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REVIEW

Michael Ristow

Neurodegenerative disorders associated with diabetes mellitus

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Abstract More than 20 syndromes among the significant and increasing number of degenerative diseases of neuronal tissues are known to be associated with diabetes mellitus, increased insulin resistance and obesity, disturbed insulin sensitivity, and excessive or impaired insulin secretion. This review briefly presents such syndromes, including Alzheimer disease, ataxia-telangiectasia, Down syndrome/trisomy 21, Friedreich ataxia, Huntington disease, several disorders of mitochondria, myotonic dystrophy, Parkinson disease, Prader-Willi syndrome, Werner syndrome, Wolfram syndrome, mitochondrial disorders affecting oxidative phosphorylation, and vitamin B_1 deficiency/inherited thiamine-responsive megaloblastic anemia syndrome as well as their respective relationship to malignancies, cancer, and aging and the nature of their inheritance (including triplet repeat expansions), genetic loci, and corresponding functional biochemistry. Discussed in further detail are disturbances of glucose metabolism including impaired glucose tolerance and both insulin-dependent and non-insulin-dependent diabetes caused by neurodegeneration in humans and mice, sometimes accompanied by degeneration of pancreatic beta-cells. Concordant mouse models obtained by targeted disruption (knock-out), knock-in, or transgenic overexpression of the respective transgene are also described. Preliminary conclusions suggest that many of the diabetogenic neurodegenerative disorders are related to alterations in oxidative phosphorylation (OXPHOS) and mitochondrial nutrient metabolism, which coincide with aberrant protein precipitation in the majority of affected individuals.

Keywords Diabetes · Neurodegeneration · Insulin · Genetics · Mitochondria

MICHAEL RISTOW received his M.D. degree in internal medicine at the University of Cologne, Germany. Following postdoctoral study at Harvard Medical School/Joslin Diabetes Center, Boston, USA, he is currently a senior group leader at the German Institute for Human Nutrition Potsdam-Rehbrücke and Assistant Professor at the Charité University Medicine in Berlin. His research interests include the role of mitochondrial metabolism in the development of diseases associated with aging, including diabetes mellitus, obesity, and cancer.

M. Ristow (✉)
Department of Clinical Nutrition,
German Institute for Human Nutrition, Potsdam-Rehbrücke,
114 Arthur-Scheunert-Allee, 14558 Nuthetal-Berlin, Germany
e-mail: mr@mristow.org
Tel.: +49-33200-88771, Fax: +49-33200-88777

M. Ristow
Department of Endocrinology, Diabetes, and Nutrition,
Campus Benjamin Franklin, Charité University Medicine,
Berlin, Germany

Introduction

Neurodegenerative disorders affect a major proportion of the general population, especially with increasing age. Neurodegeneration is defined as progressive impairment of any neuronal function. It either affects specific neurons or compromises neuronal function in a less focused manner. Accordingly, highly specific neuronal functions may be affected causing, for example, visual or hearing impairment in some syndromes while others cause a more diffuse impairment of brain or neuronal functions as observed, for example, dementia. Two groups of neurodegenerative disorders may thus be distinguished. One consists of a large number of syndromes that typically affect individuals of younger age or even children [1]. These disorders are commonly caused by single gene mutations

Table 1 Neurodegenerative disorders associated with increased prevalence of diabetes mellitus (*DIDMOAD* diabetes insipidus and diabetes mellitus with optic atrophy and deafness, *IGT* impaired glucose tolerance, *MELAS* myopathy, encephalopathy, lactic acidosis, and strokelike episodes, *MERRF* myoclonic epilepsy associated with ragged-red fibers, *MIDD* maternally inherited diabetes and deafness, *MTTE* mitochondrial transfer RNA for glutamic acid, *MTTI* mitochondrial transfer RNA for isoleucine, *MTTK* mitochondrial transfer RNA for lysine, *MTTL1* mitochondrial transfer RNA for leucine 1, *MTTS2* mitochondrial transfer RNA for serine 2)

Disorder	OMIM	locus/loci	Affection	Inheritance	Mouse model	Diabetes mellitus
Aceruloplasminemia	604290	3q25	Ceruloplasmin	Autosomal recessive	No	Typical
Alström syndrome	203800	2p13	ALMS1	Autosomal recessive	No	Typical
Ataxia-telangiectasia	208900	11q22.3	ATM	Autosomal recessive	Yes	Extreme insulin resistance
Alzheimer disease	104300	Several	Several (at least four)	Unknown	Yes	Recent evidence
Bardet-Biedl syndrome	209900	Several	BBS1–8	(Autosomal recessive)	No	Frequent
Cerebellar ataxia, deafness, and narcolepsy	604121	Unknown	Unknown	Autosomal dominant	No	Frequent
Down syndrome	190685	Trisomy 21	DSCR1–4, others	Sporadic	Yes	Frequent
Feigenbaum syndrome	209010	Unknown	Unknown	Unknown	No	Typical
Friedreich ataxia	229300	9q13	Frataxin	Autosomal recessive	Yes	Frequent
Herrmann syndrome	172500	Unknown	Unknown	Autosomal dominant	No	Typical
Huntington disease	143100	4p16.3	Huntingtin	Autosomal dominant	Yes	Frequent
Kearns-Sayre syndrome	530000	mtDNA	Various	Sporadic	No	Frequent
Klinefelter syndrome	none	XXY duplicat.	Not applicable	Sporadic	No	Frequent
MTTE	590025	mtDNA	tRNA (Glu)	Maternal	No	Typical
MTTL1 (including MELAS and MIDD)	590050	mtDNA	tRNA (Leu)	Maternal	No	Frequent
MTTI	590045	mtDNA	tRNA (Ile)	Maternal	No	G4284A
MTTK (including MERRF)	590060	mtDNA	tRNA (Lys)	Maternal	No	A8296G
MTTS2	590085	mtDNA	tRNA (Ser)	Maternal	No	Typical
Myotonic dystrophy 1 (MD1)	160900	19q13	DMPK	Autosomal dominant	Yes	Frequent
Narcolepsy	161400	17q21, 4p13	Hypocretin (receptor)	Variable	Yes	Frequent
Norrie disease	310600	Xp11.4	Norrin/NDP	X-linked	No	Rare
Parkinson disease	168600	Several	Parkin, SNCA, tau	Variable	Yes	Mainly IGT
Prader-Willi syndrome	176270	15q11-q13	SNRPN and others	(Autosomal dominant)	Yes	Frequent
Thiamine-responsive megaloblastic anemia	249270	1q23	THTR1	Autosomal recessive	Yes	Typical
Spinocerebellar ataxia 3/Machado-Joseph disease	109150	14q24	ATX3	Autosomal dominant	Yes	Rare
Spinocerebellar ataxia 6	183086	19p13	α1A-Ca^{2+}-channel	Autosomal dominant	No	Rare
Turner syndrome	none	X monosomy	Not applicable	Sporadic	No	Frequent
Werner syndrome	277700	8p12	WRN and others	Autosomal recessive	Yes	Typical
Wolfram syndrome/DIDMOAD	222300	4p16.1	Wolframin	Autosomal recessive	No	Typical
Woodhouse-Sakati syndrome	241080	Unknown	Unknown	Unknown	No	Typical

in the nuclear or mitochondrial genomes and follow the lines of Mendelian or maternal transmission [1]. The other group of disorders frequently affects elderly persons and is accompanied by symptoms of generalized aging, including diabetes mellitus, obesity, the metabolic syndrome, and various types of malignancies. Werner syndrome [2] is the only disorder known to belong to both of these two groups. This disorder, caused by a single gene mutation, specifically affects children but also includes symptoms of general aging, including diabetes mellitus and cancer [1, 3, 4].

More than 100 inherited syndromes of neurodegeneration have now been described [1]. Of these, more than 20, including most of the more frequent ones, are associated with diabetes mellitus (Table 1), indicating that approximately 20% of neurodegenerative disorders are associated with diabetes mellitus. Compared to the overall incidence of diabetes mellitus in the general population of 4–8% [5], individuals suffering from neurodegenerative disorders exhibit a significantly higher prevalence of diabetes mellitus, although accurate overall statistics are lacking.

Diabetes mellitus is defined as inappropriate glucose metabolism leading to impaired removal of glucose from the circulation. While insulin mediates the clearance of glucose from blood by activating glucose transport into the cytosol, absolute or relative lack of insulin and/or impaired insulin action at its receptor causes delayed or almost absent metabolism of circulating glucose [6, 7, 8, 9, 10, 11, 12]. Non-insulin-dependent diabetes (type 2) diabetes mellitus is the most prevalent form of diabetes mellitus and affects mainly middle-aged and elderly individuals; sedentary life-style, obesity, and the so-called metabolic syndrome are well-established risk factors. According to the criteria of the World Health Organization (WHO), other types of diabetes include the so-called type 1 diabetes mellitus, which is caused by autoimmune destruction of pancreatic β-cells and predominantly affects younger individuals, gestational diabetes, and a group termed "other specific types." The latter includes various syndromic entities, including Down syndrome, Friedreich ataxia, Huntington chorea, Klinefelter's syndrome, Lawrence-Moon-Biedel syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome, Turner's syndrome, and Wolfram's syndrome'[13]. In addition to these, several other syndromes typically coincide with diabetes mellitus (see Table 1). In this regard it should be noted that type 2 diabetes mellitus itself is not a genetically defined entity but is a polygenic disease presumably caused by multiple combinations of gene mutations that affect both nuclear and mitochondrial genomes. Furthermore it should be mentioned that a small percentage of type 2 diabetes cases have been found to be associated with defined mutations of the mitochondrial genome (see below), and that intermediate triplet repeat expansions of the Friedreich ataxia gene have been found to be associated with common type 2 diabetes (see below). Recent evidence suggests that impaired mitochondrial metabolism is an essential feature of common type 2 diabetes [14, 15, 16, 17, 18]. Hence it is plausible that typical neurodegenerative disorders and type 2 diabetes share common genetic and/or biochemical features. This review briefly summarizes the current knowledge on such syndromes specifically in regards to diabetes mellitus and discusses potential unifying mechanisms among such disorders.

Aceruloplasminemia [OMIM 604290]

This autosomal-recessively inherited disorder is caused by a deficiency in ceruloplasmin, which normally catalyzes the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) [1]. Aceruloplasminemia was first described in 1994 [19]. It is characterized by dementia, diabetes mellitus, cerebellar ataxia, and extrapyramidal symptoms, and it has been shown that the basal ganglia of affected individuals accumulate iron [1]. The age at onset is commonly that of middle life, and its associated symptoms are increased serum ferritin and decreased serum iron levels. Hepatic accumulation of iron has been reported, and involvement of mitochondrial dysfunction possibly mediated by the Fenton reaction appears likely [20, 21]. Astonishingly, while this disease typically leads to diabetes mellitus (which has not been classified further), a biochemically similar disorder named Wilson disease [22, 23, 24] has not to date been associated with disturbances of glucose metabolism. Another disorder causing systemic iron overload, hemochromatosis [25], which is caused by mutations of the *HFE* gene on chromosome 6p21.3, is typically associated with diabetes mellitus but does not cause neurodegeneration. The reasons for this apparent contrariness remain to be resolved.

Alström syndrome [OMIM 203800]

Alström syndrome (ALMS) is an autosomal-recessively inherited disorder that shares symptoms of Bardet-Biedl syndrome (see below), including retinitis pigmentosa, deafness, obesity, and diabetes mellitus [1]. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of mental impairment. The syndrome is caused by mutations within the *ALMS1* gene [26, 27] of unknown function. Alström syndrome includes many features of the metabolic syndrome [6] including hyperlipidemia, hyperuricemia, insulin resistance, hypertension, and diabetes mellitus. Furthermore, acanthosis nigricans, chronic active hepatitis (possibly based on nonalcoholic steatohepatitis) and dilated cardiomyopathy have been observed [1]. In a recent study on common type 2 diabetes and its putative relationship to mutations in the *ALMS1* gene, no significant association was detected [28]. A possible involvement of impaired mitochondrial function has tentatively been suggested [29].

Ataxia-telangiectasia (AT) [OMIM 208900]

This autosomal-recessively inherited disorder is also known as Louis-Bar syndrome [1, 30, 31]. It is caused by mutations in the *ATM* gene [32]. ATM has structural elements that resemble those of phosphatidylinositol-3 kinase (an essential part of the insulin receptor signaling cascade) [8], and loss of function of the ATM protein impairs the cellular response to DNA damage. This is not surprising as it is involved in phosphorylation of several substrates critical for DNA repair and cell cycle control [33, 34]. Clinically patients exhibit cerebellar ataxia, telangiectases, immune defects, and an increased prevalence of malignant disease. First symptoms typically occur during preschool age. Ataxia-telangiectasia causes extreme insulin resistance [35], but clinical diabetes seems to be diagnosed less frequently [36, 37, 38, 39]. While data on insulin resistance in heterozygous carriers of *ATM* mutations are unavailable, such individuals carry an increased risk for development of malignancies [40, 41, 42]. Of note, individuals with common type 2 diabetes mellitus have an increased risk for malignancies while type 1 diabetics do not. In light of the difference in nature of these two disorders, this has particular relevance. While type 2 diabetes is defined by the presence of insulin resistance accompanied by inappropriate insulin secretion [6, 8], type 1 diabetes results from an isolated deficiency in secreted insulin. The phenotypical association of insulin resistance (and hence type 2 diabetes mellitus) with cancer in general, but most pronounced in ataxia-telangiectasia, suggests a causative link between malignancies and insulin resistance. This is further supported by increased cancer rates in obese, i.e., insulin-resistant but nondiabetic, individuals, as well as by elevated serum insulin levels in insulin-resistant states, together with the well known mitogenic action of insulin both in vitro and in vivo.

Mouse models for ATM deficiency exhibit growth retardation, neurological abnormalities, infertility, and spontaneous tumor development [43, 44, 45]. Evaluation of glucose metabolism and/or insulin signaling in these models has not to date been published.

Alzheimer disease [OMIM 104300]

Alzheimer disease (AD) is by far the most frequent form of dementia [46] and the most common neurodegenerative disease [1]. While inheritance appears multifactorial (or autosomal-dominant in some families), and mitochondrial involvement is likely [47, 48], at least four subtypes of the disease have been classified on a genetic basis: type 1 is caused by mutations in the *amyloid precursor* gene [49], type 2 is related to the apoprotein-encoding *APOE4* allele on chromosome 19 [50, 51, 52] (an allele also related to hypercholesterolemia), type 3 is caused by mutations in the *presenilin-1* gene on chromosome 14 [53], and type 4 is caused by mutations in the related *presenilin-2* gene on chromosome 1 [54]. The amyloid protein [49] is a 4-kDa protein cleaved from the amyloid Aβprecursor protein by γ-secretase. Multimeric aggregates of the amyloid protein form the so-called plaque core which causes the neuronal deposits made of amyloid fibrils that are prototypical for Alzheimer disease, but which are also found in patients with Parkinson disease (see below) as well as older individuals with Down syndrome (see below). Amyloid protein deposits are commonly observed in pancreatic islets of diabetic patients [55]. These deposits consist of islet amyloid polypeptide (IAPP) [56, 57]. Of interest, treatment with insulin or metformin lower IAPP concentrations in diabetics, while treatment with the most widely used group of antidiabetic drugs, sulfonylureas, increases IAPP concentrations, i.e., therapeutic use of sulfonylureas induces a possibly detrimental effect on islet function [57].

Given the pathogenetic similarities and the fact that amyloid Aβ precursor protein and IAPP have a 90% structural similarity [58], it is not surprising that Alzheimer disease seems to predispose for insulin resistance [59], insulin hypersecretion [59], and type 2 diabetes mellitus [58]. Conversely, individuals suffering from type 2 diabetes show an increased prevalence of dementia [60, 61]. This effect is perhaps explained by the elevation in serum insulin levels (as observed in prediabetes and early type 2 diabetes), which has been associated with impaired cognitive function [62]. Mechanistically this might be due to elevated amyloid Aβ levels, which are associated with elevated serum insulin content [63].

Finally, research in recent years suggests that cholesterol modulates synthesis of β-amyloid [64], and that 3-hydroxy-3-methylglutaryl coenzyme A synthase inhibitors, by affecting cholesterol biosynthesis, may offer a treatment option for Alzheimer disease [64] while positively modulating alterations in lipid metabolism due to a diabetes mellitus [6].

Several transgenic mouse models overexpressing IAPP have been generated. While these mice generally develop diabetes mellitus subsequent to amyloid deposits [65, 66], in one line [67] mice had to be backcrossed on an o*b/ob* background, i.e., a leptin-deficient and obese mouse line, to produce a diabetic phenotype [68]. Conversely, targeted disruption of *IAPP* leads to enhanced insulin secretion and improved glucose tolerance [69]. Of interest, disruption of insulin-degrading enzyme causes increased amyloid plaque formation and glucose intolerance accompanied by hyperinsulinemia [70]. Numerous transgenic and knock-in mouse models affecting the various genes associated with Alzheimer disease have been generated; due to the number of models they cannot all be listed in this review. Importantly, none of these latter models have yet been shown to exhibit disturbances of glucose metabolism.

Bardet-Biedl syndrome [OMIM 209900]

The (in most cases) autosomal-recessively inherited disorder Bardet-Biedl syndrome (BBS) is characterized by mental retardation, pigmentary retinopathy, polydactyly,

obesity, diabetes mellitus, renal dysplasia, hepatic fibrosis, and hypogenitalism [1, 71, 72, 73]. Obesity is found in almost every patient, while diabetes affects less than 50% [74]. While the syndrome shares some similarities with Lawrence-Moon syndrome (OMIM 245800) [1], these two disorders can be distinguished by the presence of paraplegia and the absence of polydactyly, obesity, and diabetes mellitus in Lawrence-Moon syndrome [75]. Terms such as Lawrence-Moon-Bardet-Biedl or Lawrence-Moon-Biedl syndrome should therefore be avoided [1]. In addition, some features are shared with Biemond syndrome II (OMIM 210350) [1], which also causes obesity, while no diabetes has been reported. Bardet-Biedl syndrome has been linked to at least eight different genetic *loci*, referred to as *BBS1BBS8*; except for *BBS3* and *BBS5*, corresponding mutations have been identified in various pedigrees. Interestingly, heterozygous carriers possibly exhibit an increased risk for obesity, hypertension, diabetes mellitus, and renal disease [76].

Cerebellar ataxia, deafness, and narcolepsy (CADN) [OMIM 604121]

In 1995 Melberg and colleagues [77] reported a pedigree of four generations with at total of five patients showing cerebellar ataxia and sensorineural deafness; four of these also suffered from narcolepsy, among those two individuals were diabetic. Psychiatric and additional neurological symptoms including optic atrophy were observed. Genetic analyses [78] excluded *SCA-1*, *SCA-2*, *SCA-3*, *SCA-6*, *SCA-7*, and *huntingtin* gene mutations as well as linkage to *HLA-DR2* (as observed in syndromic narcolepsy, see below). Magnetic resonance imaging and computed tomography revealed profound atrophy of several brain regions [78]. Biochemical investigation of a muscle biopsy specimen in a single case indicated mitochondrial dysfunction with decreased oxidative phosphorylation and concurrently ATP production [77]. No cases have been reported outside the above mentioned pedigree [1].

Down syndrome/trisomy 21 [OMIM 190685]

The most frequent form of mental retardation is caused by a trisomy of all or major parts of chromosome 21 [79], called Down syndrome [80]. Down syndrome patients exhibit characteristic dysmorphic features, cardiac and gastrointestinal malformations, tenfold increased frequency of leukemia, significant hearing loss [1], and increased frequency of diabetes mellitus [81, 82]. Down syndrome and Alzheimer disease (see above) have subcellular similarities regarding cerebral amyloid deposits [49] and occurrence of mitochondrial dysfunction [83, 84, 85]. Descriptions of two murine models have been published [86, 87], but information on glucose metabolism in these mice is not available.

Feigenbaum syndrome [OMIM 209010]

Feigenbaum syndrome has been reported in two affected brothers exhibiting progressively impaired cognitive function, atherosclerosis, sensorineural deafness, glomerulosclerosis, proteinuria, and diabetes mellitus. Ex vivo studies in cultured fibroblasts revealed impaired mitochondrial function, with specific impairment of complexes III and IV of the respiratory chain [1, 88]. No other cases have been reported in the literature.

Friedreich ataxia [OMIM 229300]

Friedreich ataxia (FRDA) is an autosomal-recessively inherited disease leading to degeneration of spinocerebellar tracts, dorsal columns, and pyramidal tracts [1, 89] as well as cardiomyopathy causing premature death at an average age of 37 years [90]. In most cases Friedreich ataxia is caused by an intronic GAA triplet repeat expansion [91] impairing expression levels of a fully functional protein termed frataxin [92] by formation of sticky DNA and triple helices [93, 94, 95, 96, 97]. Frataxin in its mature state is an 18-kDa protein encoded in the nucleus and located at the mitochondrial matrix [98, 99]. It has been previously demonstrated that this protein directs iron-sulfur-cluster assembly [100, 101, 102] thereby affecting oxidative energy flux [103]. A conflicting hypothesis, tentatively supported by some [104] but not all [105] evidence from protein structure, suggests that frataxin functions as a multimeric iron storage protein [106, 107, 108, 109, 110, 111]. A wide body of evidence suggests a role for frataxin in promoting cellular defense against reactive oxygen species; clinical data demonstrate increased oxidative stress in patients with Friedreich ataxia [112, 113]. Findings from animal models suggest that, while the non-conditional knock-out is embryonically lethal [114], the tissue-specific targeted disruption of the *frataxin* gene in heart or neuronal tissues causes depletion of iron-sulfur-clusters, presumably accompanied by reactive oxygen species formation [115]. In vitro findings indicate that frataxin-dependent accumulation of unspecified reactive oxygen species [116] is dependent on the concurrent reduction of superoxide dismutase acitivity in frataxin-deficient states [117] and elevation in glutathione peroxidase activity in frataxin-overexpressing states [118]. These effects are probably affiliated with a secondary deregulation of intracellular iron metabolism in frataxin-deficient cells inducing the Fenton reaction. Accordingly, it seems that persons suffering from Friedreich ataxia develop malignant disorders atypical for their young age [119, 120, 121].

Despite their severely reduced life expectancy a subset (up to 30%) of Friedreich ataxia patients develops diabetes mellitus of unknown origin [122, 123, 124]. Non-diabetic Friedreich ataxia patients exhibit normal or even exceeding glucose-stimulated insulin secretion [124], but show some degree of insulin resistance [125]; this has also been observed in heterozygous carriers of the GAA repeat [126]. Once present, diabetes mellitus in Friedreich

ataxia is caused by a progressive insulin deficiency sometimes leading to keto(acido)sis [122, 123]. While studies on a possible association between the common type 2 diabetes and the *frataxin* GAA triplet repeat expansions in humans are to date inconclusive [127, 128, 129, 130, 131, 132], linkage of type 2 diabetes with the locus harboring the human *frataxin* gene at 9q13 was found in at least four different populations worldwide [133, 134, 135, 136], suggesting a role in the pathogenesis of common type 2 diabetes. Disruption of the *frataxin* gene selectively in pancreatic β-cells causes a progressive diabetes mellitus paralleled by impaired insulin secretion due to decreased β-cell mass and accumulation of reactive oxygen species [137].

Herrmann syndrome [OMIM 172500]

Herrmann syndrome has been described in a single pedigree with 14 affected individuals of five generations, exhibiting diabetes mellitus, nephropathy, epilepsy, ataxia, and deafness [1, 138]. While the transmission appears to be autosomal-dominant, no male-to-male transmission of the phenotype was observed in the pedigree. No other cases have been reported in the literature.

Huntington disease (HD) [OMIM 143100]

This autosomal-dominant disease is characterized by progressive, selective neuronal cell death associated with uncontrollable, choreatic movements [139], rigidity, seizures, and progressive dementia [1]. A typical atrophy of the caudate nucleus is observed radiographically; this affection is preceded by impaired glucose metabolism in this nucleus, which can be observed in asymptomatic individuals as well [140]. The disease has been attributed to a CAG repeat in the *huntingtin* gene [141]. Age at onset and severity of the disease are determined by both the repeat length of the expanded allele and the repeat length of the "normal" allele [142]. Regarding the function of huntingtin protein, a major hypothesis suggests that toxicity arises from the cleavage and accumulation of amino-terminal fragments containing an expanded polyglutamine region, which might be due to an increased resistance against proteolytic cleavage of mutant huntingtin [143]. Subsequently, impaired mitochondrial function and increased oxidative stress is commonly observed in both humans and mice [47, 144, 145, 146]. Huntington patients develop diabetes mellitus about seven times more often than matched healthy control individuals [147, 148]. The reasons for this concomitant disorder is unclear, although inappropriate insulin secretion is a potential reason [149]. Huntington patients experience dramatic weight loss (also called wasting or cachexia), which may be due to increased 24-h sedentary energy expenditure [150].

Several mouse models for Huntington disease have been generated; the best characterized line is termed R6/2 and was generated by transgenic expression of a mutant huntingtin [151]. When these mice are evaluated with respect to altered glucose metabolism, most authors observe pronounced diabetes [152, 153, 154, 155, 155]. In one study, however, no alterations in basal serum glucose levels were observed [156]; in another, a change was observed in only one-quarter of the animal population investigated [157]. The reasons for these inconsistencies are unclear. Interestingly, DNA vaccination of R6/2 mice is reported to ameliorate the diabetic phenotype originally observed [155].

Kearns-Sayre syndrome [OMIM 530000]

Kearns-Sayre syndrome (KSS) [158] is a mitochondrial disease frequently associated with endocrine disturbances, including growth hormone deficiency, hypogonadism, hypoparathyroidism, and diabetes mellitus [1], the latter possibly caused by a specific loss of pancreatic β-cells [159]. Insulin resistance is apparently lacking [160]. Ophthalmoplegia, pigmentary retinal degeneration, and cardiomyopathy are the key features of the syndrome. Characteristic alterations in skeletal muscle, so-called ragged red fibers, are another typical feature [161]. Genetically the disease is caused by various deletions in the mitochondrial genome affecting subunits of the respiratory complexes I, IV, and V as well as several mitochondrial tRNAs. Interestingly, identical deletions appear to cause different phenotypes, ranging from Kearns-Sayre syndrome to Pearson Marrow pancreas syndrome (OMIM 557000) [1], chronic progressive external ophthalmoplegia (e.g., OMIM 590100, OMIM 601779, OMIM 590050 (see below), OMIM 590055, and others] [1] and myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS; OMIM 54000, OMIM 590050 (see below) [1]. Until very recently [162] transgenic animals for mitochondrial mutations could not be generated for technical reasons; hence no corresponding animal model has been generated either for Kearns-Sayre syndrome or for any other mitochondrially encoded mutation, including syndromes such as MELAS, myoclonic epilepsy associated with ragged-red fibers (MERRF), and maternally inherited diabetes and deafness (MIDD) caused by mutations of *MTTE* ("mitochondrial transfer RNA for glutamic acid"), *MTTL1* ("mitochondrial transfer RNA for leucine 1"), *MTTI* ("mitochondrial transfer RNA for isoleucine"), *MTTK* ("mitochondrial transfer RNA for lysine"), and *MTTS2* ("mitochondrial transfer RNA for serine 2"; see below), has.

Klinefelter syndrome

Klinefelter syndrome is characterized by a primary endocrine disturbance associated with impaired mental capacity, hypogonadism, and hypogenitalism [163]. An increased prevalence of obesity is observed. Whether Klinefelter syndrome is a bona fide neurodegenerative

syndrome remains questionable. The disorder occurs in 1:600 live male births and is caused by duplication of the X-chromosome in a male karyotype, leading to a total of 47 instead of 46 chromosomes. Mitochondrial aberrations were observed on a morphological level [164] and may have a confounding role [165]. Diabetes mellitus is frequently observed in Klinefelter syndrome, although its cause remains elusive [38, 166, 167, 168].

Mitochondrial transfer RNA for glutamic acid [OMIM 590025]

The *MTTE* gene encodes a mitochondrial tRNA for glutamic acid. Mutations in the region encoding this tRNA (mitochondrial basepairs 14,674–14,742) cause myopathy, cerebellar ataxia, peripheral neuropathy, and diabetes mellitus [1, 169, 170].

Mitochondrial transfer RNA for leucine 1 [OMIM 590050]

The *MTTL1* gene encodes a mitochondrial tRNA for leucine with codon use UUA or UUG. Mutations in the region encoding this tRNA (mitochondrial basepairs 3,230–3,304) cause several syndromes [1], which are in part associated with diabetes mellitus, including MELAS and MIDD.

Clinical features of MELAS syndrome are episodic vomiting, seizures, and recurrent cerebral insults resembling strokes and causing hemiparesis, hemianopsia, or cortical blindness. While mutated *MTTL1* has been associated with MELAS syndrome [171, 172], other mitochondrial mutations and deletions may also contribute to the clinical phenotype of MELAS (OMIM 540000) [1].

MIDD [OMIM 520000] is characterized by occurrence of neurosensory deafness followed by diabetes mellitus [173]. The latter usually occurs in the second decade of life. While the original description of MIDD [174] focuses a 10.4 kb deletion in the mitochondrial genome, concurrent studies have associated an identical phenotype with an A3243G point mutation [175, 176, 177] affecting tRNA (Leu), which is also frequently associated with MELAS. The reasons for these apparent inconsistencies are unclear but may be due to heteroplasmy of mitochondrial mutations. There is some evidence for maternal inheritance in certain cases of type 2 diabetes mellitus [178], suggesting that one or more genetic risk factors are located in the mitochondrial genome. It should be noted that hearing impairment may be restricted to certain acoustic frequencies; hence the absence of deafness in a classical sense does not necessarily exclude diagnosis of the particular disorder. Based on several association studies it has been estimated that 1.5% of common diabetes mellitus cases may be caused by the mitochondrial A3243G mutation [179]. The primary defect leading to diabetes mellitus seems to be impaired insulin secretion [180, 181] while insulin resistance is also observed [181]. This is of interest given very recent evidence suggesting an association between altered mitochondrial metabolism and common type 2 diabetes mellitus [18].

Mitochondrial transfer RNA for isoleucine [OMIM 590045]

The *MTTI* gene encodes a mitochondrial tRNA for isoleucine. Mutations in the region encoding this tRNA (mitochondrial basepairs 4,263–4,331) typically cause cardiomyopathy [1, 182, 183, 184]. A mutation G4284A has been associated with diabetes mellitus in a single pedigree [185].

Mitochondrial transfer RNA for lysine [OMIM 590060]

The *MTTK* gene encodes a mitochondrial tRNA for lysine. Mutations in the region encoding this tRNA (mitochondrial basepairs 8,295–8,364) typically cause MERRF [1, 186, 187]. The most frequent mutation, A8344G, probably accounts for probably more than 80% of all MERRF cases [188]. A different mutation, A8296G, was found to cause a phenotype similar to MIDD, while (by definition) not affecting *MTTL1* [189, 190]. In Japan this mutation accounts for approx. 1% of all type 2 diabetes cases [190].

Mitochondrial transfer RNA for serine 2 [OMIM 590085]

The *MTTS2* gene encodes a mitochondrial tRNA for serine. Mutations in the region encoding this tRNA (mitochondrial basepairs 12,207–12,265) are rare. The exchange C12258A causes cerebellar ataxia, cataracts, and diabetes mellitus, and, as with other mitochondrial diseases, this disorder is maternally transmitted [1, 191].

Myotonic dystrophy 1 [OMIM 590025]

The autosomal-dominantly inherited disease myotonic dystrophy 1 (MD1) [192, 193] is characterized by myotonia, distal muscular dystrophy, cataracts, hypogonadism, and frontal hair loss, all usually occurring in middle life [1]. The disease is caused by a CTG triplet repeat expansion [194, 195] in the *myotonic dystrophy protein kinase* gene. The repeat is located in the 3′ untranslated region and causes diminished transcription as well as decreased transcript stability [196], and expression of the corresponding protein is diminished in affected individuals [197]. As in other trinucleotide repeat related disease, the length of expansion may determine the age at onset and severity of the disease [198]. The disease apparently affects not only (neuro)muscular junctions [197] and muscle-specific chloride channels [199] but also leads to

progressive motor and sensory neurodegeneration [200, 201] as well as cortical atrophy [202]. Magnetic resonance imaging findings suggest an increased ATP turnover rate as well as a decreased availability of ATP [203, 204], the latter resembling features of mitochondrial disorders. Diabetes mellitus is not typical for myotonic dystrophy but occurs more frequently among individuals with this disorder than in the general population, and it is characterized by hypersecretion of insulin, suggesting possible insulin resistance [205]. Several animal models exist [206, 207]; detailed information on glucose metabolism is so far lacking.

Narcolepsy [OMIM 161400]

Narcolepsy is a syndromic sleep disorder characterized by attacks of disabling daytime drowsiness and low alertness. The normal physiological components of rapid eye movement (REM) sleep, dreaming, and loss of muscle tone are uncoupled and also occur while the subject is awake, resulting in half-sleep dreams and episodes of skeletal muscle paralysis and atonia [1, 208, 209]. The disorder is associated with an increased frequency of type 2 diabetes mellitus [210, 211]. Furthermore narcolepsy patients tend to be more obese than matched control individuals [212] which has been attributed to decreased serum levels of the adipocytokine leptin [213]. In contrast to the obese phenotype, narcolepsy has been linked to a specific degenerative loss of hypocretin-positive neurons in humans [214]. Hypocretins are orexigenic peptides, i.e., induce food uptake [215]. Narcolepsy has been associated with impaired expression of hypocretins and impaired hypocretin signaling [216, 217, 218]. The mechanism by which decreased expression of orexigenic signals causes both obesity and type 2 diabetes remains to be determined [219]. The disease has been linked to HLA-DR2–DQB1-0602 by several groups [1], which, conversely, is associated with protection from autoimmune type 1 diabetes mellitus [220]. Both dog and mouse models exist [221, 222], which have not been studied in depth regarding alterations in glucose metabolism [219].

Norrie disease [OMIM 310600]

The X-linked disorder Norrie disease is characterized by pseudotumor of the retina, retinal hyperplasia, hyperplasia of retinal, ciliary, and iris pigment epithelium, hypoplasia and necrosis of the inner layer of the retina, cataract, and frequently also by hearing loss and/or mental retardation [1, 223, 224, 225]. Whether diabetes mellitus is associated with the disease remains questionable, although an increased prevalence among individuals with Norrie disease has been reported [226]. Identification of the underlying genetic aberration [227, 228, 229] led to an animal model employing targeted gene disruption [230]; information on glucose metabolism, however, is lacking.

Parkinson disease [OMIM 168600]

This disorder is the second most common neurodegenerative disease. Clinical symptoms typically include resting tremor, bradykinesia, rigidity of muscles, postural instability, and dementia [1, 231]. The syndrome usually begins in the fifth decade of life or later. Parkinson disease (PD) is characterized histologically by a loss of dopaminergic neurons in the substantia nigra and the detection of so-called Lewy bodies, intracellular inclusions, in surviving neurons in the brain, but especially the substantia nigra [232, 233, 234]. While an increased frequency of the disease in certain families has long since suggested that PD has a genetic component [235], inheritance patterns have been inconclusive. This is presumably due to incomplete penetrance of causative mutations and/or the fact that defects in numerous genes can cause the same phenotype [232, 233, 234, 236].

Results from recent studies indicate that various genes, including *α-synuclein* [237], *parkin* [238], *tau* [239], *MAOB* [240], *interleukin 1β* [241], and *N-acetyltransferase 2* [242], may play causative roles. Recent evidence suggests that PD is a filamentous disorder (as in Alzheimer and Huntington disease) where neuronal deposits of microfibrils made of aberrent α-synuclein and tau proteins synergize [243]. Mitochondrial dysfunction and oxidative stress may play a role in a considerable percentage of PD cases [244, 245, 246].

Impaired glucose tolerance is frequently observed in PD and affects up to 80% of patients [247]. While little is known about the pathogenesis of prediabetes in Parkinson disease, therapy with levodopa seems to exacerbate glucose intolerance [247]. It has been proposed that disturbances in glucose metabolism detrimentally affect the Parkinson phenotype and hence should be treated rigorously [247]. A recent mouse model overexpressing mutant human α-synuclein developed a Parkinson-like phenotype but was not evaluated for disturbances of glucose metabolism [248].

Prader-Willi syndrome [OMIM 176270]

The apparently autosomal-dominantly inherited Prader-Willi syndrome (PWS) is considered to be a methylation imprinting disorder of the long arm of chromosome 15, affecting a locus harboring the *SNRPN* gene [1]. It is characterized by extreme obesity, muscular hypotonia, mental retardation, hypogonadotropic hypogonadism, cardiac insufficiency, short stature, and small extremities [249, 250]. Typically from the age of 12 months patients develop insatiable appetite, which causes remarkable obesity, with a body mass index typically beyond 35. Hunger might be promoted by inappropriate regulation of serum levels of ghrelin [251], an orexigenic growth hormone secretagogue [252]. Diabetes mellitus occurs frequently in Prader-Willi syndrome and affects up to 25% of individuals [253, 254]. Type 2 diabetes mellitus is occasionally observed concurrently even in prepubertal chil-

dren [255, 256]. Prader-Willi patients exhibit insulin resistance but to a lesser degree than typical for their degree of obesity; instead, an impaired insulin secretion is observed, as well as an increase in hepatic insulin extraction [257]. Targeted disruption of the murine homolog of the *SNRPN* gene alone did not produce a phenotype; however, removal of a larger fragment, including a so-called imprinting center, leads to abolished expression of several genes, and the resulting mice have several symptoms typical of Prader-Willi syndrome in humans [258]. Information on glucose metabolism is so far lacking.

Thiamine responsive megaloblastic anemia syndrome [OMIM 249270]

Thiamine-responsive megaloblastic anemia syndrome (TRMA) is characterized by diabetes mellitus, megaloblastic anemia, and sensorineural deafness [1, 259, 260]. Mutations in the thiamine transporter gene *SLC19A2* cause the syndrome [261]. Symptoms [262] are similar to those of thiamine (vitamin B_1) deficiency, the so-called beriberi disease; diabetes mellitus is a typical component of both the inherited genetic disorder and the nutritional deficiency. Treatment with thiamine reverses the phenotypic components, or at least brings symptoms to a halt. Mutations in the thiamine transporter gene *SLC19A2* furthermore cause a decreased activity of complex I of the respiratory chain [263]. A recent animal model resembles the phenotype in humans [264] and suggests that diabetes mellitus due to inherited or acquired thiamine deficiency is due to a decreased insulin secretion, while sensitivity to insulin may be even increased [264]. While a follow-up mouse model obtained by a similar targeting technique was not evaluated for disturbances in glucose metabolism, in contrast to the previous study, no megaloblasts were observed [265].

Spinocerebellar ataxia 3 (SCA3)/Machado-Joseph disease [OMIM 109150]

This autosomal-dominant disorder is characterized by ataxia, spasticity, and aberrant ocular movements [1, 266]. The age at onset is usually middle life, and in the original description diabetes mellitus was associated with the disease [266]. The disorder is caused by an expansion of a CAG repeat [267, 268] in the ataxin-3 gene, which apparently is translated into polyglutamine tracts causing aberrant precipitations of the protein [269]. This was demonstrated in mice that transgenically overexpress the aberrant protein [269].

Spinocerebellar ataxia 6 [OMIM 183086]

The autosomal-dominant disorder spinocerebellar ataxia 6 (SCA6) is characterized by progressive cerebellar ataxia and atrophy, dysarthria, nystagmus, and proprioceptive sensory loss [1, 270, 271]. The underlying cause is a CAG expansion in the *CACNA1A* gene encoding the α1A-Ca^{2+} channel [270]. Increased prevalence of diabetes mellitus has been reported only in a single large Japanese pedigree [271].

Turner syndrome

Turner syndrome affects females and is characterized by short stature, absence of secondary sexual characteristics and failure of sexual maturation, impaired intelligence, cardiac abnormalities, visual impairment including nystagmus and strabismus, psychiatric illnesses [272, 273, 274, 275], and obesity [1, 276, 277]. It is caused by loss of one sex (i.e., X or Y) chromosome, resulting in a total of only 45 chromosomes instead of 46. Whether Turner syndrome is a bona fide neurodegenerative syndrome remains questionable. Turner syndrome has been associated with presumably insulin-deficient [277] disturbances in glucose metabolism and diabetes mellitus [38, 168, 277, 278, 279]; insulin resistance has not been convincingly excluded.

Werner syndrome [OMIM 277700]

The autosomal-recessive disorder Werner syndrome (WRN) [2] is characterized by scleroderma-resembling skin changes, cataract, subcutaneous calcification, premature atherosclerosis, diabetes mellitus, and prematurely aged facial features, which is already observed in children [1]. The syndrome is of particular interest since it may resemble a pronounced acceleration of normal aging. As noted above, Werner syndrome is the only disorder that unifies symptoms of a specific disorder and signs of general aging [280, 281]. A neurodegenerative phenotype, both peripherally and centrally, is present [282, 283, 284, 285]; furthermore, myocardial insufficiency [286, 287] and increased prevalence of malignant diseases have been observed [4]. Diabetes mellitus is typical for the disorder [3, 288] and is caused primarily by insulin resistance [289] that responds to insulin sensitizers [290]. Using a positional cloning approach, mutations in a gene subsequently termed *WRN* were found to be responsible for the disease [291]. WRN protein belongs to a family of DNA helicases that have been implicated in unwinding of DNA during helix replication, DNA repair, and accuracy of chromosomal segregation. An autosomal-dominant, and hence atypical, Werner syndrome has been attributed to heterozygous carriage of mutations in the *LMNA* gene encoding lamin protein [292]; aberrant lamin expression has been shown to be associated with several muscular dystrophies, cardiomyopathies, another syndrome of premature aging termed Hutchinson-Gilford progeria syndrome (OMIM 176670) [1] and disturbances of lipid deposition, so-called lipoatrophies, which are typically connected with extreme insulin resistance [293, 294, 295]. Additionally, a single nucleotide polymorphism

C1908T in the *LMNA* gene was associated with obesity in a Canadian Inuit population [296]. Lastly, aberrant lamin expression may affect serum levels of the anorexic hormone leptin [297], hence possibly influencing body weight.

A knock-out mouse lacking the helicase domain of WRN exhibited no signs of decreased life expectancy. A double-knock-out, additionally affecting the p53 tumor suppressor protein, led to decreased life expectancy and increased tumor frequency [298]; information on glucose metabolism in these mice is lacking.

Wolfram syndrome/diabetes insipidus and diabetes mellitus with optic atrophy and deafness [OMIM 222300]

Wolfram syndrome/diabetes insipidus and diabetes mellitus with optic atrophy and deafness (DIDMOAD) is inherited in an autosomal-recessive manner. Diagnosis requires the presence of an insulin-dependent diabetes mellitus, usually occurring during the first decade of life and a bilateral progressive optic atrophy [299]. Further symptoms include hearing impairment, central diabetes insipidus, ataxia, dementia, nystagmus, mental retardation, seizures, cortical atrophy [1], and psychiatric illnesses [300]. Heterozygous carriers (frequency 1:100) have an increased risk for psychiatric disorders [301, 302]. Wolfram syndrome was thought to be a primarily mitochondrial disease [303, 304], a hypothesis which was rejected after isolation of the corresponding gene. Positional cloning approaches led to the isolation of *WSF1* encoding wolframin protein [305, 306]. Wolframin may have a role in regulating intracellular calcium levels; hence impaired wolframin function might induce inappropriate apoptotic events, leading to neurodegeneration and loss of pancreatic β-cells [307].

Woodhouse-Sakati syndrome [OMIM 241080]

Woodhouse-Sakati syndrome is a rare disease characterized by hypogonadism, diabetes mellitus, absence of facial hair with thinning of capital hair, mental retardation, mild sensorineural deafness, and electrocardiographic abnormalities [1, 308, 309]. No information on modes of inheritance or affected genes is available.

Concluding remarks

In summary, most of the above mentioned neurodegenerative disorders are typically or frequently associated with diabetes mellitus or its antecessors, insulin resistance and/or impaired glucose tolerance (Table 1). Exceptionally, for Norrie disease and both spinocerebellar ataxias 3 and 6 evidence for an association with diabetes mellitus is somewhat sparse. Likewise, the associations for Feigenbaum syndrome, Herrmann syndrome, and cerebellar ataxia, deafness and narcolepsy are based on a single pedigree, and no further families have been reported. Lastly, associations with *MTTI* and *MTTK* mutations are restricted to a single polymorphism.

Diabetes mellitus is caused either by insulin resistance or decreased insulin secretion, or both (see "Introduction"). Eight of the described syndromes are clearly accompanied by increased insulin resistance, one of the main hallmarks of diabetes development (Fig. 1, left center column). Four of these disorders are associated with obesity, which is known to cause insulin resistance [6, 8]. Eight of the described syndromes are linked to decreased insulin secretion (Fig. 1, right center column), while two of these syndromes exhibit an increased secretion (Alzheimer disease, myotonic dystrophy 1), possibly associated with insulin resistance (Fig. 1). Friedreich ataxia shows a primarily increased secretion during the nondiabetic phase, which then turns into impaired secretion accompanied by overt diabetes mellitus. Five of the disorders are caused by unstable triplet repeat expansions (Fig. 1), which either cause decreased expression of a fully functional protein (Friedreich ataxia, myotonic dystrophy 1) or result in translation of an expanded polyglutamine tract (remaining disorders). Figure 1 further depicts those disorders, which—directly or indirectly—affect mitochondrial energy transfer, i.e., OXPHOS. Lastly, disorders known to cause aberrant protein precipitations via microfibril formation and concurrent mechanisms are presented (Fig. 1), as well as those disorders that lead to an increased frequency of malignant disorders (Fig. 1).

Neurons and pancreatic β-cells have a high metabolic activity and a low regeneration rate. Presumably both properties make these tissues extremely sensitive to genetic and environmental deviances, causing clinically evident damage, while other tissues remain functional. Interestingly, numerous neurodegenerative diseases as well as diabetes mellitus cause cardiomyopathy, which possibly supports this view. While these common elements may explain only a minority of neurodegeneration-associated diabetes mellitus, the reasons for deregulation of body weight, lipid metabolism, and insulin resistance are largely unexplained. As seen in Fig. 1, approximately 50% of the neurodegenerative disorders associated with diabetes mellitus show some involvement of mitochondrial dysfunction. These may possibly subclassified into disorders directly affecting mitochondria based on an evident genetic and/or biochemical link, including Friedreich ataxia, Keans-Sayre syndrome, mutations of mitochondrial transfer RNAs, and thiamine-responsive megaloblastic anemia syndrome, and into the ten disorders in which the affection of mitochondrial metabolism is unresolved. Insulin secretion is directly dependent on the OXPHOS mediated opening of the K_{ATP} channel in the pancreatic β-cell [7, 12], and hence related to both glycolytic flux [310] and mitochondrial capacity [311]. Independently of nutrient dependent stimulation of insulin secretion, the overall number of pancreatic β-cell (reflecting the balance of apoptosis and regeneration of such

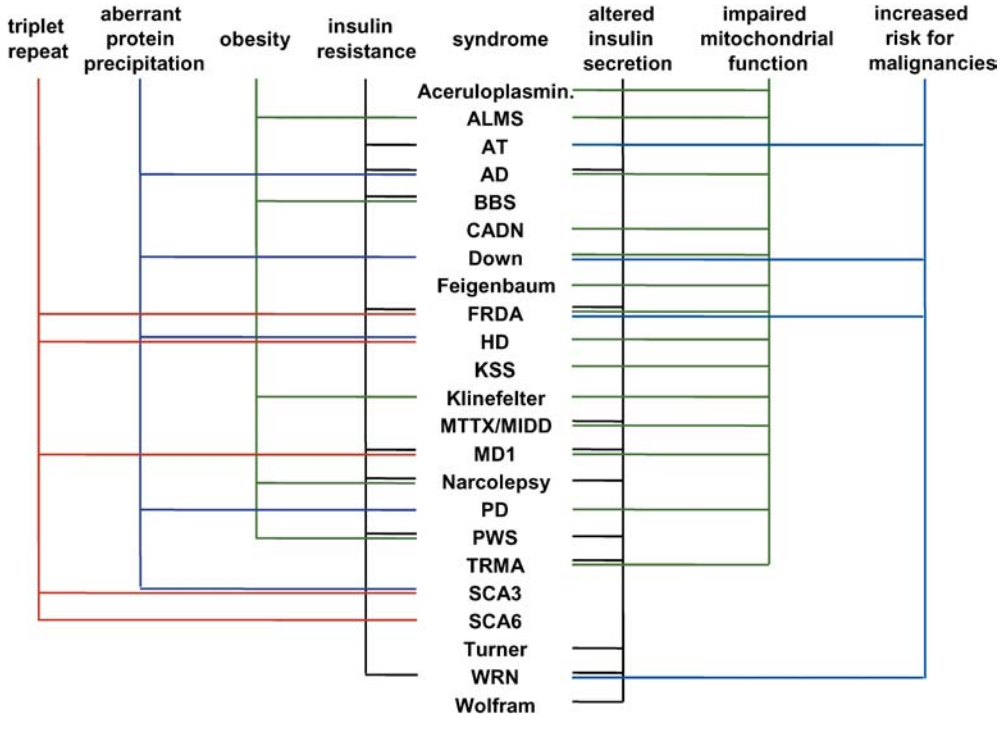

Fig. 1 Selected focus-related characteristics of some of the neurodegenerative syndromes discussed in detail in the text, specifically in regards to association with altered insulin secretion, insulin resistance, impaired mitochondrial function, obesity, aberrant protein precipitation, increased risk for malignant disorders, and the presence of triplet repeat expansions. Please note that all syndromes that have not been reported to be associated with at least one of those seven characteristics are listed in Table 1 but are omitted here

cells) is a crucial factor in the pathogenesis of type 2 diabetes [10, 11] and may be affected by mitochondrially active proteins [137, 311]. Insulin resistance also appears to be causally related to impaired OXPHOS in skeletal muscle (and possibly other compartments including adipose tissue and hepatocytes) [14, 15, 16, 17, 18]. Taken together, these data suggest that an essential mechanism for the association of neurodegeneration and diabetes mellitus is located in the mitochondria, affecting both apoptosis and nutrient metabolism and phosphorylation. Another common factor may be found in aberrant protein precipitation, which is observed in only five of the neurodegenerative disorders. On the other hand, these few disorders account for the vast majority of affected individuals (since they include Alzheimer disease, Down syndrome, Huntington disease, and Parkinson disease). Interestingly, four of these disorders, i.e., all but spinocerebellar ataxia 3, are accompanied by mitochondrial dysfunction as well.

In conclusion, numerous inherited disease cause both neurodegeneration and diabetes mellitus. While groups of phenotypical clusters can clearly be found, a unifying mechanism remains elusive but might be located—if existent at all—in unwanted alterations in mitochondrial energy metabolism and function.

Postscriptum: diabetic neuropathy

While this review focuses on diabetes mellitus as a consequence of primarily neurodegenerative disease, diabetic neuropathy is a result of diabetes mellitus, being the most frequent complication of the disease and probably the most common disease of the nervous system. Its severity is related to duration of diabetes and quality of blood glucose control. It increases progressively without ever reaching a plateau. Neuropathy is classified as either diffuse (including the most frequent symmetric sensory neuropathy, autonomic neuropathy, and symmetric motor neuropathy) or focal (affecting cranial or facial nerves, as well as singular nerves of upper or lower extremities). Neuropathy hence may lead to paralysis, paresthesia, unperceived lesions (especially at the lower extremities) followed by chronic inflammation and amputation, delayed gastric emptying, constipation, incontinence, impotence, cardiac arrhythmia, tachycardia, silent (i.e., unperceived) cardiac infarction, among other symptoms. The exact pathogenesis of diabetic neuropathy remains obscure; in general, a combination of cumulative damage to neurons and adjacent Schwann cells as well as hemorrheological abnormalities, i.e., decreased blood flow in capillaries supplying neurons are thought to contribute to diabetic neuropathy. In this regard, activation of the polyol pathway, accumulation by advanced glycation end products, damage via reactive oxygen and reactive nitrogen species, deficiency of γ-linoleic acid, impaired neuroregeneration via lack of nerve growth factor, and others have been suggested [312, 313, 314].

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