492 students of 15–22 and 18–23 years of age by questionnaire and interview, to determine the epidemiology of mild to severe palmar hyperhidrosis [25, 28]. The proportion with a positive family history was 17.9 and 25.4%, respectively. A similar cross-sectional study from Brazil interviewed 447 medical students and 45% reported a positive family history of hyperhidrosis [29]. Two retrospective and one prospective case series reviewed medical records or surveyed outpatients with hyperhidrosis, and 34.1%, 36% and 43.7% of the hyperhidrosis patients reported a familial history of hyperhidrosis [27, 30, 38]. Seven hospital based case series evaluated subjects that were referred to or had undergone thoracoscopic sympathectomy for severe hyperhidrosis and the proportion reporting familial hyperhidrosis ranged from 5.7 to 55.6% [1, 5, 6, 17, 21, 23, 26].

A recent Japanese GWAS explored the genetics behind different skin phenotypes in 11,311 females [11]. Altogether 3293 indicated that they had hyperhidrosis by assessing whether it was easy or hard to sweat. Results showed associations with SNPs for two regions on chromosome 2 and one on 16 where previous research has identified the genes PLB1, PPP1CB, and ABC11.

For hyperhidrosis patients, age of onset was significantly lower in individuals with a positive family history [27, 30], and especially in those with palmoplantar symptoms, where it often presented before puberty, whereas axillar symptoms manifested during puberty [15, 27]. The association between

Table 2 The Hornberger's diagnostic criteria for hyperhidrosis [19]

Focal, visible, excessive sweating for ≥ 6 months without apparent cause with ≥ 2 of the following:
1. Bilateral and relatively symmetric hyperhidrosis
2. Impairs daily activities
3. Frequency of at least one episode per week
4. Age of onset < 25 years
5. Positive family history
6. Cessation of focal sweating during sleep

Table 1 Recurrence risk in patients with primary hyperhidrosis

Author, Year	Patients, *n*	Familiar hyperhidrosis, *n* (%)	Empiric risk
Ro et al., 2002 [32]	49	32 (65)	Offspring 0.28 Parents 0.14 Siblings 0.07 Niece, Nephew 0.05 Aunt, Uncle 0.04
Kaufmann et al., 2003 [22]	21	13 (62)	Offspring 0.41 Siblings 0.29

anatomical region of sweat production and family history is unclear as both probands with primary axillary and palmoplantar hyperhidrosis have reported significantly more relatives with identical phenotype as themselves compared to other anatomical sites [15, 27].

Discussion

Subjects with primary axillar or palmoplantar hyperhidrosis have a high frequency of positive family history and individuals with palmoplantar symptoms are younger at disease onset, which further suggest a genetic predisposition for these phenotypes. The inheritance is reported as either autosomal dominant or recessive.

Few genetic linkage studies and GWAS have identified loci for primary hyperhidrosis, but the results are heterogeneous.

Several pathogenic mechanisms have been offered to explain primary hyperhidrosis. The AQP5 gene, located on chromosome 12q13.12 is involved in perspiration [18], and immunohistochemical analysis has shown a significantly higher presence of AQP5 in the basolateral plasma membrane and luminal membrane in the epithelial cells of sweat glands in patients with primary hyperhidrosis [10]. Also, subjects with hypohidrosis in Sjögrens syndrome had reduced expression of AQP5 [20]. However, in families with primary axillar or palmoplantar hyperhidrosis no loci have been identified on the AQP5 gene [9, 18]. Other candidate genes are PLB1 and PPP1CB on chromosome 2 that encode for phospholipase B1 and a subunit in the serine/threonine-protein phosphatase PP1, respectively [11]. Phospholipase B1 supports epidermal skin function and sperm cell exocytosis [11]. Serine/threonine-protein phosphatase PP1 is a regulatory protein that the authors hypothesize influences AQP5 function and sweat gland secretion [11]. Other suggested genes are NDR2 on chromosome 14 that is involved in nervous system growth and the ABC11 gene on chromosome 16 that encodes for an ATP binding cassette subfamily C member 11 that is linked to ear wax and axillar odor [11, 18]. There are several hereditary disorders presenting with hyperhidrosis and a variety of other symptoms. The nail-patella syndrome is an autosomal dominant genodermatosis associated with a locus on chromosome nine and pedigrees show links to hyperhidrosis [31]. Mal de Meleda is an autosomal recessive disease with palmoplantar keratoderma, hyperhidrosis, and erythema [13]. Genome analyses on two consanguineous families indicated a locus on chromosome eight [13]. X-linked mental retardation is a group of more than 100 syndromes and in a family of 13 individuals a candidate gene was identified on Xp11.4-Xp22.11, and 12 of the subjects had concomitant hyperhidrosis [34]. Hyperchlorhidrosis is a disorder with increased loss of chloride in sweating that is caused by mutation in CA12 [12]. Digital clubbing and hyperhidrosis are characteristics of primary hypertrophic osteoarthropathy, and it is caused by a mutation in 15-hydroxyprostaglandin dehydrogenase gene [3]. Palmoplantar keratoderma of Bothnian type may be linked to hyperhidrosis and in a case report a missense mutation in the AQP5 gene was identified [24]. Crisponi syndrome manifests with hyperthermia, feeding difficulties, scoliosis, and cold-induced sweating, and is the result of a mutation in the cytokine receptor-like factor 1 [2].

There are two to four million sweat glands covering the human body. Most of these are eccrine, and they are located all over the skin, including on palms and soles [16, 33]. They produce an odorless sweat and are activated by exercise, heat, and stress [16, 33]. Apocrine sweat glands are concentrated to the anogenital area, axilla, and breast, and secrete a viscid fluid into hair follicles primarily from the start of puberty [16, 33].

The sympathetic nervous system innervates sweat glands, and signals are mediated by the neurotransmitters acetylcholine and norepinephrine [33]. The exact pathophysiological mechanism behind hyperhidrosis remains unknown. However, signals from thermoregular receptors to the hypothalamic sympathetic center plays a role in sweat production. Nerve fibers then descend through the brain stem and connect to the intermediolateral column in the spinal cord before they synapse in the paravertebral sympathetic ganglion and innervate the peripheral sweat gland [16]. Morphologically is there no difference between sweat glands themselves in individuals with primary hyperhidrosis and controls [10, 36]. There is however evidence for increased number of ganglions cells, concentration of acetylcholine, and myelination in sympathetic ganglions in subjects with primary hyperhidrosis [7, 8, 37].

Several limitations are present in the reviewed studies. Methods for classification of hyperhidrosis varied between studies, including physical examination [21, 32], qualitative iodine starch tests [22], quantitative measurements [18, 38], or review of medical records [26, 27, 30]. Different surveys and interviews were used based on the Hornberger's criteria [9, 25, 28, 29] or other questionnaires [11, 15, 21]. Furthermore, disease penetrance, mode of inheritance, and reports of familial hyperhidrosis may all be affected by recall bias, as data was collected from interviews [9, 15, 21, 28, 29, 32, 38]. Owing to the socially distressing aspects of sweating, there is a risk for underreporting or disease denial [27, 32]. Similar factors can affect the sweating directly, e.g. making the differentiation between primary hyperhidrosis and hyperhidrosis secondary to e.g. social stress or anxiety, difficult. Also, the results may be biased by mostly including subjects with the severe form of hyperhidrosis [22, 23, 32], and selecting study populations with narrow age ranges [25, 28].

In view of the many possible pathogenic mechanisms that underlie hyperhidrosis and the limited data available it is clear that additional data are needed to establish the genetic background of this most distressing condition. Most obviously, this information should be derived from unbiased, data-driven analysis of the genetics on larger patient cohorts.

Acknowledgement The generous support of the Leo Foundation, Denmark (number LF 18002) is gratefully acknowledged.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Adar R, Kurchin A, Zweig A, Mozes M (1977) Palmar hyperhidrosis and its surgical treatment: a report of 100 cases. Ann Surg 186:34–41
2. Angius A, Uva P, Buers I, Oppo M, Puddu A, Onano S, Persico I, Loi A, Marcia L, Hohne W, Cuccuru G, Fotia G, Deiana M, Marongiu M, Atalay HT, Inan S, El Assy O, Smit LME, Okur I, Boduroglu K, Utine GE, Kilic E, Zampino G, Crisponi G, Crisponi L, Rutsch F (2018) Bi-allelic mutations in KLHL7 cause a crisponi/CISS1-like phenotype associated with early-onset retinitis pigmentosa. Am J Hum Genet 102:713. https://doi.org/10.1016/j.ajhg.2018.03.020
3. Bergmann C, Wobser M, Morbach H, Falkenbach A, Wittenhagen D, Lassay L, Ott H, Zerres K, Girschick HJ, Hamm H (2011) Primary hypertrophic osteoarthropathy with digital clubbing and palmoplantar hyperhidrosis caused by 15-PGHD/HPGD loss-of-function mutations. Exp Dermatol 20:531–533. https://doi.org/10.1111/j.1600-0625.2011.01248.x
4. Chen J, Lin M, Chen X, Cao Z, Tan Z, Xiong W, Tu Y, Yang J (2015) A novel locus for primary focal hyperhidrosis mapped on chromosome 2q31.1. Br J Dermatol 172:1150–1153. https://doi.org/10.1111/bjd.13383
5. Chiou TS, Chen SC (1999) Intermediate-term results of endoscopic transaxillary T2 sympathectomy for primary palmar hyperhidrosis. Br J Surg 86:45–47. https://doi.org/10.1046/j.1365-2168.1999.00992.x
6. Cohen Z, Shinar D, Levi I, Mares AJ (1995) Thoracoscopic upper thoracic sympathectomy for primary palmar hyperhidrosis in children and adolescents. J Pediatr Surg 30:471–473
7. de Moura Junior NB, das-Neves-Pereira JC, de Oliveira FR, Jatene FB, Parra ER, Capelozzi VL, Wolosker N, de Campos JR (2013) Expression of acetylcholine and its receptor in human sympathetic ganglia in primary hyperhidrosis. Ann Thoracic Surg 95:465–470. https://doi.org/10.1016/j.athoracsur.2012.10.068
8. de Oliveira FR, Moura NB Jr, de Campos JR, Wolosker N, Parra ER, Capelozzi VL, Pego-Fernandes P (2014) Morphometric analysis of thoracic ganglion neurons in subjects with and without primary palmar hyperhidrosis. Ann Vasc Surg 28:1023–1029. https://doi.org/10.1016/j.avsg.2013.11.004
9. Del Sorbo F, Brancati F, De Joanna G, Valente EM, Lauria G, Albanese A (2011) Primary focal hyperhidrosis in a new family not linked to known loci. Dermatol (Basel, Switz) 223:335–342. https://doi.org/10.1159/000334936
10. Du Q, Lin M, Yang JH, Chen JF, Tu YR (2016) Overexpression of AQP5 was detected in axillary sweat glands of primary focal hyperhidrosis patients. Dermatol (Basel, Switz) 232:150–155. https://doi.org/10.1159/000444081
11. Endo C, Johnson TA, Morino R, Nakazono K, Kamitsuji S, Akita M, Kawajiri M, Yamasaki T, Kami A, Hoshi Y, Tada A, Ishikawa K, Hine M, Kobayashi M, Kurume N, Tsunemi Y, Kamatani N, Kawashima M (2018) Genome-wide association study in Japanese females identifies fifteen novel skin-related trait associations. Sci Rep 8:8974. https://doi.org/10.1038/s41598-018-27145-2
12. Feldshtein M, Elkrinawi S, Yerushalmi B, Marcus B, Vullo D, Romi H, Ofir R, Landau D, Sivan S, Supuran CT, Birk OS (2010) Hyperchlorhidrosis caused by homozygous mutation in CA12, encoding carbonic anhydrase XII. Am J Hum Genet 87:713–720. https://doi.org/10.1016/j.ajhg.2010.10.008
13. Fischer J, Bouadjar B, Heilig R, Fizames C, Prud'homme JF, Weissenbach J (1998) Genetic linkage of Meleda disease to chromosome 8qter. Eur J Hum Genet EJHG 6:542–547. https://doi.org/10.1038/sj.ejhg.5200254
14. Gross KM, Schote AB, Schneider KK, Schulz A, Meyer J (2014) Elevated social stress levels and depressive symptoms in primary hyperhidrosis. PLoS ONE 9:e92412. https://doi.org/10.1371/journal.pone.0092412
15. Hamm H, Naumann MK, Kowalski JW, Kutt S, Kozma C, Teale C (2006) Primary focal hyperhidrosis: disease characteristics and functional impairment. Dermatol (Basel, Switz) 212:343–353. https://doi.org/10.1159/000092285
16. Hashmonai M, Cameron AEP, Connery CP, Perin N, Licht PB (2017) The etiology of primary hyperhidrosis: a systematic review. Clin Auton Res 27:379–383. https://doi.org/10.1007/s10286-017-0456-0
17. Herbst F, Plas EG, Fugger R, Fritsch A (1994) Endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limbs. A critical analysis and long-term results of 480 operations. Ann Surg 220:86–90
18. Higashimoto I, Yoshiura K, Hirakawa N, Higashimoto K, Soejima H, Totoki T, Mukai T, Niikawa N (2006) Primary palmar hyperhidrosis locus maps to 14q11.2-q13. Am J Med Genet Part A 140:567–572. https://doi.org/10.1002/ajmg.a.31127
19. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, Ahn S, Stolman LP (2004) Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 51:274–286. https://doi.org/10.1016/j.jaad.2003.12.029
20. Iizuka T, Suzuki T, Nakano K, Sueki H (2012) Immunolocalization of aquaporin-5 in normal human skin and hypohidrotic skin diseases. J Dermatol 39:344–349. https://doi.org/10.1111/j.1346-8138.2011.01327.x
21. Karimian-Teherani D, Panhofer P, Ringhofer C, Jakesz R, Prager M, Zacherl J, Bischof G, Neumayer C (2009) New epidemiological aspects of patients with severe hyperhidrosis presenting for sympathetic surgery. J Eur Acad Dermatol Venereol JEADV 23:651–655. https://doi.org/10.1111/j.1468-3083.2009.03131.x
22. Kaufmann H, Saadia D, Polin C, Hague S, Singleton A, Singleton A (2003) Primary hyperhidrosis–evidence for autosomal dominant inheritance. Clin Auton Res 13:96–98. https://doi.org/10.1007/s10286-003-0082-x
23. Kopelman D, Hashmonai M, Ehrenreich M, Bahous H, Assalia A (1996) Upper dorsal thoracoscopic sympathectomy for palmar hyperhidrosis: improved intermediate-term results. J Vasc Surg 24:194–199
24. Kroigard AB, Hetland LE, Clemmensen O, Blaydon DC, Hertz JM, Bygum A (2016) The first Danish family reported with an AQP5 mutation presenting diffuse non-epidermolytic palmoplantar keratoderma of Bothnian type, hyperhidrosis and frequent Corynebacterium infections: a case report. BMC Dermatol 16:7. https://doi.org/10.1186/s12895-016-0044-3
25. Lai FC, Tu YR, Li YP, Li X, Lin M, Chen JF, Lin JB (2015) Nation wide epidemiological survey of primary palmar hyperhidrosis in

the People's Republic of China. Clin Auton Res 25:105–108. https://doi.org/10.1007/s10286-014-0259-5
26. Lai YT, Yang LH, Chio CC, Chen HH (1997) Complications in patients with palmar hyperhidrosis treated with transthoracic endoscopic sympathectomy. Neurosurgery 41:110–113 **(discussion 113–115)**
27. Lear W, Kessler E, Solish N, Glaser DA (2007) An epidemiological study of hyperhidrosis. Dermatol Surg 33:S69–75. https://doi.org/10.1111/j.1524-4725.2006.32334.x
28. Li X, Chen R, Tu YR, Lin M, Lai FC, Li YP, Chen JF, Ye JG (2007) Epidemiological survey of primary palmar hyperhidrosis in adolescents. Chin Med J 120:2215–2217
29. Lima SO, Aragao JF, Machado Neto J, Almeida KB, Menezes LM, Santana VR (2015) Research of primary hyperhidrosis in students of medicine of the State of Sergipe, Brazil. Anais brasileiros de dermatologia 90:661–665. https://doi.org/10.1590/abd1806-4841.20153859
30. Park EJ, Han KR, Choi H, Kim DW, Kim C (2010) An epidemiological study of hyperhidrosis patients visiting the Ajou University Hospital hyperhidrosis center in Korea. J Korean Med Sci 25:772–775. https://doi.org/10.3346/jkms.2010.25.5.772
31. Pechman KJ, Bergfeld WF (1980) Palmar-plantar hyperhidrosis occurring in a kindred with nail-patella syndrome. J Am Acad Dermatol 3:627–632
32. Ro KM, Cantor RM, Lange KL, Ahn SS (2002) Palmar hyperhidrosis: evidence of genetic transmission. J Vasc Surg 35:382–386
33. Shargall Y, Spratt E, Zeldin RA (2008) Hyperhidrosis: what is it and why does it occur? Thoracic Surg Clin 18:125–132v. https://doi.org/10.1016/j.thorsurg.2008.01.001
34. Stromme P, Sundet K, Mork C, Cassiman JJ, Fryns JP, Claes S (1999) X linked mental retardation and infantile spasms in a family: new clinical data and linkage to Xp11.4-Xp22.11. J Med Genet 36:374–378
35. Strutton DR, Kowalski JW, Glaser DA, Stang PE (2004) US prevalence of hyperhidrosis and impact on individuals with axillary hyperhidrosis: results from a national survey. J Am Acad Dermatol 51:241–248. https://doi.org/10.1016/j.jaad.2003.12.040
36. Swartling C, Naver H, Pihl-Lundin I, Hagforsen E, Vahlquist A (2004) Sweat gland morphology and periglandular innervation in essential palmar hyperhidrosis before and after treatment with intradermal botulinum toxin. J Am Acad Dermatol 51:739–745. https://doi.org/10.1016/j.jaad.2004.07.030
37. Tu Y, Luo R, Li X, Lin M, Qiu M (2012) Hypermyelination and overexpression of neuregulin-1 in thoracic sympathetic nerves in patients with primary palmar hyperhidrosis. J Clin Neurosci 19:1651–1653. https://doi.org/10.1016/j.jocn.2011.12.032
38. Yamashita N, Tamada Y, Kawada M, Mizutani K, Watanabe D, Matsumoto Y (2009) Analysis of family history of palmoplantar hyperhidrosis in Japan. J Dermatol 36:628–631. https://doi.org/10.1111/j.1346-8138.2009.00732.x