Acta Biomed 2020; Vol. 91, Supplement 13: e2020002 DOI: 10.23750/abm.v91i13-S.10518

Original article

Genetic testing for autonomic dysfunction or dysautonomias

Paolo Enrico Maltese,[1] Elena Manara,[2] Tommaso Beccari,[3] Munis Dundar,[4] Natale Capodicasa,[5] Matteo Bertelli[1,2,6]

[1] MAGI'S LAB, Rovereto (TN), Italy; [2] MAGI EUREGIO, Bolzano, Italy; [3] Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy; [4] Department of Medical Genetics, Faculty of Medicine, Erciyes University, Kayseri, Turkey; [5] Magi Balkans - Rare Genetic Diseases, Tirana, Albania; [6] EBTNA-LAB, Rovereto (TN), Italy

Abstract. *Background and aim:* The autonomic system is made of two divisions called the sympathetic and parasympathetic nervous systems and extends from the central to the peripheral nervous system for controlling homeostasis. Autonomic dysfunction, also known as dysautonomia, occurs when the nerves that control involuntary bodily functions do not work properly. The aim of this mini-review is to summarize all the syndromes characterized by dysautonomia and for which the associated gene is known. *Methods:* We searched those syndromes in PubMed and OMIM database. *Results:* We found 36 genetic syndromes characterized by autonomic dysfunction. *Conclusions:* We propose genetic testing in all cases of idiopathic autonomic dysfunction. A genetic test with these genes would make it possible to determine the molecular diagnosis of new subjects and/or establish a risk of recurrence in family members for the purpose of planning appropriate preventive and/or therapeutic measures. (www.actabiomedica.it)

Key words: autonomic dysfunction, dysautonomia, genetic test

The autonomic system extends from the central to the peripheral nervous system and controls homeostasis by innervating blood vessels, smooth muscle, hair follicles, the gastrointestinal tract, the bladder, the gastrointestinal and urinary sphincters, cardiac muscle, pacemaker cells, sweat and salivary glands, the respiratory and digestive tracts, the pancreas, the pineal glands, pancreas islet cells, white and brown adipose tissue, liver cells and lymphatic tissue (1). The autonomic system therefore influences blood pressure, heart rate, vascular reactivity, bowel function, bladder function, the sexual organs, pupil diameter, sweating, thermoregulation, airway resistance, blood flow, digestion, energy balance, fluid volume, glucose homeostasis, the immune system, inflammatory processes, glandular secretions, and salt and water balance (2).

The autonomic nervous system has two distinct divisions called the sympathetic and parasympathetic nervous systems. These systems can exercise antagonist, synergistic or independent control on effector organs. Some organs are innervated by both sympathetic and parasympathetic branches with either antagonistic or synergistic function. Other organs are only innervated by one or the other (3).

The sympathetic nervous system is said to regulate "fight or flight" functions of the autonomic nervous system, and is activated in situations of fear, rage or pain. It also controls arteriole tone, urinary bladder distention when full and ejaculation in males (3).

The parasympathetic nervous system is said to regulate "rest and digest" functions due to its role in conserving energy, promoting digestion, and in waste

excretion. However, it also controls contraction of the ciliary muscle for accommodation of near vision, the lacrimal glands for tear production, the iris sphincter muscle for pupil constriction and for control of the sexual organs (3).

Autonomic dysfunction, also known as dysautonomia, occurs when the nerves that control involuntary bodily functions do not work properly. It affects communication between the central nervous system, the peripheral organs and areas of the autonomic nervous system, such as the heart, blood vessels and sweat glands. The most common symptoms of autonomic dysfunction may be dizziness, fainting on standing up, orthostatic hypotension, exercise intolerance, sweating abnormalities, digestive difficulties (such as diarrhea, constipation, difficulty swallowing), urinary problems, incontinence, incomplete emptying of the bladder, difficulty with ejaculation or maintaining an erection, vaginal dryness, inability of the pupils to react to light quickly (4).

Clinical confirmation of autonomic dysfunction is based on specific tests, of which the tilt table test with Valsalva maneuver or hyperventilation are the most common. The thermoregulatory sweat test is a good option when sweating symptoms predominate. Bladder ultrasonography and urodynamic testing are used to evaluate urinary dysfunction, whereas the blocking eyedrop test and pupillometry are used to evaluate eye abnormalities (5). Although diabetes is the most common cause of autonomic neuropathy (6), genetic syndromes with autonomic dysfunction also exist (Table 1), and the associated genes should be analyzed whenever autonomic dysfunction is detected.

Since these disorders are so heterogeneous, we developed a multi gene panel to sequence all associated genes in parallel. Early detection of any molecular causes may make early personalized treatment possible. Dysautonomias are usually among the symptoms of complex syndromes, however the genes in question may also be implicated in isolated dysautonomias. This is why we propose genetic testing in all cases of idiopathic autonomic dysfunction, i.e. without any clear involvement of an external or internal cause, like diabetes or drug-induced autonomic dysfunction. A ge-

Table 1. Genetic syndromes with their associated genes characterized by autonomic dysfunction

Gene (OMIM ID)	Disease (OMIM ID)	Inheritance	Type of autonomic dysfunction
ELP1 (*603722)	HSAN3 or familial dysautonomia (#223900)	AR	Alacrima, decreased corneal reflex, decreased taste, hypertension, postural hypotension, breath-holding episodes, constipation, hyperhidrosis, hypotonia, decreased pain/temperature perception, hyporeflexia, episodic fever
NTRK1 (*191315)	CIPA (#256800)	AR	Absent corneal sensation, decreased pain sensation, postural hypotension, anhidrosis, pain/temperature insensitivity, episodic fever
P4HTM (*614584)	HIDEA (#618493)	AR	Hypoventilation, bradypnea, sleep apnea, constipation, hypotonia, abnormal sleep behavior, hyperthermia, hypothermia
PRNP (*176640)	FFI (#600072)	AD	Apneic episodes, dysphagia, constipation, urinary retention, diaphoresis, refractory insomnia, dream enactment, somniloquism, fever
LIFR (*151443)	STWS (#601559)	AR	Pulmonary artery hypertension, respiratory insufficiency, apnea, dysphagia, hypotonia, decreased pain sensation, absent patellar reflexes, poor temperature regulation
TTR (*176300)	Transthyretin-related hereditary amyloidosis (#105210)	AD	Diarrhea, constipation, erectile dysfunction, urinary incontinence, neuropathic muscle weakness, sensory axonal polyneuropathy, hyporeflexia
DBH (*609312)	ORTHYP1 (#223360)	AR	Severe recurrent orthostatic hypotension, impaired ejaculation, nocturia, episodic hypoglycemia/hypothermia in infants

(continued on next page)

Table 1 ***(continued)***. Genetic syndromes with their associated genes characterized by autonomic dysfunction

Gene (OMIM ID)	Disease (OMIM ID)	Inheritance	Type of autonomic dysfunction
BRAT1 (*614506)	RMFSL (#614498)	AR	Bradycardia, apnea, axial hypotonia, hyperreflexia, hypertonia
SCN9A (*603415)	Paroxysmal extreme pain disorder (#167400)	AD	Episodic lacrimation, autonomic reflex syncope, tachycardia, bradycardia, episodic burning pain, nonepileptic tonic attacks
SPTLC1 (*605712)	HSAN1A (#162400)	AD	Distal sensory loss of pain, temperature, touch, vibration, neuropathic muscle atrophy/weakness, distal areflexia/hyporeflexia
LMNB1 (*150340)	ADLD (#169500)	AD	Orthostatic hypotension, abnormal bowel/bladder regulation, impotence, decreased sweating, hyperreflexia
HMBS (*609806)	AIP (#176000)	AD	Tachycardia, hypertension, respiratory paralysis, vomiting, diarrhea, constipation, urinary retention, dysuria, urinary incontinence, paralysis, autonomic neuropathy, weakness
CHRNA3 (*118503)	BAIPRCK (#191800)	AR	Impaired bladder innervation, neurogenic disturbed bladder/ureter
WNK1 (*605232)	HSAN2A (#201300)	AR	Impaired corneal reflex, decreased taste sensation, gastroesophageal reflux, painless fractures, neurogenic joint degeneration, impaired pain, temperature, position and touch sensation in distal extremities, hyporeflexia, areflexia, hypotonia
PHOX2B (*603851), *GDNF* (*600837), *RET* (*164761), *ASCL1* (*100790), *EDN3* (*131242)	CCHS (#209880)	AD	Decreased pupil light responses, periodic apnea, decreased sensitivity to hypercapnia/hypoxemia, constipation, increased sweating, poor temperature regulation
AAAS (*605378)	AAAS (#231550)	AR	Alacrima, anisocoria, abnormal cardiovascular reflexes, postural hypotension, achalasia, abnormal sweating, distal muscle weakness/ atrophy, hyperreflexia
SCN9A (*603415)	CIP (#243000)	AR	Anosmia, hyposmia, neuropathic joints, painless fractures, distal painless ulcers, hypohidrosis, anhidrosis, decreased temperature sensation, hyporeflexia
CRLF1 (*604237)	CISS1 (#272430)	AR	Neck muscle hypertonia, dyspnea, feeding difficulties, sweating induced by cold exposure, poor sweating induced by heat, tetanus-like muscle contractions, episodic hyperthermia
CDKL5 (*300203)	EIEE2 (#300672)	XLD	Breath-holding episodes, hyperventilation, constipation, gastroesophageal reflux, hypotonia, sleep difficulties
GLA (*300644)	Fabry disease (#301500)	XL	Hypertension, episodic diarrhea, vomiting, tenesmus, hypohidrosis, muscle cramps, episodic acroparesthesias and pain
RAB7 (*602298)	CMT2B (#600882)	AD	Distal limb muscle weakness/atrophy, hyporeflexia, areflexia
NOTCH2NLC (*618025)	NIID (#603472)	AD	Constipation, fecal/urinary incontinence, bladder dysfunction, distal muscle weakness, sensorimotor peripheral neuropathy, hyporeflexia, slow nerve conduction
IGHMBP2 (*600502)	DSMA1 (#604320)	AR	Respiratory failure, tachypnea, diaphragm weakness/paralysis, hyporeflexia, decreased pain perception, excessive sweating, constipation, bladder incontinence

(continued on next page)

Table 1 ***(continued)***. Genetic syndromes with their associated genes characterized by autonomic dysfunction

Gene (OMIM ID)	Disease (OMIM ID)	Inheritance	Type of autonomic dysfunction
DDC (*107930)	Aromatic L-amino acid decarboxylase deficiency (#608643)	AR	Hypotension, eating difficulties, gastroesophageal reflux, diarrhea, constipation, truncal hypotonia, hyperreflexia, sleep disturbances, paroxysmal sweating, temperature instability
NGF (*162030)	HSAN5 (#608654)	AR	Painless fractures, distal pain insensitivity
SOX10 (*602229)	PCWH (#609136)	AD	Alacrima, olfactory bulb agenesis, anosmia, intestinal aganglionosis, neonatal hypotonia, areflexia, hyporeflexia, distal muscle wasting/ weakness, decreased nerve conduction velocity, distal sensory impairment
TCF4 (*602272)	PTHS (#610954)	AD	Intermittent breathing, hyperventilation, constipation, gastroesophageal reflux, hypotonia, incoordination, hypotonia
SPR (*182125)	DOPA-responsive dystonia due to sepiapterin reductase deficiency (#612716)	AD, AR	Axial hypotonia, hypersomnolence, sleep disturbances
FAM134B (*613114)	HSAN2B (#613115)	AR	Impaired pupil response to light, urinary incontinence, episodic hyperhidrosis, impaired pain and temperature sensation, hyporeflexia, areflexia
ECE1 (*600423)	HCAD (#613870)	AD	Tachycardia, hypertension, core temperature 40.5°C
DST (*113810)	HSAN6 (#614653)	AR	Alacrima, decreased/absent corneal reflex, bradycardia, tachycardia, blood pressure vasomotor instability, respiratory insufficiency, episodic apnea, poor feeding, episodic sweating, neonatal hypotonia, areflexia, decreased pain response, idiopathic fever
GMPPA (*615495)	AAMR (#615510)	AR	Alacrima, achalasia, dysphagia, feeding difficulties
SCN11A (*604385)	HSAN7 (#615548)	AD	Diarrhea, constipation, painless fractures, hyperhidrosis, mild muscle weakness, insensitivity to pain
PRDM12 (*616458)	HSAN8 (#616488)	AR	Absent corneal reflex, decreased tearing, decreased sweating, insensitivity to pain/temperature
TXN2 (*609063)	COXPD29 (#616811)	AR	Poor feeding, hypotonia, peripheral neuropathy
SLC18A2 (*193001)	PKDYS2 (#618049)	AR	Noisy breathing, increased sweating, axial hypotonia, appendicular hypertonia, disrupted sleep, hyperreflexia, temperature instability

AAAS = achalasia-addisonianism-alacrima syndrome; AAMR = alacrima, achalasia, mental retardation syndrome; ADLD = adult-onset demyelinating leukodystrophy; AIP = porphyria acute intermittent; BAIPRCK = autonomic bladder dysfunction with impaired pupil reflex and secondary congenital anomalies of kidney and urinary tract; CCHS = congenital central hypoventilation syndrome; CIP = congenital indifference to pain; CIPA = congenital insensitivity to pain with anhidrosis; CISS = Crisponi/cold-induced sweating syndrome; CMT = axonal Charcot-Marie-Tooth disease; COXPD = combined oxidative phosphorylation deficiency; DSMA = distal spinal muscular atrophy; EIEE = early infantile epileptic encephalopathy; FFI = fatal familial insomnia; HCAD = Hirschsprung disease, cardiac defects, autonomic dysfunction; HIDEA = hypotonia, hypoventilation, impaired intellectual development, dysautonomia, epilepsy, eye abnormalities; HSAN = hereditary sensory and autonomic neuropathy, type III; NBIA = neurodegeneration with brain iron accumulation; NIID = neuronal intranuclear inclusion disease; OCCM = occipital cortical malformations; ORTHYP = orthostatic hypotension; PCWH = peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, Hirschsprung disease; PKDYS2 = infantile parkinsonism-dystonia; PTHS = Pitt-Hopkins syndrome; RMFSL = lethal neonatal rigidity and multifocal seizure syndrome; STWS = Stuve-Wiedemann syndrome

netic test with these genes would make it possible to determine the molecular diagnosis of new subjects and/or establish a risk of recurrence in family members for the purpose of planning appropriate preventive and/or therapeutic measures.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Janig W. Integrative action of the autonomic nervous system: neurobiology of homeostasis. Cambridge: Cambridge University Press, 2006.
2. Gibbons CH. Basics of autonomic nervous system function. Handb Clin Neurol 2019; 160: 407-18.
3. Wehrwein EA, Orer HS, Barman SM. Overview of the anatomy, physiology, and pharmacology of the autonomic nervous system. Compr Physiol 2016; 6: 1239-78.
4. https://www.healthline.com/health/autonomic-dysfunction
5. Sánchez-Manso JC, Muppidi V, Varacallo M. Autonomic Dysfunction. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430888/
6. https://www.mayoclinic.org/diseases-conditions/autonomic-neuropathy/symptoms-causes/syc-20369829

Received: 3 September 2020
Accepted: 14 October 2020
Correspondence:
Stefano Paolacci
Via delle Maioliche, 57/D, Rovereto (TN), Italy
E-mail: stefano.paolacci@assomagi.org