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REVIEW ARTICLE

Familial dysautonomia

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Abstract
Familial dysautonomia (FD) is an autosomal recessive hereditary sensory and autonomic neuropathy (HSAN, type 3) expressed at birth with profound sensory loss and early death. The FD founder mutation in the *ELP1* gene arose within the Ashkenazi Jews in the sixteenth century and is present in 1:30 Jews of European ancestry. The mutation yield a tissue-specific skipping of exon 20 and a loss of function of the elongator-1 protein (ELP1), which is essential for the development and survival of neurons. Patients with FD produce variable amounts of ELP1 in different tissues, with the brain producing mostly mutant transcripts. Patients have excessive blood pressure variability due to the failure of the IXth and Xth cranial nerves to carry baroreceptor signals. Neurogenic dysphagia causes frequent aspiration leading to chronic pulmonary disease. Characteristic hyperadrenergic "autonomic crises" consisting of brisk episodes of severe hypertension, tachycardia, skin blotching, retching, and vomiting occur in all patients. Progressive features of the disease include retinal nerve fiber loss and blindness, and proprioceptive ataxia with severe gait impairment. Chemoreflex failure may explain the high frequency of sudden death in sleep. Although 99.5% of patients are homozygous for the founder mutation, phenotypic severity varies, suggesting that modifier genes impact expression. Medical management is currently symptomatic and preventive. Disease-modifying therapies are close to clinical testing. Endpoints to measure efficacy have been developed, and the ELP1 levels are a good surrogate endpoint for target engagement. Early intervention may be critical for treatment to be successful.

Keywords Familial dysautonomia · HSAN III · Labile blood pressure · Baroreflex · Autonomic crisis

Introduction

Familial dysautonomia (FD) was first described by New York pediatricians Conrad Riley and Richard Day in 1949 [1]. Their original paper included five patients who reacted to mild anxiety with psychomotor agitation, arterial hypertension, tachycardia, skin flushing, and profuse sweating. At other times, patients had severe orthostatic hypotension and syncope. Fear or anger made them vomit; they never cried with tears, failed to complain when their feet were immersed in cold water, and died before adulthood. The authors called the disorder familial dysautonomia as the children were all of Ashkenazi Jewish descent, and it is also referred to as Riley–Day Syndrome [2].

FD is classified as hereditary sensory and autonomic neuropathy (HSAN) type 3 [3]. The clinical hallmark of HSANs is reduced sensitivity to pain and temperature [4]. The classification of HSANs was based on the age at onset and the dominant clinical features, but now relies on finding the pathogenic mutations [3]. Each HSAN, and there are at least nine, is due to specific genetic mutations that affect the production of one or more proteins highly expressed in neurons, disrupting the development and survival of selective neuronal populations. [5]. The mutation responsible for FD is in the elongator protein 1 gene (*ELP1*, formerly *IKBKAP*) [6]. In addition to reduced sensitivity to pain and temperature, patients with FD have a complex neurological phenotype, with unique autonomic abnormalities [4].

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Genotype

FD is caused by a single-point founder mutation (IVS20 + 6 T > C) in the ELP1 gene located on the long arm of chromosome 9q, in the donor site of intron 20 (Fig. 1) [6]. This mutation produces variable splicing defects and tissue specific reductions in ELP1 protein levels [7] Haplotype analysis traced the origin of the founder mutation to the sixteenth century in an Ashkenazi Jewish individual living within the Pale of Settlement between the Black Sea and the Baltic Sea [4, 8]. A genetic bottleneck occurred in the Jewish community. (Fig. 1A), following the forced crusades and expulsions across Europe, which created an extreme founder event predating the fourteenth century [9]. The remaining population, estimated to be as little as a few hundred surviving individuals [9], was legally restricted to live within the tight geographical constraints of the Pale of Settlement [4]. Over subsequent generations, the population expanded dramatically (Fig. 1A), with very little admixture, which created a homogeneous modern Ashkenazi Jewish lineage, which carry high levels of pathogenic variants [9].

Transmission is autosomal recessive, and 99.9% of the cases are homozygous for the common founder mutation [6]. The carrier rate in the Ashkenazi Jewish population is around 1:30 but rises to 1:17 in Jews with Polish lineage. Waves of migration from Eastern Europe carried the founder mutation to other continents (Fig. 1B). Currently, affected patients live in the UK, USA, South America, Australia, and the Middle East. The highest number of known cases nowadays are from the USA and Israel.

In recent years, babies homozygous for the founder mutation were born in families unaware of Jewish genetic heritage [10], which suggests that the mutation was introduced into other population clusters, with subsequent founding events, for example, in Mexico, where the mutation became established in closely related families in smaller towns. With the widespread use of whole-genome analysis in undiagnosed cases, several patients with FD-compatible phenotypes have been described that are heterozygous for the *ELP1* mutations, with the founder mutation (i.e., IVS20 + 6 T > C) paired with another pathogenic genetic variant in the other allele (AGD & HK, personal communication).These rare heterozygotes tend to have a milder phenotype [11], which suggests that the severity of the second pathogenic mutation can influence the expression of phenotypic severity.

ELP1 is the scaffolding subunit of the human elongator complex that facilitates transcriptional elongation of longer genes, expressly neurodevelopmental genes, and has distinct roles in the development of different neuronal subtypes [12, 13]. ELP1 is a highly conserved protein expressed in all cells with a nucleus (Fig. 2). Mutations in *ELP1* influence pre-mRNA splicing through aberrant skipping of exon 20, resulting in lower synthesis of ELP1 [14]. Mutations in *ELP1* are consistent with the innervation failure observed in FD mice [12]. Also, ELP1 is involved in modulating the expression of genes and gene sets with unique expression patterns, such as *Dbx-1*, which has a pivotal role in interneuron differentiation in the ventral spinal cord, or *Nr2e1*, a critical stem cell fate determinant in the mouse retina [12]. Recent mouse models showed that by steadily raising ELP1 levels, the downregulation of select neurodevelopmental genes was gradually restored in ELP1 knockout mouse models [12].

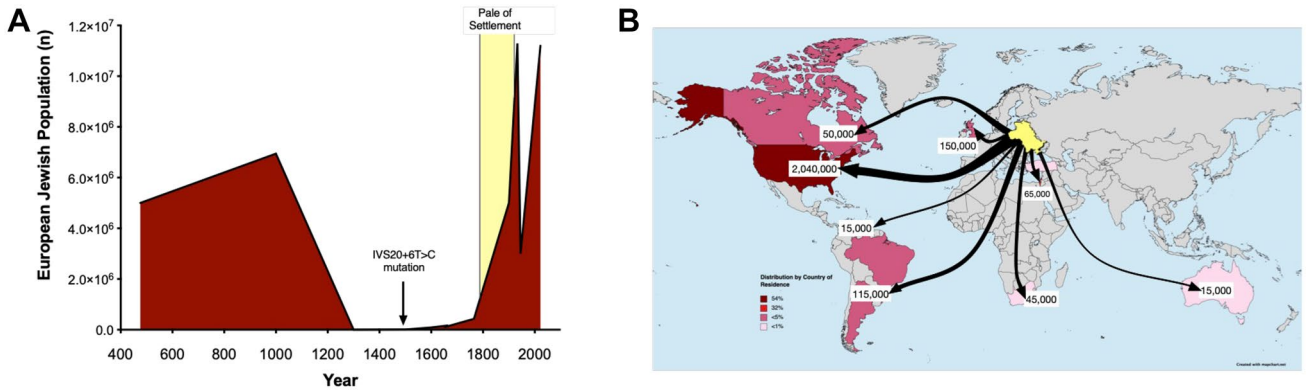

Fig. 1 Origins and geographical dispersion of the FD mutation. **A** Graphic shows the European (Ashkenazi) Jewish population over time. Severe population constriction occurred with the crusades and forced expulsions creating a genetic bottleneck. The remaining founders underwent a period of rapid population expansion within the demarked area of the Pale of Settlement (1791–1917). **B** Map shows major migration routes from the Pale of Settlement prior to the 1900's. Country colors show population distribution of FD patients captured at the New York University (NYU) database. Note, the highest number of patients are currently residing in the USA and Israel. *Adapted from* [4]

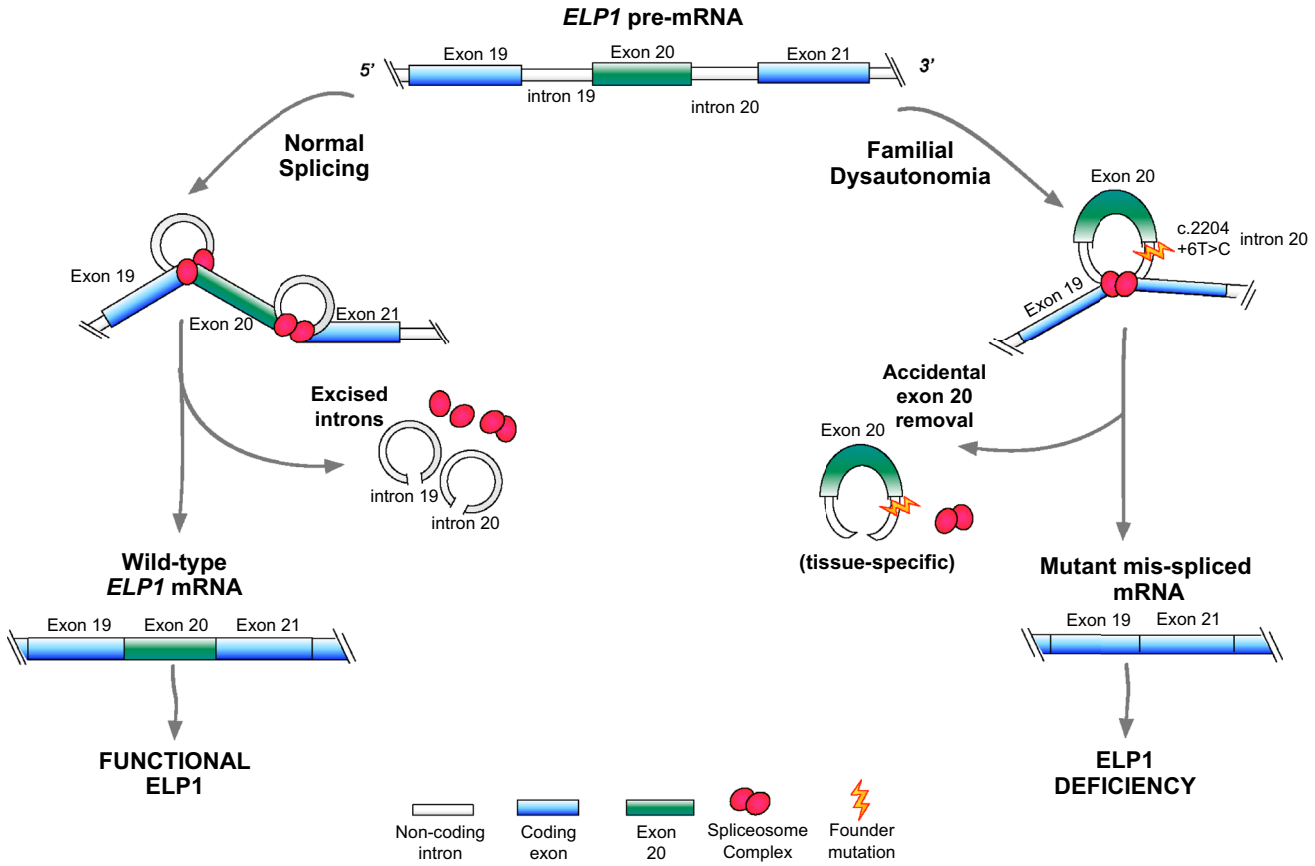

Fig. 2 Schematic representation of aberrant splicing of the ELP-1 gene with the founder mutation. The single base pair change leads to accidental skipping of exon 20, producing a mutant mRNA transcript, which results in a tissue-specific defect in ELP-1 protein, primarily impacting the nervous system. Adapted from [4]

Demographics

FD is a rare disease that has benefited from centralized care and a robust clinical research platform. The New York University (NYU) FD Patient Registry began in 1970, evolved into a natural history study, and today contains clinical and laboratory data of 670 genetically confirmed cases from around the world. At the time of writing, 327 registered patients are alive, 54% are females, and almost half are between 25 and 44 years old. Only 20% are younger than 18 years old, reflecting the availability of prenatal counseling and testing. This is organized at the prenatal step, within the orthodox communities, who meet through professional "matchmakers" who are privy to genetic testing information and can prevent marriage between carriers, or with the education in other Jewish communities.

New patients are mostly born from families unaware of Jewish ancestry. This delays detection as FD is not considered early in the differential diagnosis. Indeed, most children with FD that have no knowledge of traceable Jewish heritage are diagnosed around the age of 4–5 years. With the widespread use of whole-exome analysis, new genetic variants have been identified but are always combined with the founder mutation.

Life expectancy has increased; the oldest patient alive today is 65 years of age (Fig. 3). Patients live in a wide geographic distribution and advances in telemedicine have facilitated outreach to families that live outside New York (NY), giving them access to standardized virtual assessments, coordinated care across international medical teams, and the opportunity to participate in research trials [15, 16].

Clinical phenotype

The FD clinical phenotype entails widespread sensory deafferentation caused by underdeveloped somatic sensory and afferent autonomic neurons, with their cell bodies in the dorsal root and sympathetic ganglia (Table 1). In contrast, efferent (motor) somatic and sympathetic neurons are reduced in number, but functionally spared. This lack of development in many types of afferent neurons during embryogenesis prevents visceral and somatic information from reaching the brain.

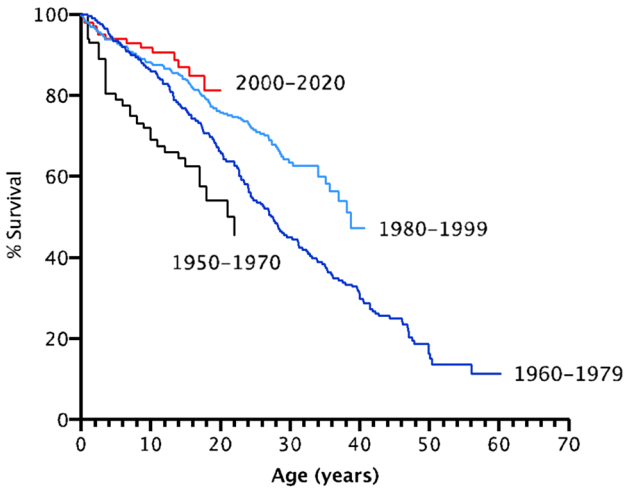

Fig. 3 Kaplan–Meier survival analysis of FD. Kaplan–Meier survival analysis shows improvement in life expectancy in patients with enhanced survival overtime. In the last decade, guidelines to prevent respiratory complications and better manage blood pressure fluctuations have been implemented

Afferent baroreflex failure

The main phenotypic feature of FD is blood pressure instability due to baroreceptor deafferentation [17]. Baroreflex neurons are part of a negative feedback loop that adjusts autonomic activity throughout the heart, vasculature, and kidney, preventing blood pressure from rising or falling excessively [18]. The afferent baroreflex signals provide tonic inhibition of sympathetic vasoconstrictor neurons. They do so with inhibitory projections from the nucleus of the solitary tract (NTS) to the rostro ventrolateral medulla (RVLM), which house the pre-sympathetic (pattern generating) neurons with fibers that descend through the spinal cord [17].

Afferent baroreflex failure is characterized by loss of incoming barosensory information to the brainstem via the glossopharyngeal (IX) and vagus (X) nerves (Fig. 4A). Signals from the baroreceptors embedded in the walls of the heart and lung vessels do not reach the NTS in the brainstem [18, 19]. Hence, because the brain is unable to detect the stretch in the blood vessel walls, it is incapable of modulating changes in sympathetic efferent activity that maintain the blood pressure constant, resulting in volatile blood pressure (Figs. 4B) [17].

Hypertension

FD patients have multiple spikes of hypertension throughout the day caused by ordinary events such as answering phone calls, eating, or playing video games (Figs. 4C) [20–22]. Both negative emotions (fear, anger, or tension) and positive emotions (excitement or anticipation of something pleasurable) produce autonomic crisis, with excessive activation of sympathetic efferent neurons [21, 22] increasing circulating norepinephrine, dopamine, and vasopressin, Patients have abrupt, severe episodes of hypertension, tachycardia, blotching, and forceful retching and vomiting. Crises occur due to direct cortical activation of pre-sympathetic fibers

Table 1 Clinical features produced by sensory deafferentation

Localization	Deficit
I Retinal ganglion cells	Visual deficits leading to blindness
II Olfactory nerve	Hyposmia/anosmia
V Trigeminal nerve	Absent corneal reflexes Lack of reflex tearing Neurotrophic keratopathy Corneal opacities Corneal perforations
VII Facial nerve	Hypogeusia
VIII Vestibular nerve	Impaired vestibular-spinal reflexes
IX Glossopharyngeal nerve	Lack of gag reflex Neurogenic dysphagia resulting in broncho aspiration Afferent baroreflex failure with blood pressure instability
X Vagus nerve	Blunted hypoxic drive resulting in sleep apnea and breath-holding spells Afferent baroreflex failure with blood pressure instability
Small sensory nerve fibers	Reduced pain and temperature sensation Painless bone fractures, burns, and repeated injuries
Myelinated nerves in muscle spindles	Loss of proprioception Sensory ataxia, spinal and lower limb deformities
Von Economo neurons of the insular cortex	Abnormal social behavior, difficulty forming relationships Increased anxiety and vomiting attacks

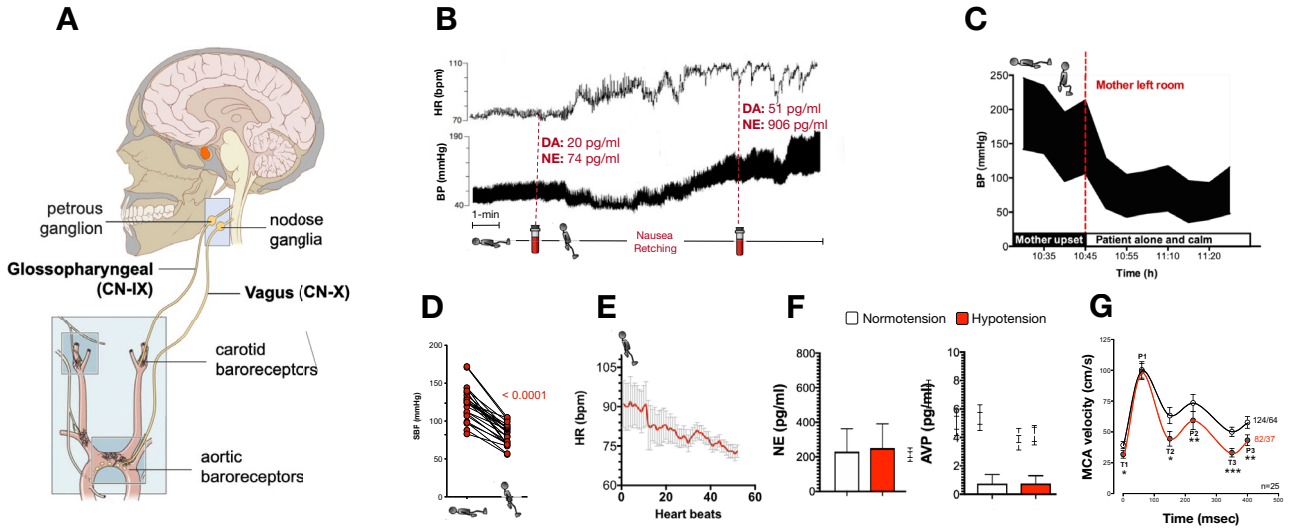

Fig. 4 Cardiovascular autonomic phenotype of FD. **A** Anatomically, the mutation affects the development of cranial nerves IX and X, which relay information from baroreceptors (PEIZO channels) that sense distortion of the aortic arch and carotid sinus and form the afferent limb of the brainstem's baroreflex. **B** Shows beat-to-beat blood pressure and heart rate recordings in a 28-year-old female patient that experienced a hypertensive crisis with vomiting. Catecholamine samples taken prior to and during the vomit crisis show increased circulating dopamine and norepinephrine levels. **C** Mother-induced hypertension occurring in a young man with FD. Note, blood pressure returned to normal levels when his mother left the room and was calm. **D** Fall in blood pressure on standing in patients with FD compared with controls. **E** Hypotension-induced bradycardia seen over successive heart beats accompanying the hypotensive response elicited by the onset of upright tilt. **F** Neuroendocrine response to hypotension (red) shows an absence of norepinephrine and vasopressin release (AVP), typical of afferent baroreflex failure. **G** Preserved cerebral blood flow in response to hypotension (red line) over the pulse wave. The intrinsic ability of the vessels to maintain blood flow constant over a wide range of pressure helps prevent syncope on standing. Adapted from [33]. Adapted from [21]. Adapted from [22, 24, 26, 32]. Adapted from [18]

in the RVLM, the source of neuronal connections to the sympathetic vasoconstrictor neurons in the periphery [21]. The hemodynamic changes are grossly exaggerated because sympathetic activation is not buffered by the normal inhibitory baroreflex feedback [23]. During crises, high arginine vasopressin production causes hyponatremia [21].

Long-term follow up of these patients showed the catastrophic consequences of volatile blood pressure, including a progressive decline in renal function and left ventricular hypertrophy [24, 25].

Catecholamine studies

Severe nausea, retching, and vomiting is due to increase dopamine spillover into the circulation, which activates the chemoreceptor trigger zone in the area postrema outside the blood–brain barrier In contrast to cortical arousal, hemodynamic orthostatic stress fails to increase sympathetic activity in FD patients [21, 26]. Urinary catecholamine studies show elevated metabolites of dopamine, but the metabolites of norepinephrine are low. This is due to a bottleneck at the enzymatic rate-limiting step of dopamine-beta-hydroxylase, which is not upregulated in FD [27].

The efferent post-ganglionic sympathetic neurons are reduced in FD patients, and the sympathetic ganglia throughout the spinal cord are visibly small [28]. Yet, patients have elevated plasma dopamine and normal norepinephrine (NE) levels [16, 21, 26]. These findings contrast with other peripheral autonomic neuropathies with low circulating levels of NE for a similar degree of efferent denervation [17, 21]. FD is a developmental disease, and neuron plasticity likely enables the development of denervation suprasensitivity. In line with this, flurodopamine scans of the heart demonstrated reduced uptake of radiolabeled tracer by sympathetic neurons [29], and pathologic studies showed abundant levels of tyrosine hydroxylase in the remaining sympathetic efferent nerve terminals [30]. Recently, induced pluripotent stem cells (iPSC)-derived neurons of FD patients [34] showed reduced NE transporter expression, decreased intracellular NE, decreased NE re-uptake, and excessive extracellular NE [31]. These adaptive defects may allow a more extended period of NE in the synaptic cleft to exert a pressor effect. Pathology studies following fatal myocardial infarction during autonomic crisis in FD were consistent with catecholamine toxicity with contraction band necrosis [25].

Hypotension

The loss of afferent baroreflex signally produces excessive sympathetic activity, but fails to elicit an increase in sympathetic activity when required, i.e., when venous return falls due to orthostatic stress. (Fig. 4D). The normal inverse relationship between blood pressure and heart rate is absent in FD. Instead, there is a parallel change of blood pressure and heart rate (Fig. 4E). Beat-to-beat recordings show that atropine has no effect on the bradycardia that happens when the blood pressure falls [21], indicating that the heart's slowing is not the result of vagal nerve activation but rather the blunt reaction of a denervated heart to decreased ventricular filling [21]. Conversely, the heart rate increases by several beats when the patient is placed in the head-down posture, simulating a "Bainbridge" or atrial reflex.

In the upright position, blood pressure falls, often to very low levels, without neuroendocrine compensation (Fig. 4F). Patients can tolerate very low blood pressures without syncope [32]. One possible explanation for their ability to withstand hypotension is the expanded autoregulatory capacity of the cerebral circulation [33]. Unlike the periphery, the cerebral vessels are mostly controlled by myogenic and metabolic mechanisms, with little input from the nervous system, except perhaps at times of extreme exercise [34]. FD patients do not develop hypocapnia on standing, which would ordinarily constrict the cerebral vessels (Fig. 4G). Transcranial Doppler measures during hypotension in patients with FD, showed that the cerebral vasculature had a remarkable pulsatile rhythm when upright, which may help maintain cerebral blood flow [33].

During sleep, both blood pressure and heart rate decrease. Many patients show exaggerated nocturnal dipping profiles, while their renal function is normal. With renal insufficiency, nocturnal dipping profiles may become blunted or reversed, which can further exacerbate kidney damage.

Afferent chemoreflex failure

Patients with FD have poor ventilation responses [35, 36]. Peripheral chemoreceptor neurons in the carotid and aortic bodies sense partial pressure of oxygen (pO_2) in the arterial blood, triggering the respiratory drive. Like baroreceptors, chemoreceptors relay their signals through the glossopharyngeal nerve fibers (cranial nerve IX) that synapse at the nucleus of the solitary tract in the medulla. Because of their absence, sensitivity to hypoxia is blunted and patients with severe hypoxia cannot mount an appropriate ventilatory response. Central chemoreceptors monitor pH-dependent variations in CO_2 (pCO_2) in the cerebrospinal fluid (CSF). The ventilatory response to hypercapnia in patients with FD is also diminished [36, 37].

Hypoxia and hypercapnia elicit bradycardia and hypotension instead of the expected tachycardia and hypertension [38]. Young patients may suffer breath-holding spells after crying or laughing, resulting in severe hypoxia, hypotension, and decerebrate posturing before breathing resumes. Almost all FD patients have sleep-disordered breathing; obstructive apnea events are more severe and frequent in children, while hypoventilation progressively worsens with age. Hypotension and syncope arise in environments with low oxygen, such as high altitude, airplane travel, and underwater swimming [38]. Sudden death during sleep occurs during the second and third decades of life [4, 35, 38].

Proprioceptive ataxia

FD patients exhibit severe ataxia caused by loss of proprioceptive acuity due to the absence of functional muscle spindle afferents [39]. Performance is impaired in both upper and lower extremities, shown by impaired precision grip, a weak sense of movement at the knees, positive Romberg test, and marked gait ataxia characterized by lateral body sways and increased speed [40].

Natural history

FD is expressed at birth and has complete penetrance, but phenotypic severity varies considerably [32]. Newborns have poor sucking reflexes, neurogenic dysphagia, and aspiration pneumonia. Feeding difficulties are one of the first recognized signs, with few babies managing to breast feed and support their nutritional needs. Babies cry without tears and have no corneal nor gag reflexes, reduced fungiform papillae in the tongue, absent deep tendon reflexes, and very mild or absent responses to pain and temperature sensation.

In infancy, patients develop a characteristic facial appearance with mild hypertelorism, upper lip flattening, lower jaw prominence, malocclusion, sialorrhea, delayed dental age, perioral soft tissue lesions caused by recurrent biting, intentional or accidental self-extraction of the teeth, and small hands and feet. Developmental delay and cognitive impairment are variable.

As they mature, there is a progressive loss of visual acuity due to retinal nerve atrophy and recurrent corneal scarring. The speech becomes dysarthric, and the gait is more ataxic. Neurogenic joint deformities, *pes cavus,* and kyphoscoliosis become evident. Most patients are legally blind and require walking aids around age 20 years. Common complications include autonomic crises, chronic lung disease, recurrent bone fractures or dislocations, skin ulcers, and infections. Patients develop anemia of chronic disease and suffer from hyponatremia, seizures, aseptic necrosis of the hips or knees, and chronic renal failure, which is worsened by labile blood

pressure. Patients are prone to develop *Clostridium difficile* infection after recurrent antibiotic treatments. Aspiration pneumonia remains the leading cause of death.

Treatment

Currently, there are no disease-modifying therapies for FD, but there are preventive and symptomatic treatments for many of the common complications [38]. Treatment approaches are depicted in Fig. 5. These range from interventions that target acute (often life threatening) problems to procedures aimed to prevent long-term complications.

General measures

Percutaneous endoscopic gastrostomy (PEG)

Early placement of a PEG tube is widely used to support nutritional requirements and prevent aspiration into the airway due to neurogenic dysphagia.[38] The PEG tube is often placed in early infancy and is kept for life. Its use

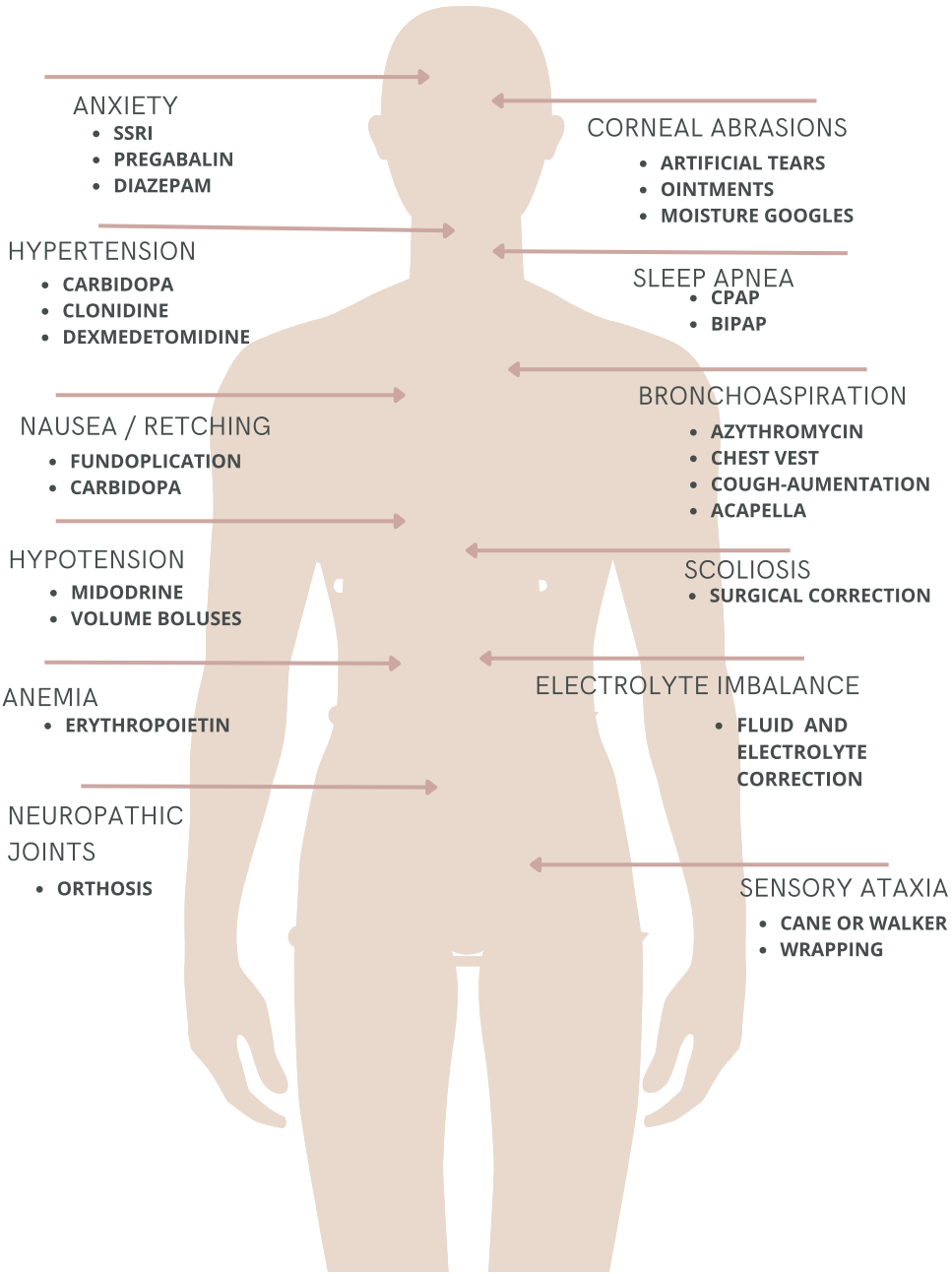

Fig. 5 Treatment options

varies between patients, some adults learn to eat solid food with precautionary measures, but most avoid "wet" food. Patients remain at risk of aspiration of thin liquids throughout life, and require medications and fluids to be administered through the PEG tube. Gastro-jejunal tube nutrition is recommended when gastroesophageal reflux is contributing to respiratory disease.

Fundoplication

Fundoplication is used frequently in FD but is controversial. Gastroesophageal reflux is common and results in aspiration of the gastric contents into the airway. While this procedure is routinely performed in FD patients, the failure rate to avoid reflux is around 16%. As motility in the gut is already affected, fundoplication surgery can impact gastric emptying, resulting in "dumping syndrome" and worsening of esophageal motility. On the other hand, cases of esophageal tear or esophageal rupture after forceful vomiting during autonomic crisis have only occurred in FD patients without fundoplication.

Corneal care

Lagophthalmos and dry eye make patients prone to corneal injuries, even with mild stimuli like the air blowing directly from an oxygen mask. Restoration of ocular surface function and integrity allows for corneal remodeling, particularly in younger patients. Thick gel formulations to lubricate the eyes and artificial tears are needed several times daily to avoid corneal ulcerations from alacrimia. The autologous serum is a blood-derived eye drop that provides an environment comparable to natural tears. Protection of the eyes with lenses or goggles is paramount to prevent accidental corneal abrasions, particularly during bi-level positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), or mechanical ventilation. Prosthetic replacement of the ocular surface ecosystem (PROSE) is a treatment that involves the design and custom fabrication of Food and Drug Administration (FDA)-approved eye prosthetic devices. These devices simulate contact lenses but are made from two high gas-permeable polymers to align with the supporting sclera, and a transitional and optic portion to vault the cornea. The device is filled with artificial tears at the time of application and removed daily for cleaning and disinfection [41].

Pulmonary therapy

Because of their weakened coughing, patients with FD require chest clearance aids to eliminate secretions.[32, 38] Postural drainage with position and manual techniques such as chest percussion and vibration must be performed several times daily. High-frequency chest wall oscillation inflatable vests provide intermittent compression that help mobilize secretions. Mechanically assisted cough augmentation is an innovative technique to deliver positive pressure through a mask, tracheostomy tube, or mouthpiece in the airways, with a rapid shift to negative pressure, aiming to recruit lung volumes, prevent atelectasis, and improve cough effectiveness. It is an excellent alternative to traditional suctioning. Lung expansion vibratory airway clearance devices such as Acapella, with or without bronchodilators, break up mucus and promote respiratory secretions. FD patients usually use a combination of these devices in sessions of 20–30 min, two or three times per day.

Noninvasive ventilation

Continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BIPAP) during sleep reduces the risk of sudden death during sleep even in patients with mild sleep-disordered breathing. Many children require a desensitization protocol to avoid developing phobias surrounding sleeping with a mask. Techniques to improve compliance include counseling, encouraging the patient to wear the mask during the day, and using the ramping mechanism to gradually increase the degree of pressure once the person has fallen asleep.

Speech and swallow therapy

Eating by mouth remains a risk throughout life. Massive aspiration is an early cause of death in FD, underscoring the lifelong need to protect the airway in patients who opt to continue oral intake. Signs of aspiration include a wet voice, coughing when eating or drinking, and choking. Regular video fluoroscopic swallow studies help assess bronchoaspiration risk when patients eat by mouth, followed by regular speech and swallowing therapies.

Spine surgery

Bracing for spinal deformities can cause inadvertent pressure ulcers and inhibit chest wall movements. Corrective scoliosis surgery may improve vital capacity and slow the decline of respiratory function, but the fusion of the spine can limit chest wall compliance. Surgical interventions require consideration of the stage of development and extendable inserted rods to allow growth.

Neuropathic deformities

Lack of pain sensation causes inadvertent trauma and prevents the patient from avoiding positions or activities that can damage the joints, increasing the risk for neuropathic arthropathies, aseptic necrosis, and rotational misalignment

of the external tibial. Tailored prosthetic devices delay or improve the formation of calluses or injuries.

Symptomatic treatments

Carbidopa

The off-label use of carbidopa is a significant breakthrough for these patients. Carbidopa exerts its effect by blocking peripheral catecholamine synthesis and effectively reducing dopamine levels without causing sedation or respiratory depression because it does not cross the blood–brain barrier. Carbidopa reduces the severity of nausea, vomiting attacks, and blood pressure variability in FD. [15] It is tapered up slowly to achieve a dose of 200 mg administered three times daily [16].

Clonidine

Clonidine is widely used to restrain sympathetic activity during adrenergic crises. [32, 42] This centrally acting alpha 2 adrenergic agonist is used in acute crisis or as a regular night or early morning medication to blunt sympathetic activation centrally. Doses used vary between 0.05 and 0.1 mg one or more times per day [43]. The transdermal patch of 0.1–0.3 mg per 24 h is preferable for long-term management as it provides stable blood levels and prevents rebound hypertensive crises. Side effects include fatigue, sedation, hypotension, and agitation with withdrawal. Clonidine has individual variability in its hemodynamic and sedative effects and must be adjusted carefully.

Benzodiazepines

Diazepam is a GABA(A) receptor agonist with anxiolytic, anticonvulsant, and muscle relaxant effects. It effectively treats autonomic crisis, usually at 5 mg every 8 h or 0.1 mg/kg in children [32]. It can cause respiratory arrest and urinary retention, and its long-term use can result in depression of mood, excessive sedation, addiction, and impaired ventilatory drive.

Dexmedetomidine

Dexmedetomidine is a centrally acting alpha 2 adrenergic agonist with greater selectivity and a shorter half life than clonidine. Intravenous infusions are effective in treating refractory adrenergic crises. Doses are slowly up-titrated every 30 min until therapeutic response, defined as a reduction of nausea, retching, or vomiting and blood pressure below 140/90 mmHg. The starting rate is 0.1–0.2 mcg/kg/h with a maximum rate of 1.4 mcg/kg/h [43, 44]. It requires monitoring in the intensive care unit, which limits its use.

Midodrine

Midodrine is a short-acting alpha-1 adrenergic receptor agonist that increases vascular tone and blood pressure and improves orthostatic tolerance. Rather than a fixed schedule of administration, it can be taken on an "as-needed basis" before physical activities that require standing. It should not be used within 3 h before bedtime [32].

Fludrocortisone

Fludrocortisone is a synthetic mineralocorticoid that enhances renal sodium tubular reabsorption and increases blood pressure. It can cause hypokalemia and cardiac and renal fibrosis [24, 32], worsen supine hypertension, and potentially increase the risk of sudden unexpected sleep death [35]. High doses given over long periods are associated with a faster decline in glomerular filtration rate, mostly likely due to exacerbation of hypertension or direct fibrotic effects on the heart [24].

Pregabalin

Pregabalin is a derivative of GABA that has antiepileptic, anxiolytic, and analgesic effects. In FD, it is used to lessen hyperadrenergic autonomic crises [45]. Treatment initiates with 25 mg at night and slow up-titration in weekly increments. There are no controlled trials to establish efficacy.

Erythropoietin

If anemia is present, oxygen-carrying capacity is decreased, which can worsen exercise tolerance and exacerbate orthostatic hypotension, likely the result of higher free nitric oxide due to less binding to hemoglobin. Treatment with erythropoietin to achieve hemoglobin levels above 12 mg/dl improved orthostatic symptoms and tolerance to standing [32].

Chronic antibiotic therapy

Chronic oral azithromycin three times per week can be helpful in FD patients who have bronchiectasis and frequent pulmonary exacerbations. Inhaled tobramycin or gentamicin can be an alternative for patients colonized with *Pseudomona aeruginosa* [38]. Viral respiratory infections are also common, and a low suspicious index should trigger the use of antiviral medications or monoclonal antibodies.

Botulinum toxin

Frequent applications of botulinum toxin to salivary glands ameliorate sialorrhea. Injections are tailored to each patient

in one or both parotid and major salivary glands. Experienced injectors can perform the procedure in their office, using a topical anesthetic cream before the injection and ultrasound guidance. Effects are transitory, and injection treatments must be repeated every few months. The protective effect of saliva on dental decay is lost when controlling drooling, resulting in cavities, infections, and teeth loss [46].

Glycopyrrolate

Glycopyrrolate reduces salivary and pharyngeal secretions by blocking muscarinic cholinergic receptors, used at a dose of 1–8 mg daily through the gastric tube [32]. Caution is needed as it can also decrease lacrimation, contributing to corneal injuries.

Prognosis

The mortality rate is high, mainly due to recurrent aspiration pneumonia or sudden death during sleep, presumably due to respiratory arrest, cardiac arrhythmias, electrolyte imbalance, and lack of arousal responses. Lung failure and chronic renal injury are leading causes of morbidity and mortality. All patients have visual impairment due to progressive optic neuropathy. Life expectancy is now longer because of improved medical management. Quality of life requires careful patient, caregiver, and physician coordination. Ongoing monitoring is needed, given the patients' difficulty reporting symptoms due to sensory deficits.

Disease-modifying treatments

Disease-modifying treatments are being developed to correct the splicing defect and increase wild-type ELP1 and its downstream effects in cells. (Table 4). It is hoped that this approach will impact disease progression.

Small molecules

In 1984, kinetin, a plant growth factor, was found to correct the FD splicing defect. Kinetin increases the production of wild-type ELP1 mRNA in FD cell lines by increasing normal splicing. Kinetin is used orally, but has very low potency, and higher doses result in severe vomiting. The *NIH blueprint lead optimization program* resulted in new kinetin-derived compounds with much higher potency, and further modifications by industry partners created an even more potent derivative splicing enhancer, which are being tested in animal models [47, 48].

Antisense oligonucleotides (ASOs)

Antisense oligonucleotides (ASOs) are synthetic oligonucleotides designed to bind to mRNA and correct genetic diseases. Krainer et al. used FD-targeted ASOs in a mice model of FD to correct the ELP1 splicing defect and provided proof of concept of increased levels of wild-type ELP1 in several tissues. ASOs have a dose-dependent efficacy. It is possible that its use in FD will require intrathecal infusions [49].

Gene therapies

Intracerebral ventricular, subretinal, or intravitreal injections of gene therapies using viral or nonviral vectors aim to express a healthy copy of the *ELP1* gene. Recently, an adeno-associated virus delivered an exon-specific small nuclear RNA, designed to cause the inclusion of ELP1 exon 20 in a phenotypic mouse model of FD. Postnatal systemic and intracerebral ventricular treatment increased wild-type ELP1 in the animals' brains, dorsal roots, and trigeminal ganglia, and the ataxic gait improved [50].

Future directions and challenges to overcome

Powering clinical trials with sufficient patients is challenging due to the rarity of FD and the decrease in birth rates. The disease is slowly progressive, and patients take decades to develop specific features and hit disease milestones. There are legitimate ethical concerns around placebo use. Tests to use as clinical endpoints may be limited to patients who can cooperate, and available questionnaires do not have standard references, or the proxy answers differ from the patients. Better designs of clinical trials combining real-world measures from smartwatches, virtual reality games, surrogate biomarkers, and machine learning may be helpful to collate all measures and determine a profile that can be widely applied. However, the determination of the families and the devoted patient advocacy organizations will overcome these challenges.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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