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Sex differences in the epidemiology, clinical features, and pathophysiology of trigeminal autonomic cephalalgias

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ABSTRACT

Emerging evidence suggests that primary headaches, classified as trigeminal autonomic cephalalgias (TACs), may exhibit sex and gender differences in clinical features, mechanisms, and treatment responses. While epidemiological and clinical gender-specific differences have been widely reported for cluster headache, limited evidence is available for other TACs. In this narrative review, we have analyzed the existing data on the influence of sex and gender on cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, and hemicrania continua. Given the role of calcitonin gene-related peptide (CGRP) in migraine and cluster headache, sex and gender differences in the levels and function of CGRP in preclinical models and patients are reported. Future studies are warranted to elucidate the role of sex and gender in the complex interplay of genetic and neurochemical factors in TACs.

Key words: trigeminal autonomic cephalalgias, cluster headache, sex differences.

Introduction

Gender medicine is a rapidly growing field with several implications for the understanding of diseases and their clinical management. Awareness of the marked differences between males and females in the prevalence, clinical manifestation, disease progression, and treatment of many diseases, including pain conditions such as primary headaches, is increasing (1).

Although the terms "sex" and "gender" are often used interchangeably, they do not refer to the same concepts and do not always align (2). In humans, sex refers to the biological characteristics that differentiate male, female, and intersex individuals. This distinction is based on attributes such as chromosomal complement, reproductive organs, specific hormones, and environmental factors that influence the expression of phenotypic traits in sexually reproducing organisms. Sex is a complex, dynamic, context-dependent, and interacts with gender and other social factors (3). Gender definition includes the social, psychological, cultural, and behavioral aspects of self-identification (4). In this narrative review, we refer to individuals who identify with the gender at birth, women as cis women and men as cis men (2).

We underline that while limited, emerging evidence has highlighted the differentiation of primary headaches according to gender, most studies covered by this review have addressed sex differences. Several primary headaches (5) exhibit a distribution that varies based on sex (1). For instance, migraine, which is highly prevalent, affecting more than one billion people worldwide, is three times more frequent in women. In contrast, the less prevalent cluster headache (CH), which belongs to the subgroup of the trigeminal autonomic cephalalgias (TACs), shows the opposite trend, being three times more frequent in males (1,6,7). Additional and rarer TACs encompass paroxysmal hemicrania, hemicrania continua, and short-lasting unilateral neuralgiform headache attacks (SUNHA) (5). SUNHA has been sub-categorized in two subtypes based on the associated autonomic symptoms: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) that show a less clear distinction in clinical presentations, attack characteristics, and treatment response based on sex and gender differences.

Except for CH, epidemiological data on TACs are limited, as they primarily derive from case series or small-scale studies (8,9), thus providing poor estimates of the prevalence and incidence of TACs (independently to sex) (10). In 2017, the *RegistRare Network*, comprising a collaborative network of Italian tertiary headache centers (8), systematically collected clinical data on rare headaches over a three-year period. They reported a 4.1% prevalence of rare headaches in patients referring to tertiary Headache Centers, of which 81.3% were TACs (8). Sex and gender investigations relative to TACs were performed mostly in CH, whereas more limited information is available for other TACs. In addition, the key role of calcitonin gene-related peptide (CGRP) in CH (although with contrasting data) should also be considered among the mechanisms of TACs, although few studies have been performed in these conditions. In this narrative review, we report the sex and gender differences in epidemiology, clinical features, and treatment of TACs.

Overview of trigeminal autonomic cephalalgias

All TACs, including CH, may appear in both episodic and chronic form, whereas hemicrania continua presents in a remitting or unremitting subtype. Compared to other primary

headaches, TACs usually have very distinct and stereotyped characteristics that include strictly unilateral pain localization and the presence of ipsilateral autonomic-trigeminal symptoms. They are characterized by very short attack durations (except for hemicrania continua and CH), occurring several times a day. Although there is no firm conclusion on TAC mechanisms, these conditions seem to have a common pathophysiology (11-13) involving the hypothalamus in its posterior, lateral, and paraventricular nuclei, the trigeminovascular complex, and parasympathetic fibers, with a crucial role of the sphenopalatine ganglion through the trigeminal autonomic reflex. Nevertheless, the pathophysiology of TACs remains elusive and is one of the most challenging tasks in clinical medicine (9,11-13).

Cluster headache. CH is the most frequent TAC and epidemiological studies have found a prevalence of 41-381 individuals per 100 000 (0.04-0.4%)(9), is divided into two forms based on the duration of the headache attacks: episodic (eCH) and chronic (cCH). eCH typically occurs in bouts that last from about 7 days to 1 year with remission periods lasting at least three months between bouts. cCH, which fulfills the criteria to be defined a rare disease, persists for more than one year without remission or with remission periods lasting less than three months (5). Both forms are characterized by unilateral pain, which could be orbital, supraorbital, temporal, or in any combination of these sites. CH attacks (if untreated) usually last 15-180 minutes and are accompanied by ipsilateral autonomic symptoms (including ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and/or eyelid edema) and restlessness (9). The quality of pain is described in various ways, including sharp, drilling, knife-like piercing, or stabbing. The pain often peaks within 10-15 minutes and remains intensely severe for the duration of the attack (9).

Paroxysmal hemicrania. In the following rare TACs, consistent prevalence data on the general population are still lacking. Only a few studies reported the prevalence among patients evaluated in tertiary headache center. Paroxysmal hemicrania is a very rare disease with an exact prevalence still unknown (14). Although with considerable variability, a recent metanalysis (15) reported a relative frequency of 0.3% (95%CI 0.2-0.5%) among patients evaluated in tertiary headache centers. Paroxysmal hemicrania manifests with attacks characterized by severe, strictly unilateral pain located in the orbital, supraorbital, or temporal regions, or a combination of these sites, lasting 2-30 minutes and occurring from once every other day to up to eight times a day. The pain is associated with ipsilateral autonomic symptoms. Thus, differing from CH, paroxysmal hemicrania attacks are more frequent, have a reduced duration, and completely respond to a therapeutic dose of indomethacin (12,16). Paroxysmal hemicrania (PH) is also subdivided in episodic or chronic, with chronic paroxysmal hemicrania lasting for more than one year with interruption of less than three months.

Short-lasting unilateral neuralgiform headache attacks. SUNCT and SUNA, which encompass the two forms of SUNHA, are very rare primary headaches (17,18), whose frequency has poorly evaluated. Both can be classified as episodic or chronic. Episodes entail moderate to severe, strictly unilateral pain lasting from a few seconds to minutes (2-3), occurring at least once a day. They are often accompanied by pronounced lacrimation and redness of the eye on the same side. Episodic SUNCT or SUNA are characterized by attacks that occur in periods lasting from 7 days to 1 year, separated by remission periods lasting ≥3 months, whereas chronic SUNCT or SUNA are characterized by attacks that occur for more than 1 year without remission (5,19,20).

Hemicrania continua. Hemicrania continua is a rare primary headache (21), with a metanalysis reporting a pooled relative frequency of 1.8% (95%CI 1.0-3.3) in patients treated in headache centers (22). This headache is often underdiagnosed (23). In contrast to paroxysmal hemicrania, which shows several and distinct bouts of headaches per day, hemicrania continua is characterized by a chronic persistent and strictly unilateral pain accompanied by ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and/or eyelid edema, and restlessness or agitation (5,12). Like paroxysmal hemicrania, hemicrania continua is highly responsive to indomethacin (5). Hemicrania continua is distinguished between remitting (with interruption of the pain of at least 24 hours) and unremitting form (the pain is continuous). Exacerbations in hemicrania continua are commonly associated with ipsilateral autonomic features, such as conjunctival injection, lacrimation, and ptosis (23).

Sex differences in epidemiology

CH predominantly affects men (9,24), as indicated by the male-to-female ratio of approximately 2-3:1 in the Europe and North America population, and 3-9:1 in East Asia and India (9). However, over the past few decades, this ratio is steadily decreasing from an initial estimate of 6:1 in the 1960s to approximately 2-3:1 in the 2020 (9). The reasons for the decline in male predominance are not entirely understood, but it has been speculated that the shift may be due to improved diagnostic accuracy rather than a true change in the sex ratio. Indeed, the male predominance in CH can be attributed to a higher likelihood of misdiagnosis (*e.g.*, with migraine) in female patients, a trend supported by a recent Danish study (25). Another factor that may have contributed to the change in the ratio is the shift in the societal and environmental habits of women, such as increased stress, alcohol consumption, and smoking (26).

According to some studies, the onset of CH in women tends to exhibit a bimodal distribution in the age onset, with attacks appearing around the age of 20 or at the age of 50 to 60 (1,27). Furthermore, a significant proportion of female CH patients experience their first attack during menopause (1,27). In contrast, a recent study on 874 patients with CH does not confirm the bimodal tendency in women regarding disease onset (28). In men, the third decade of life is the most frequent period for CH insurgence (9). CH seems to start earlier in women than in men, whereas an early report suggested a delayed initiation (28,29). A higher proportion of female patients shows CH onset before the age of 20 years, and cCH was diagnosed more commonly in females than in males (28).

SUNA was shown to have a male-to-female ratio of 1:1.7, indicating an almost double prevalence in females (19). According to previous studies, SUNCT disorders have a male predominance, with a male-to-female ratio of 1.3:1 (19). A systematic review reported a male-to-female ratio of 1.5:1 for SUNCT, indicating a slight male prevalence (30). In a study comprising 24 patients of both sexes, the only two patients affected by both SUNCT and SUNA attacks were male (31). Finally, the higher male-to-female ratio in SUNCT was reported as 4:1 (14). Thus, the conclusion that SUNCT is more prevalent in males and SUNA in females seems to have limited supporting evidence. In fact, contrasting results were reported in a study including 24 patients (20), where a female prevalence in SUNCT was found, with a female-to-male ratio of 7:5. Another study demonstrated that in a cohort of 161 patients affected by SUNA and SUNCT, there was a slightly higher percentage of females (60.9%) compared to males (39.1%) (30). Stratified according to sex, a higher prevalence was reported for females in SUNA (60.7% *vs* 30.3%),

whereas in SUNCT both sexes were affected almost equally, with only a slight female prevalence (52.9% *vs* 47.1%) (30).

Paroxysmal hemicrania and hemicrania continua have been considered two conditions predominantly affecting females, with a male-to-female ratio of 1:2 for both (32). The female-to-male ratio was reported as 2.7, based on over 100 cases, which is close to the ratio for migraine, suggesting a potential influence of sex steroids (1). However, a more recent study indicates that paroxysmal hemicrania appears to affect both males and females equally (16). The major limitation of these studies is the small number of cases, which prevents firm conclusions on the epidemiological distribution of the rarest TACs according to sex. A summary of the distribution according to sex of the five types of TACs is reported in **Table 1**.

Genetic features

In the last three decades, numerous studies led by the International Cluster Headache Consortium have been performed and are currently ongoing. Almost 30 year ago, a complex segregation analysis in CH implicated a role of an autosomal dominant gene in CH (33), with a lower penetrance of this gene in women than in men (33,34). On the other hand, aligning with previous studies, females are predominant in familial cases (35). A more recent study on 874 CH patients reported that more female than male patients had a positive family history of CH (15% *vs* 7%) (28). Various associations between CH and the *rs2653349* polymorphism of the *HCRTR2 gene* have been reported (36). The less common allele A appears to reduce the risk of developing the disease, whereas allele G increases the risk (37). The *rs2653349* polymorphism is distributed differently between sexes, for the rare allele A:A *vs* G:G and G:A genotypes (OR 2.78; p=0.08), indicating a higher presence of male homozygotes for the protective mutant A:A allele than female homozygotes (36).

Calcitonin gene-related peptide in headache disorders

CGRP is considered one of the most important neuropeptides of the trigeminovascular system implicated in migraine mechanisms (38). Two forms of CGRP are known: αCGRP, expressed by and released from central and peripheral terminals of a subpopulation of primary sensory neurons consisting of unmyelinated C-fiber and myelinated Ad-fiber nociceptors, and bCGRP, expressed and released from intrinsic neurons of the gastrointestinal system (39). The role of CGRP in CH has been suggested based on the findings of increased CGRP levels in blood taken from jugular circulation during spontaneous or provoked attacks (40,41). In interictal periods of eCH patients CGRP plasma levels were higher than those found in cCH patients (42). However, it should be underlined that systemic blood samples taken from the cubital vein, like in this case (42), due to a remarkable dilution factor and short neuropeptide half-life, may not reflect the subtle changes of CGRP released from a small proportion of primary sensory neurons, as those of one-sided TG-nerve terminals. More importantly, one randomized clinical trial (RCT) with monthly subcutaneous injection of 300 mg galcanezumab in eCH met its primary endpoint, which was the reduction of the weekly attack frequency (43). These findings led to the FDA approval of galcanezumab 300 mg for the prevention of eCH (44), whereas the EMA declined its approval. However, an RCT with galcanezumab in cCH (43) or other anti-CGRP mAbs (fremanezumab and eptinezumab) for the treatment of eCH (45 46) and cCH provided negative results. An open-label study with eptinezumab in cCH is still ongoing (47).

Several studies have proposed sex differences in CGRP metabolism and function in rodents. TG neurons in female mice exhibit increased expression of αCGRP (38). Additionally, shifting the focus to human studies, sex differences in CGRP-induced vasodilatation were found in middle meningeal arteries, with females under 50 showing a less potent CGRP response compared to males of the same age (48). No differences were found in older patients (48), suggesting that both sex and age play a role in the pathophysiology of primary headache. Since hormone levels change with age, the authors suggested that the age dependence could be explained by the fluctuating levels of hormones (48). Moreover, the smaller response to CGRP in young females could be attributable to the desensitization of CGRP receptors (48).

Monoclonal antibodies against CGRP or its receptor (anti-CGRP mAbs) or gepants (small molecules blocking the CGRP receptor) do not or poorly cross the blood brain barrier (49). Thus, the pro-migraine effect of CGRP should be localized at a peripheral site (50). Research indicates a sexual dimorphism in the transmission of nociceptive information and CGRP expression between male and female DRG neurons (51). These results suggest differences in the pathophysiological mechanisms between sexes and, consequently, in the response to anti-CGRP treatments (51). However, the target of CGRP responsible for migraine or possibly CH pain is unknown. Sex-specific differences have been found in CH due to different levels of gene expression associated with CGRP, or with differences in behavioral response to inflammation (52). In contrast with anti-CGRP mAbs, a gender difference seems to be present in the results of clinical trials in the response to the small molecule CGRP receptor antagonists (gepants) used as acute treatment, male patients being apparently less or non-responsive (53).

Schwann cells via different cellular and molecular mechanisms have been implicated in models of neuropathic (54), and

Table 1. Sex rates in the epidemiology of trigeminal autonomic cephalalgias.

TAC type	Male-to-female ratio	References
Cluster headache	3.5:1 2.5:1	Manzoni *et al.*, 1998 (75) Bahra *et al.*, 2002 (59)
SUNCT	1.3:1 5:7 1.5:1	Cohen *et al.*, 2006 (19) Williams and Broadley, 2008 (20) Lambru *et al.*, 2020 (30)
SUNA	1:1.7	Cohen *et al.*, 2006 (19)
Paroxysmal hemicrania	1:2 1:2.7	Antonaci and Sjaastad, 1989 (32) Lieba-Samal and Wöber, 2011 (1)
Hemicrania continua	1:2	Antonaci and Sjaastad, 1989 (32)

TAC, trigeminal autonomic cephalalgias; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.

inflammatory pain (55), and optogenetic stimulation results in mechanical hypersensitivity by targeting cutaneous Schwann cells (56). CGRP receptor components have been found in two peripheral glial cells, the satellite glial cells that surround neuronal cell bodies in dorsal root ganglia (57), and more recently in Schwann cells (58), which wrap peripheral nerve fibers. However, in this CGRP receptor- and Schwann cell-dependent proalgesic mechanism, no difference was found between female and male mice (58).

The putative influence of sex hormones

The relationship between sex hormones and migraines has been studied extensively, but this association in other types of primary headaches is still unclear (1). There is some evidence indicating that sex hormones are implicated in TACs, including paroxysmal hemicrania and CH (1). Estrogens seem to play a protective role in CH, and the reduced level of estrogens in menopause could trigger CH bouts (1). However, studies evaluating the relationship between menstrual cycle/menopause and CH have not provided any meaningful association (28). It is worth noting that, in CH women, disease onset usually corresponds with important changes in the levels of sexual hormones (*i.e.*, menarche, post-partum, menopause) (24).

Some studies have reported an association between CH and hormonal levels, with more severe attacks occurring during the menstrual period (59,60). Retrospective studies examining hormonal changes in women (59-61) showed no implication of hormonal changes in women and CH (1). The onset of CH in relation to hormonal changes was reported in females as follows: 11% during puberty, 6% during pregnancy, and 12% during and 24% after menopausal transition (1). The relationship between menstruation or the use of oral contraceptives and CH are inconsistent, with some studies reporting no association (59,60). Overall, it has been found that contraception and hormonal replacement therapy does not seem to have effects on CH (59). Both male and female CH patients exhibit low testosterone levels, and testosterone supplementation may have a beneficial effect (62). During pregnancy, from 5% to 23% of female patients experienced an overall improvement of CH (59,60).

Early studies reported that individuals with CH have alterations in the circadian secretion of luteinizing hormone (LH), cortisol, and prolactin (63). Moreover, the production of cortisol, LH, follicle-stimulating hormone (FSH), prolactin, growth hormone (GH), and thyroid-stimulating hormone (TSH) could also be altered (63). The hypothalamus plays a significant role in the circadian rhythm, which may be implicated in the peculiar CH chronobiological pattern. The specific temporal feature of CH seems to differ between sexes (9). As mentioned before, both sexes experience bouts during the night, but female patients are more prone to have attacks during the night and early morning hours. Additionally, a greater percentage of female patients (13%) reported sleeping less than 5 hours per night compared to males (8%), which could be attributed to the more frequent nighttime attacks (28). However, there is still no clear evidence on the relationship between CH and hormonal changes in women.

Regarding chronic paroxysmal hemicrania, a study explored the relationship between menstrual cycle, oral contraceptives, and pregnancy, showing that 4 out of 15 women reported an improvement, whereas 11 out of 15 reported a major impairment during menstruation (32). No relationship was found on the influence of oral contraceptives, but, in pregnancy, 9 out of 10 patients did not experience bouts (32). Interestingly, headaches started immediately postpartum in five patients (32). However, these data must be considered with caution due to the small number of the patients examined. Finally, only one case report of a woman with hemicrania continua and attacks linked to menstruation has been reported so far (64). The absent clinical association seems to be consistent with hemicrania continua.

Sex differences in disability, triggers, and comorbidities

Psychiatric comorbidities, such as depression, anxiety, and aggressive behavior, have been linked to patients with CH, but gender differences have not been reported (65-67). However, depression and anxiety appear more frequently in the female CH population. More recent data obtained in America (68) and Korea (69) confirmed a higher presence of depression and anxiety in CH women. On the other hand, CH men are commonly associated with a higher percentage of snoring and smoking habits (24,65,70,71). The prevalence of smoking is significantly higher in CH patients compared to the general population, and this habit seems to contribute to the development of CH (24,72). Furthermore, the ability of alcoholic drinks to trigger CH attacks seems more likely in male patients (54% *vs* 48% p=0.01), whereas sleep disturbances trigger attacks more commonly in females (31% *vs* 20%, p=0.001) (9,28). A Danish study showed that CH patients have a higher mean body mass index (BMI) compared to controls (70), which was higher in male CH patients compared to females (28). Specifically, a significantly higher BMI compared to the general population was found only in male patients, a feature that was attributed to poor lifestyle (28). Finally, female patients more commonly tend to have other primary headache disorders in comorbidity with CH (28).

Sex differences in clinical symptoms

Several pain disorders, including migraine or fibromyalgia, are more common in women than men. CH is a clear exception to this trend, being more frequent in men (73). In spite of the difference in prevalence, CH women report the same number of attacks per day as men (68,74) and the duration of CH attacks is reported to be shorter (29,75) or longer in women. Cranial autonomic symptoms associated with CH attacks are less severe and frequent in women who have experienced a late disease onset (68,74). When individual cranial autonomic symptoms were considered, a lower frequency of attack-associated miosis and ptosis was found in women, but similar frequency of lacrimation, nasal congestion, and rhinorrhea were found, suggesting a less severe sympathetic dysfunction in women, while the parasympathetic component remains similar between sexes (29). The finding of increased occurrence of ptosis and eyelid edema in CH women compared to men (25) was confirmed by another study (28). Symptoms more typical of migraine, like photophobia and phonophobia, are equally frequent in CH patients of both sexes (9). An increased incidence of nausea and vomiting was reported in female patients (29,68,75). However, in another study increased incidence of nausea but not vomiting were assessed in female patients (29).

Migraine-like symptoms in CH are more common in female patients who do not have a concurrent history of migraine. However, gender-related differences in CH have been questioned, suggesting an overlap with migraine features in female subjects (15). By evaluating data from 163 male and 87 female CH patients, no differences in the primary outcome were found. However, a higher frequency of nausea, osmophobia, ptosis, and nasal congestion was reported by female patients (24). Other factors more frequent in females included the distribution of pain across the head, with women more frequently experiencing pain in the zygomatic, parietal, and frontal regions (24). The pain intensity does not differ between sexes. Overall, female patients

may display a more severe phenotype or form of disease for patients with late CH onset (21). Moreover, female patients experience restlessness more frequently than males, but in general the associated symptoms occur with similar frequencies in male and female patients (28). Very few studies have investigated the differences of clinical features in other TACs. A male-to-female ratio of 1.6:1 in the vascular compression of the trigeminal nerve was reported (31). However, the implication of neurovascular compression in the pathophysiology of SUNCT/SUNA remains uncertain. Nonetheless, the role of the trigeminal autonomic reflex in these syndromes is well-recognized (13). In chronic paroxysmal hemicrania, a study describing 84 patients (25 males and 59 females) showed a great variability in attack duration, but no difference between females and males in terms of mean attack duration or frequency (32).

Sex differences in the response to treatments

Greater occipital nerve (GON) infiltration with corticosteroids has demonstrated efficacy in treating eCH in multiple observational studies (76). No significant correlations between sex and the response to GON injections have been reported in either eCH or cCH. Regarding pharmacological treatments, one study suggested that CH women seem more responsive to acute medications, such as high-flux oxygen, as well as to preventive treatments (77). However, another study showed that women achieved a remission from CH bouts following any CH preventive therapies less frequently than men (78) (**Table 2**). Additional evidence suggests that CH women respond less or more slowly than men to pharmacological preventative treatments (50% *vs* 87%) (79,80). Two studies found that men exhibited a higher utilization rate of acute oxygen treatment and responded better to nasal spray medications (59,68). Finally, evaluation of the superiority of high-flux oxygen compared to a placebo by a logistic model indicated that sex was not a significant variable (81), as confirmed by subsequent studies (77). Up to now, no report on differences in treatment response between men and women in CH with medicine against the CGRP pathway has been published. Further research is needed to assess any potential gender influence on different acute and preventive treatments in CH. To the best of our knowledge, no study has been undertaken with anti-CGRP mAbs or gepants in the other rarer TACs.

Table 2. Sex differences in response rates to preventive and acute treatments for cluster headache.

Treatments	Response rate	
	Male, %	Female, %
Acute treatment		
Oxygen	71.6	52.8
Triptans	74.6	70.7
Preventive treatment		
Verapamil	50.7	51.8
Greater occipital nerve blocks	76.3	50.7

Data extrapolated from Fourier *et al.*, 2023 (28).

Conclusions

While epidemiological findings depict a clear gender difference regarding CH with a higher male prevalence, they remain substantially inconclusive in the other rarer TAC forms. More research, and particularly collaborative investigations for studies enrolling higher numbers of patients, are necessary for a better evaluation of sex- and gender-related differences in the prevalence/incidence, clinical presentation, pathophysiological issues, and treatment options for TACs. This data could be useful to improve the accuracy of diagnoses and personalize treatments, and to optimize the overall management of these highly disabling and rare diseases.

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