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A recessive ataxia diagnosis algorithm for the next-generation sequencing era

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50

51 Abstract

52 **Objective:** Differential diagnosis of autosomal recessive cerebellar ataxias can be
53 challenging. A ranking algorithm that predicts the molecular diagnosis based on the
54 clinical phenotype of a patient has been developed to guide genetic testing and to
55 align genetic findings with the clinical context.

56 **Methods:** An algorithm that follows clinical practice, including patient history,
57 clinical, MRI, electromyography and biomarker features, was developed following a
58 review of the literature on 67 autosomal recessive cerebellar ataxias and personal
59 clinical experience. Frequency and specificity of each feature were defined for each
60 autosomal recessive cerebellar ataxia, and corresponding prediction scores assigned.
61 Clinical and paraclinical features of patients are entered into the algorithm, and a
62 patient's total score for each autosomal recessive cerebellar ataxia is calculated,
63 producing a ranking of possible diagnoses. Sensitivity and specificity of the algorithm
64 were assessed by blinded analysis of a multinational cohort of 834 patients with
65 molecularly confirmed autosomal recessive cerebellar ataxia. The performance of the
66 algorithm was assessed versus a blinded panel of autosomal recessive cerebellar
67 ataxia experts.

68 **Results:** The correct diagnosis was ranked within the top 3 highest-scoring diagnoses
69 at a sensitivity or specificity of >90% for 84% and 91% of the evaluated genes,
70 respectively. Mean sensitivity and specificity of the top 3 highest-scoring diagnoses
71 were 92% and 95%, respectively. The algorithm outperformed the panel of ataxia
72 experts ($P=0.001$).

73 **Interpretation:** Our algorithm is highly sensitive and specific, accurately predicting
74 the underlying molecular diagnoses of autosomal recessive cerebellar ataxias, thereby
75 guiding targeted sequencing or facilitating interpretation of next-generation
76 sequencing data.

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78 **Keywords:** Ataxia; Molecular genetics; Cerebellar function; Genetics: movement
79 disorders; Clinical practice

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82

83 **Introduction**

84 Clinical heterogeneity and rarity of some neurological disorders may challenge the
85 ability of clinicians to make timely diagnoses. This is true for autosomal recessive
86 cerebellar ataxia (ARCA), a complex group of rare disorders ¹⁻⁴. The revolution in
87 molecular genetics, especially next-generation sequencing (NGS) ⁵, has led to the
88 identification of new ARCA-causing genes or novel phenotypes of known
89 ARCA-causing genes, improving our understanding of these disorders and our ability
90 to diagnose them ^{6, 7}. However, NGS generates a huge amount of data, including
91 variants of unknown significance (VUS) that may be difficult and time-consuming to
92 correctly interpret and establish relationships between potential pathogenic variants
93 and observed phenotypes ⁸.

94 There is therefore an unmet need for a tool to assist physicians and geneticists in
95 providing a comprehensive and balanced differential diagnosis (DD) of ARCAs. A
96 DD tool that predicts the gene responsible for a phenotype by converting clinical and
97 paraclinical data into a shortlist of likely molecular diagnoses could significantly
98 increase the speed and yield of diagnosis for ARCAs, subsequently improving patient
99 care, particularly in cases where treatments are available.

100 Our study aimed to create and validate a tool for the DD of patients with suspected
101 ARCA.

102 **Materials and methods**

103 **The Recessive Ataxias ranking differential Diagnosis ALgorithm**
104 **(RADIAL)**

105 A diagnostic algorithm for ARCA based on literature and expert opinion has been
106 produced to guide neurologists who may encounter patients with ataxia in clinical
107 practice (**Fig. 1**). Recessive disorders (herein referred to as entities, each defined by
108 mutations in specific gene(s)) with ataxia as a common, but not necessarily an initial
109 or prominent feature, were identified from the literature according to previously
110 published recommendations ^{1,2}.

Publications were identified by PubMed search for English language articles between January 1995–January 2016, using the following terms: “recessive cerebellar ataxia”, “recessively inherited cerebellar ataxia”, or “inherited cerebellar ataxia”, and screened for reports of molecularly confirmed cases of recessively inherited disorders with cerebellar ataxia in order to include the majority of the most common ARCA; 281 manuscripts were used to describe the entities included in the algorithm (Supplementary Table 2). To describe entities, 124 individual clinical and paraclinical findings including routine biomarkers (so-called features), were identified and refined by expert opinion.

The relationship between each feature and each entity was defined by frequency and/or specificity according to the literature and clinical experience of CT and MA, as follows:

- High frequency (H) – feature occurs in $\geq 50\%$ of patients with the entity
- Low frequency (L) – feature occurs in $< 50\%$ of patients with the entity. Where not clearly definable, low frequency is assumed
- Specific (S) – feature presents in $< 10\%$ of entities
- Not present (0) – feature not considered to be associated with the entity
- Not known (NK) – feature not reported with the entity, but with insufficient evidence to exclude association

These classifications were combined as necessary, e.g. HS, high frequency and specific; LS, low frequency and specific.

For each entity, scores were assigned based on an assessment of the frequency and specificity of features, with more frequent and specific features scoring highest, and weighted based on the perceived importance for DD. Based on the opinion of MA, NK, 0, L, H, LS, and HS were arbitrarily scored 0, –1, 1, 3, 7 and 9, points respectively, for clinical features, neuroimaging and electromyography, whereas scores were doubled for age of onset, severity of disease progression and biomarkers (Table 1). For example, if a patient with suspected ARCA has a *cataract*, they would score +3 points for cerebrotendinous xanthomatosis, in which *cataract* is high

frequency (H), but would score -1 points for Friedreich's ataxia, in which *cataract* is not reported (0). A second patient who does not present with *cataract* would score 0 points for both cerebrotendinous xanthomatosis and Friedreich's ataxia.

The outcome of this process was RADIAL, comprising a knowledgebase that defines the association of each clinical and paraclinical feature with each entity, with a corresponding score assigned to each feature-entity association (**Supplementary File 1**).

ARCA patient clinical features data collection

Diagnostic performance of RADIAL was assessed by applying it blindly to a population of patients with molecularly confirmed ARCA, for whom a description of clinical and paraclinical features at the time of molecular diagnosis was available.

The clinical and paraclinical features recorded at the time of molecular diagnosis of a worldwide patient cohort were collected by retrospective chart review between February–May 2016. The persons responsible for data collection from collaborating centres were blinded to the scoring and weighting of features within the algorithm.

All patient data were blinded by the contributor so that names, addresses or other identifying information were not available to any other party involved in the analysis or review of the data. All investigators adhered to local privacy laws and regulations to ensure patient confidentiality. Patients gave written consent and ethical approval for the study was provided by the local ethics committee of the Strasbourg University Hospital, France.

Statistical analysis

Performance assessment of RADIAL

Features of each patient were assessed against the knowledgebase according to the aforementioned calculation method. For each patient, the sum of scores for each feature was calculated for each entity. The total score for each entity defined its position on a ranked list of most likely (highest score) to least likely (lowest score) molecular diagnoses. Algorithm performance was a measurement of sensitivity, and specificity. Correct patient classification was defined as a ranking of the correct

169 diagnosis within the first, third, and fifth highest scores. The primary outcome of the
170 performance assessment was the ability of RADIAL to correctly predict entities
171 within the Top 3 highest scores. Other outcomes were: correctly predicting entities
172 within the Top 1 and Top 5 highest scores; average sensitivity and specificity for all
173 patients; the ability of RADIAL to correctly identify an entity compared to that of a
174 panel of ARCA experts and correlation between performance and the total number
175 and/or number of specific clinical features per entity.

176 *Blind evaluation against an ARCA expert panel*

177 The ability of RADIAL to correctly identify an entity within the Top 3 highest scores
178 was compared against a blind evaluation by a panel of five ARCA experts (FM, MP,
179 MS, CT and BW) in a sample of 100 patients for each expert, randomly selected from
180 the patient cohort. The experts were given the same list of features provided by the
181 investigators for the algorithm assessment, and produced a ranked shortlist of the
182 three most likely diagnoses for each patient. The experts were able to consult the
183 literature (e.g. PubMed) and were allowed as much time as required to complete the
184 task. The three most likely diagnoses were compared against the Top 3 diagnoses
185 provided by RADIAL for the same 100 patients. For mutations in *FXN* gene, the
186 diagnosis was considered correct when Friedreich's ataxia, LOFA and v-LOFA was
187 proposed. Statistical differences were assessed by McNemar's exact test.

188 Correlation was tested using Pearson correlation coefficient. All statistical analyses
189 were performed using the statistical package SAS v9.3.

190 **Results**

191 **The RADIAL**

192 The algorithm knowledgebase contains 67 individual ARCAs (**Supplementary**
193 **Table 3**), and was populated using the clinical findings of a total of 2,906 patients
194 from the 281 manuscripts (**Supplementary Table 2**) and clinical experience. The
195 well-described variants LOFA and v-LOFA were considered a single entity distinct
196 from Friedreich's ataxia within the knowledgebase and these analyses^{9, 10}. The
197 RADIAL knowledgebase contains 8,308 individual correlations between 67 entities
198 and 124 features (**Supplementary File 1**).

199 **Details of the patient cohort**

200 Data of 834 patients from 18 different countries and representing 45 distinct entities
201 were collected (**Supplementary Table 4**). Among these 834 patients, 618 (74%) were
202 reported in the literature used to create the knowledgebase, corresponding to 21% of
203 the 2,906 patients used to create the knowledgebase.

204 A broad symptomatology was reported in the patient cohort; a summary of the
205 symptomatology observed in the entire cohort and in the 8 entities with ≥ 30 patients is
206 presented in **Supplementary Table 5**.

207 **Algorithm performance**

208 Of the 45 entities tested, 91% (41/45) were ranked within the Top 3 highest-scoring
209 diagnoses at a specificity of $>90\%$ and 84% (38/45) at a sensitivity of $>90\%$
210 (**Supplementary Table 6**). Among these entities, the correct diagnosis was the
211 highest scoring in 23 entities (51%), and was always found within the Top 16 highest
212 scoring entities. The Top 3 highest scoring diagnoses had an average sensitivity and
213 specificity of 92.2% and 95.4%, respectively (**Supplementary Table 7 and Fig. 2**).
214 The highest scoring diagnosis had an average sensitivity and specificity of 77.1% and
215 99.3% respectively. The Top 5 highest scoring diagnoses had an average sensitivity
216 and specificity of 96.8% and 91.1%. Average sensitivity and specificity plots
217 including all tested disorders are shown in **Fig. 2**. *ADCK3*¹¹, *OPAI*¹², *PNPLA6*¹³,
218 *STUB1*¹⁴ and *SYNE1*¹⁵ and LOFA/vLOFA^{9, 10} were not identified within the Top 3
219 scores with a sensitivity $>90\%$.

220 Assessment of the correlation between the number of specific features associated with
221 each entity and RADIAL performance, and between the total number of features
222 associated with each entity and RADIAL performance, showed that neither the
223 number of total signs ($r=0.052$, $P=0.730$) nor specific signs ($r=-0.033$, $P=0.830$)
224 influence discriminatory ability (**Fig. 3**).

225 ***RADIAL versus expert panel challenge***

226 RADIAL performed well compared with a panel of 5 ARCA experts. In five series of
227 100 patients randomly selected from the patient cohort, RADIAL placed the correct

228 diagnosis in the Top 3 highest scoring entities in 95.2% of patients versus 77.8%
229 identified by the experts ($P<0.001$; McNemar's exact test) and as the highest scoring
230 entity in 80.6% of patients versus 67.6% identified by the experts ($P<0.001$;
231 McNemar's exact test). The experts required an average of 7.2 hours [range: 6–10] to
232 complete their 100 cases.

233 Discussion

234 This study describes RADIAL, an algorithm that aims to improve the DD approach
235 towards ARCA by using patients' features to predict the underlying responsible gene.
236 Sensitivity and specificity of the algorithm in correctly identifying the diagnosis
237 within the Top 3 highest scoring entities was excellent, even outperforming a panel of
238 ARCA experts.

239 In clinical practice, use of RADIAL should be considered in all patients suspected
240 with ARCA. The diagnostic workup outlined in **Fig. 1** takes a stepwise approach to
241 the patient with ataxia^{1, 2, 16, 17}, also indicating how the point of suspecting ARCA is
242 reached.

243 Performance of RADIAL depends on accurate identification of the patient's features,
244 and could be impaired in the absence of sufficiently detailed information. In such
245 cases, the algorithm could be used to guide clinical investigations based on the
246 features of the highest scoring entities from the knowledgebase. The knowledgebase
247 could also clarify the clinical phenotype in a 'genotype-first'^{18, 19} (i.e. genotyping
248 before phenotyping), or 'reverse phenotyping' (i.e. phenotyping following genotyping
249 according to genetic results) method²⁰. However, due to the risk of missing a correct
250 diagnosis, we would not recommend a 'genotype-first' approach, and 'reverse
251 phenotyping' should be considered with caution. Regardless of where in the
252 diagnostic workup it occurs, a sufficiently detailed phenotypic evaluation is always
253 mandatory. RADIAL could also be used to identify one high likelihood entity which
254 can be confirmed by single gene sequencing. Thus, in this 'phenotype-first' approach,
255 the algorithm could also guide molecular analyses. Whether the 'phenotype-first' or
256 'genotype-first' approach is followed, the entity ranking provided by RADIAL
257 supports identification of the gene responsible for the phenotype. Indeed, RADIAL

258 should be considered as an interface between phenotype and genotype, enabling each
259 one to complement the other.

260 Beyond its efficacy to predict the underlying molecular defect based on clinical data,
261 RADIAL will provide guidance on best-practice for the diagnostic work-up of
262 patients with suspected ARCA, including medical history, clinical examination, and
263 paraclinical signs, serving as a reminder to assess many features that may otherwise
264 be overlooked.

265 Given the performance of RADIAL, it could facilitate the interpretation of large
266 volumes of data provided by NGS (panel gene sequencing, whole exome or whole
267 genome sequencing), and pathogenicity of VUS could be more easily determined²¹.
268 For instance, the probability of a VUS being pathogenic when the affected gene is not
269 within the Top 16 entities should be very low, whereas a VUS in a high-ranking gene,
270 especially one within the Top 3, is much more likely, facilitating interpretation of
271 NGS data and guiding searches for a second mutation in the same gene. The good
272 sensitivity of RADIAL is important to avoid a missed diagnosis. Conversely, the good
273 specificity provides confidence in the identified top scoring genes, especially when
274 use of RADIAL follows molecular analyses. In such cases, RADIAL could be helpful
275 to identify which VUS are pathogenic mutations responsible for the phenotype and
276 which VUS are polymorphisms.

277 RADIAL also represents an up-to-date knowledgebase comprising clinical
278 descriptions of 67 individual ARCAs based on the integration of numerous references
279 and expert clinical experience. The 67 entities described in the knowledgebase include
280 the majority of the most common ARCAs, but are not an exhaustive list since there
281 are several other recessively inherited diseases that may include cerebellar ataxia.
282 Some of these diseases have not been included in the current knowledgebase as they
283 lack sufficiently detailed information on their clinical features (e.g. *KIAA0226*)^{22, 23}.
284 Several other entities included in the knowledgebase could be viewed as
285 controversial, as cerebellar ataxia is not the initial or most prominent feature of the
286 disease. However, the entities were included in the knowledgebase because cerebellar
287 ataxia was sufficiently well-described as a clinical feature. Following this initial
288 study, periodic updates of the knowledgebase as the literature grows could add or
289 redefine associations between features and entities further improving performance of

290 RADIAL, particularly for entities that are currently poorly characterised, and allowing
291 addition of new entities. One may hypothesize that increasing the number of entities
292 covered by the algorithm, may increase its superiority to the experts.

293 RADIAL performance is limited by the quality and completeness of data published in
294 the literature. The knowledgebase should be helpful to any physician facing ataxia, or
295 interested in becoming more specialised within this field. The extensive list of
296 features allows a very precise description of each entity (124 features equates to over
297 2.1×10^{37} pairwise combinations) leading to good differentiation between entities,
298 even those with similar but non-identical phenotypes. The performance and flexibility
299 of RADIAL means that an exhaustive assessment of all the signs in patients suspected
300 with ARCA is not required for good performance, and that accurate diagnoses for
301 many patients are possible with few clinical features. A second class of entities,
302 including *ADCK3*¹¹, *OPA1*¹², *PNPLA6*¹³, *STUB1*¹⁴ and *SYNE1*¹⁵, are still poorly
303 recognised by RADIAL. These entities are unlikely to appear near the top of the
304 ranked lists, but should be considered as DD when genetic analyses are inconclusive
305 and the clinical phenotype does not clearly match the highest scoring entities. The
306 poorer performance of RADIAL in recognising these entities might be attributable to
307 an intrinsic difficulty in their identification due to pleiotropic, overlapping clinical
308 phenotypes (e.g. pure cerebellar ataxia in *ADCK3* and *SYNE1*)^{11, 15}, the lack of
309 helpful biomarkers, or limitations in our classification of their specific clinical
310 features due to their novelty (e.g. *PNPLA6* and *STUB1*)^{24, 25}. RADIAL was not able
311 to recognise vLOFA and LOFA as effectively as Friedreich's ataxia. However, given
312 that the former are variants of Friedreich's ataxia, the performance of RADIAL is
313 successful at identifying *FXN* gene mutations. Moreover, Friedreich's ataxia,
314 including LOFA and v-LOFA, is not diagnosed by NGS, therefore validating a VUS
315 on the basis of such diagnoses is not pertinent.

316 The use of real-life clinical data to test the accuracy of RADIAL addresses many of
317 the limitations discussed above, as the excellent diagnostic performance suggests that
318 the knowledgebase provides a good representation of the clinical characteristics of
319 each entity. This is reinforced by the algorithm outperforming an ARCA expert panel
320 in correctly identifying diagnoses in both the Top 1 and Top 3 positions, a method
321 commonly used to validate the performance of diagnostic algorithms, despite recent

evidence showing that the superiority of the physician is maintained over several algorithms²⁶. In the same way, the potential interest of computer based evaluation of photos to diagnose facial dysmorphism has been recently studied²⁷.

The true incidence of ARCAs observed in clinical practice is not reflected in the patient cohort. We were particularly interested in testing the algorithm with a broad sample of entities, especially those that are not well known and/or difficult to diagnose, which is not the case for Friedreich's ataxia, the most frequent ARCA¹. Since the ranking calculation does not take into account the prevalence/incidence of a disease we do not believe that this negatively impacted the validation. To obtain a sufficient quantity of data to robustly validate RADIAL performance, it was necessary to obtain previously reported patient data with clear-cut molecular diagnoses by retrospective chart review. Unfortunately the main limitation of this approach is that many patients who were used to assess the final algorithm were also used to construct the knowledgebase; this is more problematic with the rarer entities for which the published cases may represent the majority of the global patient population. Regardless, many more patients whose data were used in construction of the knowledgebase were not assessed in the study. It is also of worth considering that the data reported in the literature are generally less precise and detailed than the clinical data provided by the collaborators. Thus, even if we used the same patients, their data to create the tool and to evaluate the tool were not identical. Moreover, the strength of RADIAL is not only to identify a specific disorder, but rather to identify a specific disorder amongst 67 other entities, which is much more difficult. Finally, that the expert panel were able to correctly identify the diagnosis in the majority of cases also supports the accuracy of the phenotypic definitions of each entity that were used to construct the knowledgebase. Taken together, these arguments support the genuinely very good diagnostic performance of RADIAL.

Another consideration, is the difficulty in accurately determining the frequency and specificity of clinical features, especially in rare entities where reported patient numbers are low. Future large-scale prospective real-world validation of RADIAL should be undertaken to address these concerns, further validate and, if necessary, refine RADIAL. A prospective study would also allow the opportunity to assess utility of RADIAL for interpretation of NGS-derived data, and assess whether

354 RADIAL can predict the pathogenicity of novel VUS. For this purpose, RADIAL is
355 available to all healthcare professionals as a free-to-use electronic application.
356 RADIAL can be accessed online at <http://radial-ataxia-algorithm.com/> or as an offline
357 version in the manuscript supplementary material (**Supplementary File 2**).

358 This algorithmic approach may be of further interest for many other diseases with
359 inherent diagnostic difficulties, including neurological (e.g. autosomal dominant
360 cerebellar ataxias, hereditary spastic paraplegias, neuropathy, myopathy, complex
361 dystonia, and early dementia) and non-neurological disorders.

362 In summary, we have developed a tool that facilitates the differential diagnosis of
363 autosomal recessive cerebellar ataxias. RADIAL uses patient's features to produce a
364 list of potential diagnoses ranked by likelihood, and which may be used to inform
365 further confirmatory clinical or genetic testing, and assist the interpretation of next-
366 generation sequencing data.

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397 Author contributions

398 MA, CT, MR, MK and JVTM contributed to conception and design of the study; MR,
399 CT, JVTM, FM, MS, BvdW, MP, MK, SAK, MA contributed to the acquisition and
400 analysis of the data; MR, CT, JVTM, FM, MS, BvdW, MP, MK, SAK, MA
401 contributed to drafting the text, preparing figures and approving the final manuscript.

402 Members of the RADIAL working group (**Supplementary Table 1**) who were not
403 authors, contributed patient data but did not have substantial involvement in drafting
404 the manuscript.

406 Potential conflicts of interests

407 MA reports travel grants and personal fees from Actelion Pharmaceuticals Ltd.

408 SAK is an employee of Actelion Pharmaceuticals Ltd.

409 MP reports a patent *Direct molecular diagnosis of Friedreich's ataxia* with royalties
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414 Supplementary material

415 **7 Supplementary Tables and 2 Supplementary File**

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489 **Figure legends**

490

491 **Figure 1:** Algorithm outline.

492

493 **Figure 2:** Average sensitivity and specificity for all patients related to the window
494 size, defined as the position of the entity in the ranking list.

495

496 **Figure 3:** Relationship between the total number of features (x-axis), the number of
497 specific features (y-axis), and the required window size, defined as the position of the
498 entity in the ranking list, to reach 90% sensitivity (diameter of bubble increases as
499 performance decreases). The figure shows the lack of association between
500 performance of the algorithm and the number of features. Pearson correlation
501 coefficient for total number of features vs window size: $r=0.052$, $P=0.730$; specific
502 number of features vs window size: $r=-0.033$, $P=0.830$.

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Table 1: Convention for notation and scoring for frequency and/or specificity for each category of signs and symptoms included in the algorithm.

Category	Clinical features	Neuro-imaging	Electro-myography	Age of onset	Rapid disease progression	Biomarkers
NK	0	0	0	0	0	0
0	-1	-1	-1	-2	-2	-2
L	1	1	1	2	2	2
H	3	3	3	6	6	6
LS	7	7	7	14	14	14
HS	9	9	9	18	18	18

0, No association; L, Low frequency (<50% of patients); LS, Low frequency (<50% of patients) and specific (<10% of entities); H, High frequency ($\geq$ 50% of patients); HS, High frequency ($\geq$ 50% of patients) and specific (<10% of entities); NK, extent of association not known.

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Figure 1: Algorithm outline.

79x66mm (300 x 300 DPI)

Figure 2: Average sensitivity and specificity for all patients related to the window size, defined as the position of the entity in the ranking list

78x43mm (300 x 300 DPI)

Accepted

Figure 3: Relationship between the total number of features (x-axis), the number of specific features (y-axis), and the required window size, defined as the position of the entity in the ranking list, to reach 90% sensitivity (diameter of bubble increases as performance decreases). The figure shows the lack of association between performance of the algorithm and the number of features. Pearson correlation coefficient for total number of features vs window size: $r=0.052$, $P=0.730$; specific number of features vs window size: $r=-0.033$, $P=0.830$.

77x43mm (300 x 300 DPI)

Accept

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Supplementary Table 2: All articles used in developing the knowledgebase separated by entity.

Entity	Citation
Multiple entities	Abele et al. Brain 2002;125:961–8
	Anderson et al. J Clin Pathol 2005;1305–10
	Anheim et al. Neurogenetics 2010;11:1–12
	Anheim et al. New Eng J Med 2012;366:636–46
	Boddaert et al. J Neuroradiology 2010;37:220–30
	Brusse et al. Clin Genet 2007;71:12–24
	Degardin et al. Cerebellum 2012;11:289–99
	Fasano et al. Brain 2010;133:3635–48
	Fogel and Perlman. Lancet Neurol 2007;6:245–57
	Fogel et al. JAMA Neurol 2014;71:1237–46
	Gasser et al. Eur J Neurol 2010;17:179–88
	Giordano et al. J Neurol 2013;260:2175–6
	Hara et al. Arch Neurol 2007;64:545–51
	Head et al. Ann Neurol 2005 ;58 :234–41
	Jara-Prado et al. Epilepsy Res 2014 ;108:1501–10
	Jobling et al. Brain 2015;138:1505–17
	Kleta et al. Nature Genet 2004;36:999–1002
	Klockgether. Lancet Neurol 2010;9:94–104
	Klockgether. Curr Opin Neurol 2011;24:339–45
	Koenig. Seminar Ped Neurol 2003;10:183–92
	Le Ber et al. Curr Neurol Neurosci Rep 2005;5:411–7
	Manto & Marmolino. Cur Opin Neurology 2009;22:419–29
	Mégarbané et al. Am J Med Genet 2001;101:135–41
	Nemeth et al. Brain 2013;136:3106–18
	Nia et al. J Neurol 2014;261:S559–68
	Palau and Espinos. Orphanet J Rare Dis 2006;1:47
	Pandolfo. Nat Clin Pract 2008;4:86–96
	Rass et al. Cell 2007;130:991–1004
	Shapira. Lancet 2006;368:70–82
	Taroni & DiDonato. Nat Rev Neurosci 2004;5:641–55
	Tusa & Hove. J Child Neurol 1999;14:621–7
	Van de Warrenburg et al. Eur J Neurol 2014;21:552–62
	Vermeer et al. J Med Genet 2011;48:651–9
	Wagner et al. J Neurol Neurosurg Psychiatry 2008;79:672–7
	Wardle et al. J Neurol 2009;256:343–8
AAAS	Kimber et al. J Neurol Neurosurg Psychiatry 2003;74:654–7
	Vallet et al. J Neurol 2012;259:39–46
ABHD12	Chen et al. Hum Mutat 2013;34:1672–8
	Eisenberger et al. Orphanet J Rare Dis 2012;7:59
	Fiskerstrand et al. Am J Hum Genet 2010;87:410–7
	Yoshimura et al. Ann Otol Rhinol Laryngol 2015;124:77S–83S
ACO2	Spiegel et al. Am j Hum Genet 2012;90:518–23
ADCK3	Gerards et al. Mitochondrion 2010;10:510–5
	Horvath et al. J Neurol Neurosurg Psychiatry 2012;83:174–8
	Lagier-Tourenne et al. Am J Hum Genet 2008;82:661–72
	Liu et al. J Neurol Neurosurg Psychiatry 2014;85:493–8
	Mignot et al. Orphanet J Rare Dis 2013;8:173
	Mollet et al. Am J Hum Genet 2008;82:623–30

	Montero et al. Cerebellum 2007;6:118–22
ANO10	Balreira et al. J Neurol 2014;261:2192–8
	Chamova et al. J Neurol 2012;259:906–11
	Minnerop and Bauer. JAMA Neurol 2015;72:238–9
	Muruyama et al. Clin Genet 2014;85:296–7
	Renaud et al. JAMA Neurol 2014;71:1305–10
	Vermeer et al. Am J Hum Genet 2010;87:813–9
APTX	Bohelga et al. BMC Med Genet 2011;12:27
	Castellotti et al. Neurogenetics 2011;12:193–201
	Criscuolo et al. Ann Neurol 2005;57:777
	Hirano et al. Ann Neurol 2007;61:162–74
	Le Ber et al. Brain 2003;126:2761–72
	Moreira et al. Nat Genet 2001;189–93
	Salvatore et al. J Neurol 2008;255:45–48
	Shahwan et al. Dev Med Child Neurol 2006;48:529–32
	Yakoseki et al. Brain 2011;134:1387–99
ATM	Ambrose & Gatti. Blood 2013;121:4036–45
	Chun & Gatti. DNA Repair 2004;1187–96
	Crawford et al. Neurology 2000;54:1505–9
	Crawford et al. Arch Dis Child 2006;91:610–1
	Dar et al. J Neurosci 2006;26:7767–74
	Lavin et al. Br Med Bulletin 2007;81:129–47
	Lewis et al. Ann Neurol 1999;46:287–95
	Lohmann et al. J Neurol 2015;262:1724–7
	Meissner et al. Mov Disord 2013;28:1897–9
	Meneret et al. Neurology 2014;83:1087–95
	Micol et al. J Allergy Clin Immunol 2011;128:392–9
	Oba et al. Acta Neuropathol 2010;119:513–20
	Paull. Annu Rev Biochem 2015;84:711–38
	Silvestri et al. J Neurol 2010;257:1738–40
	Sunders–Pullman et al. Neurology 2012;78:649–57
	Verhagen et al. Neurology 2009;73:430–7
	Verhagen et al. Hum Mut 2012;33:561–71
ATP7B	Bandmann et al. Lancet Neurol 2015 ;14 :103–13
BTD	Hymes et al. Hum Mutat 2001;18:375–81
	Wolf. Mol Genet Med 2011;104:27–34
	Wolf. Genet Med 2012;14:565–75
C10ORF2	Echaniz–Laguna et al. Neurogenetics 2010;11:21–5
	Hakonen et al. Brain 2007;130:3032–40
	Hakonen et al. Hum Mol Genet 2008;17:3822–35
	Nikali et al. Hum Mol Genet 2005;14:2981–90
	Park et al. Neurogenetics 2014;15:171–82
CA8	Kaya et al. Am J Med Genet 2011;156:826–34
CP	McNeill et al. Eur Neurol 2008;60:200–5
	Schneider et al. Mov Disord 2012;27:42–53
CYP27A1	Lagarde et al. Mov Disord 2012;27:1805–10
	Mignarri et al. J Inherit Metab Dis 2014;37:421–9
	Moghadasian et al Arch Neurol 2002;59:527–9
	Nie et al. Orphanet J Rare dis 2014;9:179
	Pilo–de–la–Fuente et al. Eur J Neurol 2011;18:1203–11
	Su et al. Mov Disord 2010;25:452–8
DARS2	Isoghanni et al. J Med Genet 2010;47:66–70
	Scheper et al. Nat Genet 2007;39:534–9
	Tzoulis et al. J Neurol 2012;259:292–6

DNAJC19	Davey et al. J Med Genet 2006;43:385–93
	Ojala et al. Pediatr Res 2012;72:432–7
FA2H	Kruer et al. Ann Neurol 2010;68:611–8
	Tonelli et al. Eur J Neurol 2012;19:e127–9
	Zaki et al. Clin Genet 2015;88:95–7
FXN	Bayot et al. BMC Med 2011;9:112
	Boesch et al. Ann Neurol 2007;62:521–4
	Burk et al. Mov Disord 2009;24:1779–84
	Coppola et al. Hum Mol Genet 2009;18:2452–61
	Corben et al. Brain Cogn 2011;76:140–5
	De Michele et al. Neurology 1996;47:1260–4
	Durr et al. New Eng J Med 1996;335:1169–75
	Durr. Lancet Neurol 2002;1:370–4
	Evans–Galea et al. Neurogenetics 2011;12:307–13
	Fortuna et al. Brain 2009;132:116–23
	Gottesfeld et al. J Neurochem 2013;126:147–54
	Koeppen et al. Acta Neurologica 2011;122:323–30
	Koeppen. J Neurochem 2013;126:4–10
	Mariotti et al. Neurology 2003;60:1676–9
	Pandolfo et al. Arch Neurol 2008;65:1296–303
	Pandolfo et al. J Neurol 2009;256:3–8
	Pandolfo and Pastore. J Neurol 2009;256:9–17
	Rasmussen et al. J Neurol Neurosurg Psychiatry 2006;77:1370–2
	Reetz et al. Lancet Neurol 2015;14:174–82
	Ribai et al. Arch Neurol 2007;64:558–64
	Sanz–Gallego et al. Cerebellum Ataxias 2014;1:10
	Weidemann et al. J Neurochem 2013;126:88–93
GAN	Buyse et al. Am J Med Genet 2010;152A:2802–4
	Demir et al. J Neurol Neurosurg Psychiatry 2005;76:825–32
GBE1	Billot et al. J Neuro Sci 2013;324:179–82
	Dainese et al. Gene 2013;515:376–9
	Mochel et al. Ann Neurol 2012;72:433–41
GOSR2	Boisse Lomax et al. Brain 2013;136:1146–54
	Corbett et al. Am J Hum Genet 2011;88:657–63
	Van Egmond et al. Mov Disord 2014;29:139–43
GRID2	Coutelier et al. Neurology 2015;84:1751–9
	Hills et al. Neurology 2013;81:1378–86
GRM1	Guergueltcheva et al. 2012;91:553–64
HEXA	Deik and Saunders–Pullman. Muscle Nerve 2014;49:768–71
	Maegawa et al. Pediatrics 2006;118:e1550
HEXB	Delnooz et al. J Neurol Neurosurg Psychiatry 2010;81:968–72
	Maegawa et al. Pediatrics 2006;118:e1550
HSD17B4	Lieber et al. BMC Med Genet 2014;15:30
	Lines et al. Neurology 2014;82:963–8
	Pierce et al. Am J Hum Genet 2010;87:282–8
KCNJ10	Bockenhauer et al. New Eng J Med 2009;360:1960–70
	Cross et al. Dev Med Child Neurol 2013;55:846–56
	Scholl et al. Proc Nat Acad Sci USA 2009;106:5842–7
KCTD7	Blumkin et al. J Neurol 2012;259:2590–8
	Farhan et al. Epilepsia 2014;55:e106–11
	Staropoli et al. Am J Hum Genet 2012;91:202–8
	Van Begaert et al. Ann Neurol 2007;61:579–86
MARS2	Bayat et al. PLoS Biol 2012;10:e1001288
MRE11	Fernet et al. Hum Mol Genet 2005;14:307–18

	Uchisaka et al. J Pediatr 2009;155:435–8
MTPAP	Crosby et al. Am J Hum Genet 2010;87:655–60
MTTP	No publications identified dealing specifically with this entity
NEU1	Canafoglia et al. Neurology 2014;82:2003–6 Lai et al. Eur J Neurol 2009;16:912–9
NPC1/NPC2	Anheim et al. J Neurol 2014;261:174–9 Josephs et al. J Neurol Neurosurg Psychiatry 2003;74:528–9 Klunemann et al. Ann Neurol 2002;52:743–9 Mengel et al. Orphanet J Rare Dis 2013;8:166 Patterson et al. Lancet 2007;6:765–72 Schicks et al. Neurology 2013;80:1169–70 Sevin et al. Brain 2007;130:120–33 Shulman et al. Neurology 1995;45:1739–43 Vanier. Orphanet J Rare Dis 2010;5:16 Walterfang et al. Orphanet J Rare Dis;7:76 Wraith et al. J Inherit Dis 2014;37:93–101
OPA1	Bonifert et al. Brain 2014;137:2164–77 Bonneau et al. Brain 2014;137:1–4 Marelli et al. Brain 2011;134:e169
OPA3	Yahalom et al. J Neurol 2014;261:2275–82
PEX10	Okumoto et al. Hum Mol Genet 1998;7:1399–405 Regal et al. Ann Neurol 2010;68:259–63 Warren et al. Am J Hum Genet 1998;63:347–59
PEX7	Nanetti et al. J Clin Neurol 2015;11:197–9 Van den Brink et al. Am J Hum Genet 2003;72:471–77
PHYH	Bompaire et al. JIMD Reports 2015;19:7–10 Fertl et al. J Neurol Neurosurg Psychiatry 2001;70:563–7 Jansen et al. Nat Genet 1997;17:190–3 Mihalik et al. Nat Genet 1997;17:185–9 Weinstein et al. J Clin Apheresis 1999;14:181–4 Wierzbicki et al. J Neurochem 2002;80:727–35
PIK3R5	Al Tassan et al. Hum Mut 2012;33:351–4
PK1/PRICKLE1	Bassuk et al. Am J Hum Genet 2008;83:572–81 Berkovic et al. Brain 2005;128:652–8
PLA2G6	Karkheiran et al. Tremor Other Hyperkinet Mov (NY) 2015;5:317 Kurian et al. Neurology 2008;70:1623–9 Salih et al. PLoS One 2013;8:e76831 Schneider et al. Mov Disord 2012;27:42–53
PMM2	Barone et al. J Neurol 2015;262:154–64 Monin et al. Orphanet J Rare Dis 2014;9:207 O’Sullivan et al. Mov Disord 2006;21:869–72 Serrano et al. Orphanet J Rare Dis 2015;10:138 Vermeer et al. J Neurol 2007;254:1356–8
PNKP	Bras et al. Am J Hum Genet 2015;96:474–9
PNPLA6	Deik et al. J Neurol 2014;261:2411–23 Synofzik et al. Brain 2014;137:69–77 Tarnutzer et al. J Neurol 2015;262:194–202
POLG	Tchikviladze et al. J Neurol Neurosurg Psychiatry 2015;86:646–54 Echaniz-Laguna et al. Arch Neurol 2010;67:1140–3 Farnum et al. Biochim et Biophys Acta 2014;1837:1113–21 Tzoulis et al. Brain 2006;129:1685–92 Tzoulis et al. Brain 2010;133:1428–37
POLR3A	Bernard et al. Am J Hum Genet 2011;89:415–23 Daoud et al. J Med Genet 2013;50:194–7

	Saitsu et al. Am J Hum Genet 2011;89:644–51
	Wolf et al. Neurology 2014;83:1898–1905
POLR3B	Daoud et al. J Med Genet 2013;50:194–7
	Saitsu et al. Am J Hum Genet 2011;89:644–51
	Synofzik et al. Neurology 2013;81:e145
	Tetreault et al. Am J Hum Genet 2011;89:652–5
	Wolf et al. Neurology 2014;83:1898–1905
SACS	Boulal et al. J Mol Neurosci 2009;39:333–6
	Duquette et al. Mov Disord 2013;28:2011–14
	Gazulla et al. J Neurol 2012;259:869–78
	Gerwig et al. Neurology 2010;75:2133
	Girard et al. Proc Natl Acad Sci USA 2012;109:1661–6
	Martin et al. Am J Neuroradiol 2007;28:1606–8
	Pablo et al. Mol Vis 2011;17:1871–6
	Parfitt et al. Hum Mol Genet 2009;18:1556–65
	Synofzik et al. Orphanet J Rare Dis 2013;8:41
	Tzoulis et al. PLoS One 2013;8:e66145
	Vermeer et al. Neurogenetics 2008;9:207–14
SCARB2	Berkovic et al. Am J Hum Genet 2008;82:673–84
	Dibbens et al. Ann Neurol 2009;66:532–36
	Perandones et al. Mov Disord 2014;29:158–9
SETX	Airoidi et al. Neurogenetics 2010;11:91–100
	Anheim et al. Brain 2009;132:2688–98
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Supplementary Table 3: Full list of genes and disorders included in the differential diagnosis algorithm with disorders included in the retrospective analyses in bold.

Gene	Disorder
AAAS	Achalasia-addisonianism-alacrimia syndrome (Triple A or Allgrove syndrome)
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)
ACO2	Infantile cerebellar-retinal degeneration
ADCK3	ARCA2
ANO10	ARCA3
APTX	Ataxia-oculomotor apraxia 1
ATM	Ataxia-telangiectasia
ATP7B	Wilson disease
BTD	Biotinidase deficiency
C10ORF2	Infantile onset spinocerebellar ataxia (IOSCA)
CA8	Cerebellar ataxia and mental retardation with or without quadrupedal locomotion 3
CP	Aceruloplasminemia
CYP27A1	Cerebrotendinous xanthomatosis
DARS2	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation
DNAJC19	3-methylglutaconic aciduria, type V
FA2H	Spastic paraplegia 35
FXN	Friedreich ataxia, late-onset Friedreich ataxia and very late-onset Friedreich ataxia
GAN	Giant axonal neuropathy-1
GBE1	Adult polyglucosan body disease
GOSR2	Epilepsy, progressive myoclonic 6
GRID2	Spinocerebellar ataxia, autosomal recessive 18
GRM1	Spinocerebellar ataxia, autosomal recessive 13
HEXA	Tay-Sachs disease
HEXB	Sandhoff disease
HSD17B4	Perrault syndrome 1
KCNJ10	Epilepsy ataxia sensorineural deafness and tubulopathy (EAST) syndrome
KCTD7	Epilepsy, progressive myoclonic 3, with or without intracellular inclusions
MARS2	Spastic ataxia 3, autosomal recessive
MRE11	Ataxia-telangiectasia-like disorder
MTPAP	Ataxia, spastic, 4
MTTP	Abetalipoproteinemia
NEU1	Sialidosis, type I
NPC1/NPC2	Niemann-Pick disease Type C
OPA1	Behr syndrome
OPA3	3-methylglutaconic aciduria, type III
PEX10	Peroxisome biogenesis disorder 6A
PEX7	Peroxisome biogenesis disorder 9B
PHYH	Refsum disease
PIK3R5	Ataxia-oculomotor apraxia 3

PK1/PRICKLE1	Epilepsy, progressive myoclonic 1B
PLA2G6	PLA2G6 associated neurodegeneration (PLAN) Infantile neuroaxonal dystrophy 1
PMM2	Congenital disorder of glycosylation, type Ia (CDG1a)
PNKP	Ataxia-oculomotor apraxia 4
PNPLA6	Boucher-Neuhauser syndrome
POLG	Sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO)
POLR3A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism
POLR3B	Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism
SACS	Autosomal recessive spastic ataxia of Charlevoix-Saguenay
SCARB2	Epilepsy, progressive myoclonic 4, with or without renal failure
SETX	Ataxia-oculomotor apraxia 2
SIL1	Marinesco-Sjogren syndrome
SLC9A1	Lichtenstein-Knorr syndrome
SNX14	Spinocerebellar ataxia, autosomal recessive 20
SPG7	Spastic paraplegia 7, autosomal recessive
SPTBN2	Spinocerebellar ataxia, autosomal recessive 14
STUB1	Spinocerebellar ataxia, autosomal recessive 16
SYNE1	Spinocerebellar ataxia, autosomal recessive 8
SYT14	Spinocerebellar ataxia, autosomal recessive 11
TDP1	Spinocerebellar ataxia plus neuropathy (SCAN1)
TDP2	Spinocerebellar ataxia, autosomal recessive 23
TPP1	Spinocerebellar ataxia, autosomal recessive 7
TTPA	Ataxia with vitamin E deficiency
VLDLR	Cerebellar hypoplasia and mental retardation with or without quadrupedal locomotion 1
VWA3B	Spinocerebellar ataxia, autosomal recessive 22
WDR73	Galloway-Mowat syndrome
ZNF592	Cerebellar Ataxia with Mental retardation, Optic atrophy and Skin abnormalities (CAMOS)

Supplementary Table 4: Number of patients included in the analyses by molecularly confirmed diagnosis.

Gene	Disease name	Number of patients (%)
Total		834 (100)
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)	9 (1.1)
ADCK3	ARCA2	13 (1.6)
ANO10	ARCA3	14 (1.7)
APTX	Ataxia-oculomotor apraxia 1	58 (7.0)
ATM	Ataxia-telangiectasia	44 (5.3)
ATP7B	Wilson disease	9 (1.1)
C10ORF2	Infantile onset spinocerebellar ataxia (IOSCA)	24 (2.9)
CP	Aceruloplasminemia	1 (0.1)
CYP27A1	Cerebrotendinous xanthomatosis	21 (2.5)
DARS2	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	8 (1.0)
FXN (FRDA)	Friedreich's ataxia	20 (2.4)
FXN (LOFA)	late-onset Friedreich's ataxia and very late-onset Friedreich's ataxia	40 (4.8)
GAN	Giant axonal neuropathy-1	6 (0.7)
GBE1	Adult polyglucosan body disease	7 (0.8)
GOSR2	Epilepsy, progressive myoclonic 6	12 (1.4)
GRM1	Congenital cerebellar ataxia, autosomal recessive, associated with mental retardation	10 (1.2)
HSD17B4	Perrault syndrome 1	3 (0.4)
KCNJ10	Epilepsy, ataxia, sensorineural deafness and tubulopathy (EAST) syndrome	1 (0.1)
MRE11	Ataxia-telangiectasia-like disorder	10 (1.2)

NEU1	Sialidosis, type I	26 (3.1)
NPC1/NPC2	Niemann-Pick disease Type C	57 (6.8)
OPA1	Behr syndrome	4 (0.5)
OPA3	3-methylglutaconic aciduria, type III	10 (1.2)
PEX10	Peroxisome biogenesis disorder 6A	3 (0.4)
PEX7	Peroxisome biogenesis disorder 9B	10 (1.2)
PHYH	Refsum disease	1 (0.1)
PLA2G6	PLA2G6 associated neurodegeneration (PLAN) Infantile neuroaxonal dystrophy 1	11 (1.3)
PMM2	Congenital disorder of glycosylation, type Ia (CDG1a)	29 (3.5)
PNKP	Ataxia-oculomotor apraxia 4	11 (1.3)
PNPLA6	Boucher-Neuhauser syndrome	14 (1.7)
POLG	Sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO)	15 (1.8)
POLR3A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism	20 (2.4)
POLR3B	Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism	30 (3.6)
SACS	Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	38 (4.6)
SCARB2	Epilepsy, progressive myoclonic 4, with or without renal failure	15 (1.8)
SETX	Ataxia-oculomotor apraxia 2	60 (7.2)
SNX14	Spinocerebellar ataxia, autosomal recessive 20	7 (0.8)
SPG7	Spastic paraplegia 7, autosomal recessive	23 (2.8)
STUB1	Spinocerebellar ataxia, autosomal recessive 16	9 (1.1)
SYNE1	Spinocerebellar ataxia, autosomal recessive 8	26 (3.1)
TTPA	Ataxia with vitamin E deficiency	69 (8.3)

<i>VLDLR</i>	Cerebellar hypoplasia and mental retardation with or without quadrupedal locomotion 1	15 (1.8)
<i>VWA3B</i>	Spinocerebellar ataxia, autosomal recessive 22	3 (0.4)
<i>WDR73</i>	Galloway-Mowat syndrome	13 (1.6)
<i>ZNF592</i>	Spinocerebellar ataxia, autosomal recessive 5	5 (0.6)

Supplementary Table 5: Summary of the disease characteristics for the entire patient cohort and for the 8 ARCA with a sample size of ≥30 patients.

Sign/symptom	Total	<i>APT</i>	<i>AT</i>	<i>FX</i> (<i>LOFA</i>)	<i>NPC1</i> <i>NPC2</i>	<i>POLR3B</i>	<i>SACS</i>	<i>SETX</i>	<i>TTPA</i>
N	834	58	44	40	57	30	38	60	69
Age of onset of ataxia	821	54	44	40	56	30	38	58	69
<10 years	395 (47.4)	50 (86.2)	31 (70.5)	0 (0.0)	16 (28.1)	26 (86.7)	27 (71.1)	3 (5.0)	15 (21.7)
≥10 years	426 (51.1)	4 (6.9)	13 (29.5)	40 (100.0)	40 (70.2)	4 (13.3)	11 (28.9)	55 (91.7)	54 (78.3)
Speed of progression	641	44	44	40	41	23	30	29	27
Slow (can walk unaided 20 years after disease onset)	252 (30.2)	6 (10.3)	17 (38.6)	17 (42.5)	2 (3.5)	1 (3.3)	23 (60.5)	5 (8.3)	19 (27.5)
Rapid (required assistance to walk 20 years after disease onset)	389 (46.6)	38 (65.5)	27 (61.4)	23 (57.5)	39 (68.4)	22 (73.3)	7 (18.4)	24 (40.0)	8 (11.6)
Ocular symptoms	225	0	34	1	0	3	38	0	3
Telangiectasia	34 (4.1)	0 (0.0)	34 (77.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cataract	45 (5.4)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinitis pigmentosa / retinal degeneration / chorioretinal dystrophy	43 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.3)
Optic atrophy	82 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Red cherry macula	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal nerve fibre layer hypertrophy	38 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (100.0)	0 (0.0)	0 (0.0)
Ocular motor symptoms	521	52	34	13	55	29	36	38	13
Diplopia / strabismus	117 (14.0)	14 (24.1)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	5 (8.3)	2 (2.9)

Gaze evoked nystagmus	230 (27.6)	29 (50.0)	7 (15.9)	12 (30.0)	0 (0.0)	28 (93.3)	30 (78.9)	0 (0.0)	7 (10.1)
Hypometric saccades	128 (15.3)	12 (20.7)	15 (34.1)	1 (2.5)	0 (0.0)	7 (23.3)	34 (89.5)	0 (0.0)	0 (0.0)
Slow saccades	61 (7.3)	0 (0.0)	10 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (10.5)	0 (0.0)	0 (0.0)
Saccades of elevated latencies	11 (1.3)	0 (0.0)	5 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oculomotor apraxia/oculocephalic dissociation	136 (16.3)	36 (62.1)	26 (59.1)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	35 (58.3)	4 (5.8)
Vertical supranuclear gaze palsy	78 (9.4)	0 (0.0)	0 (0.0)	0 (0.0)	55 (96.5)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Progressive external ophthalmoplegia	43 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tonic upgaze	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Movement disorders	275	24	24	0	43	6	0	11	0
Chorea	79 (9.5)	18 (31.0)	4 (9.1)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	5 (8.3)	0 (0.0)
Dystonia	174 (20.9)	10 (17.2)	19 (43.2)	0 (0.0)	42 (73.7)	6 (20.0)	0 (0.0)	8 (13.3)	0 (0.0)
Myoclonus	104 (12.5)	3 (5.2)	12 (27.3)	0 (0.0)	7 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parkinsonism	23 (2.8)	0 (0.0)	5 (11.4)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cortico-spinal tract	417	6	3	32	33	7	38	6	59
Enhanced/diffused tendon reflexes	267 (32.0)	0 (0.0)	3 (6.8)	17 (42.5)	32 (56.1)	7 (23.3)	33 (86.8)	0 (0.0)	1 (1.4)
Extensor plantar reflexes	293 (35.1)	6 (10.3)	3 (6.8)	26 (65.0)	7 (12.3)	1 (3.3)	38 (100.0)	6 (10.0)	59 (85.5)
Spasticity	198 (23.7)	0 (0.0)	1 (2.3)	13 (32.5)	13 (22.8)	7 (23.3)	32 (84.2)	0 (0.0)	9 (13.0)

Cognitive & psychiatric	354	28	3	3	52	28	0	0	0
Hallucinations and/or delusions	27 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	12 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive decline	226 (27.1)	0 (0.0)	0 (0.0)	2 (5.0)	51 (89.5)	20 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)
Mental retardation / delayed developmental milestones	228 (27.3)	28 (48.3)	3 (6.8)	0 (0.0)	10 (17.5)	20 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment resistant psychiatric symptoms	24 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Disruptive/aggressive behaviour in childhood	13 (1.6)	0 (0.0)	0 (0.0)	1 (2.5)	2 (3.5)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Neurological	510	58	20	30	35	2	7	58	67
Absence of tendon reflexes	335 (40.2)	58 (100.0)	19 (43.2)	19 (47.5)	0 (0.0)	0 (0.0)	1 (2.6)	58 (96.7)	67 (97.1)
Myopathy (skeletal)	18 (2.2)	0 (0.0)	0 (0.0)	7 (17.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy	142 (17.0)	0 (0.0)	1 (2.3)	2 (5.0)	19 (33.3)	1 (3.3)	2 (5.3)	0 (0.0)	0 (0.0)
Deafness	73 (8.8)	0 (0.0)	0 (0.0)	4 (10.0)	12 (21.1)	1 (3.3)	5 (13.2)	0 (0.0)	0 (0.0)
Cataplexia	20 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	20 (35.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anosmia	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quadrupedal gait	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stridor	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke-like episodes	23 (2.8)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autonomic dysfunction	57 (6.8)	0 (0.0)	0 (0.0)	11 (27.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Musculo-skeletal	344	27	3	18	5	26	35	29	35
Pes cavus	228 (27.3)	21 (36.2)	0 (0.0)	12 (30.0)	0 (0.0)	0 (0.0)	35 (92.1)	29 (48.3)	31 (44.9)
Scoliosis	128 (15.3)	15 (25.9)	3 (6.8)	10 (25.0)	5 (8.8)	2 (6.7)	1 (2.6)	0 (0.0)	12 (17.4)
Loss of the dorsal kyphosis	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Adducted thumbs	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oligodontia	42 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (86.7)	0 (0.0)	0 (0.0)	0 (0.0)
Short fourth metacarpal / metatarsal bones	7 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Short fifth metacarpal / metatarsal bones	9 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoporosis	53 (6.4)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Coarsened facial features	17 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Visceral & gastrointestinal	138	0	0	6	39	0	0	0	3
Hepatomegaly	26 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	22 (38.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Splenomegaly	42 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	37 (64.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiomyopathy / pericardial effusions / cardiac arrhythmia	20 (2.4)	0 (0.0)	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)
Diabetes	16 (1.9)	0 (0.0)	0 (0.0)	4 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	19 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malabsorption	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Vomiting	24 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure	20 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Achalasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cryptorchidism	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Skin	54	0	25	0	0	0	0	0	0
Xanthoma	17 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Telangiectasias	24 (2.9)	0 (0.0)	24 (54.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Café-au-lait spots	18 (2.2)	0 (0.0)	18 (40.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Frizzly/kinky hair	6 (0.70)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Xeroderma / ichthyosis	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Miscellaneous	108	0	18	6	7	13	0	0	1
Recurrent infections	15 (1.8)	0 (0.0)	6 (13.6)	0 (0.0)	7 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancies	13 (1.6)	0 (0.0)	5 (11.4)	3 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system defects	13 (1.6)	0 (0.0)	13 (29.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Obesity	17 (2.0)	0 (0.0)	1 (2.3)	3 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adrenal insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Alacrimia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Hypogonadotropic hypogonadism	59 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (43.3)	0 (0.0)	0 (0.0)	0 (0.0)
Neuroimaging data	672	54	20	32	44	30	0	55	65
Obvious cerebellar atrophy	447 (53.6)	54 (93.1)	18 (40.9)	7 (17.5)	16 (28.1)	30 (100.0)	0 (0.0)	55 (91.7)	6 (8.7)
No cerebellar atrophy	207 (24.8)	0 (0.0)	2 (4.5)	24 (60.0)	28 (49.1)	0 (0.0)	0 (0.0)	0 (0.0)	59 (85.5)
Spinal cord atrophy	33 (4.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellar white-matter changes	99 (11.9)	0 (0.0)	1 (2.3)	1 (2.5)	0 (0.0)	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke-like lesions	18 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anterior superior cerebellar atrophy	14 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Olivary nuclei hyperintensity	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
T2-weighted linear hypointensities in The pons	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebral leukopathy	96 (11.5)	0 (0.0)	0 (0.0)	1 (2.5)	3 (5.3)	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Brainstem atrophy	85 (10.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	18 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)
Small pituitary	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperintensities in the pons	39 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypointensity of basal ganglia	17 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bilateral middle cerebellar peduncles hyperintensities	45 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)

Simplified cerebral gyration	15 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thin corpus callosum	61 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	22 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)
Electro-myography	628	55	14	36	46	12	38	57	68
Axonal sensorimotor neuropathy	240 (28.8)	53 (91.4)	9 (20.5)	0 (0.0)	1 (1.8)	0 (0.0)	38 (100.0)	57 (95.0)	2 (2.9)
Pure sensory neuropathy	126 (15.1)	0 (0.0)	0 (0.0)	26 (65.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	41 (59.4)
Demyelinating component of the neuropathy	79 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	38 (100.0)	0 (0.0)	0 (0.0)
No peripheral neuropathy	246 (29.5)	2 (3.4)	5 (11.4)	10 (25.0)	44 (77.2)	12 (40.0)	0 (0.0)	0 (0.0)	25 (36.2)
Biomarker evidence	358	44	44	0	2	1	0	54	69
Elevated serum lactic acid level	6 (0.7)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased serum vitamin e level	69 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	69 (100.0)
Decreased serum cholesterol &/or triglycerides	11 (1.3)	0 (0.0)	3 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased serum vitamin a, d and/or k	14 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abetalipoproteinemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acanthocytosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated serum LDL cholesterol level	44 (5.3)	19 (32.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated serum creatine kinase level	28 (3.4)	8 (13.8)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Decreased serum immunoglobulin level	34 (4.1)	0 (0.0)	17 (38.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.0)	0 (0.0)

Decreased serum albumin level	60 (7.2)	33 (56.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated serum alpha-fetoprotein level	126 (15.1)	17 (29.3)	43 (97.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	54 (90.0)	0 (0.0)
Hexosaminidase a deficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hexosaminidase b deficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated serum phytanic acid level	12 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated serum cholestanol level	21 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased coenzyme q10 level	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased ceruloplasmin serum level	10 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased iron serum level	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased copper serum level	10 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated 24 hours urinary copper	9 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated serum oxysterol level	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Altered urinary oligosaccharides	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated 3-methylglutaconic acid and/or elevated 3-methylglutaric acid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated aspartate transaminase and/or elevated alanine transaminase	14 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	18 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Glycogen branching enzyme activity decreased in leukocytes	7 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serum biotinidase enzyme activity decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated ferritin serum level	6 (0.7)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased neuraminidase activity in fibroblasts	11 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Karyotype translocations	19 (2.3)	0 (0.0)	19 (43.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type 1 transferrin isoform pattern and/or abnormal serum transferrin glycosylation by isoelectrofocusing or immunofixation	16 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased leukocytes phosphomannomutase activity	21 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated pristanic acid level	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coagulations anomalies and thrombotic events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Supplementary Table 6: Size of ranking window, defined as the position of the entity in the ranking list, required to meet 90% sensitivity for each disorder

	To reach 90% sensitivity		
	Window size	Sensitivity	Specificity
ABHD12	3	1.000	0.978
ADCK3	4	0.923	0.961
ANO10	3	0.929	0.966
APTX	3	0.914	0.937
ATM	1	1.000	0.975
ATP7B	1	1.000	0.970
C10ORF2	1	0.958	0.989
CP	1	1.000	0.999
CTX	1	1.000	0.998
DARS2	3	1.000	0.936
FXN (FRDA)	1	0.900	0.989
FXN (LOFA)	10	0.900	0.884
GAN	1	1.000	1.000
GBE1	1	1.000	0.954
GOSR2	1	1.000	0.999
GRM1	2	1.000	0.973
HSD17B4	1	1.000	0.995
KCNJ10	2	1.000	0.986
MRE11	2	1.000	0.999
NEU1	2	0.962	0.985
NPC1/NPC2	2	0.947	1.000
OPA1	4	1.000	0.999
OPA3	1	0.900	0.987
PEX10	1	1.000	1.000
PEX7	1	0.900	1.000
PHYH	5	1.000	0.977
PLA2G6	1	0.909	0.966
PMM2	2	0.966	0.968

<i>PNKP</i>	1	0.909	0.995
<i>PNPLA6</i>	16	0.929	0.894
<i>POLG</i>	1	0.933	0.998
<i>POLR3A</i>	1	1.000	0.962
<i>POLR3B</i>	2	0.900	0.974
<i>SACS</i>	1	1.000	0.992
<i>SCARB2</i>	2	0.933	0.933
<i>SETX</i>	1	0.900	0.994
<i>SNX14</i>	1	1.000	1.000
<i>SPG7</i>	3	0.913	0.959
<i>STUB1</i>	10	1.000	0.692
<i>SYNE1</i>	9	0.962	0.847
<i>TTPA</i>	1	0.913	0.973
<i>VLDLR</i>	2	1.000	0.994
<i>VWA3B</i>	1	1.000	0.999
<i>WDR73</i>	1	1.000	1.000
<i>ZNF592</i>	3	1.000	0.996

Supplementary Table 7: Sensitivity and specificity of the algorithm for correctly placing disorders into the Top 1, Top 3, or Top 5 places of output lists ranked by total score.

	Top 1		Top 3		Top 5	
Gene	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
<i>ABHD12</i>	0.889	0.999	1.000	0.978	1.000	0.955
<i>ADCK3</i>	0.538	1.000	0.846	0.987	0.923	0.948
<i>ANO10</i>	0.500	0.995	0.929	0.966	0.929	0.924
<i>APTX</i>	0.793	0.999	0.914	0.937	0.983	0.823
<i>SETX</i>	0.900	0.994	1.000	0.929	1.000	0.854
<i>ATM</i>	1.000	0.975	1.000	0.851	1.000	0.792
<i>ATP7B</i>	1.000	0.970	1.000	0.895	1.000	0.840
<i>TTPA</i>	0.913	0.973	1.000	0.933	1.000	0.907
<i>C10ORF2</i>	0.958	0.989	1.000	0.905	1.000	0.814
<i>CP</i>	1.000	0.999	1.000	0.968	1.000	0.933
<i>CTX</i>	1.000	0.998	1.000	0.956	1.000	0.893
<i>DARS2</i>	0.500	1.000	1.000	0.936	1.000	0.877
<i>FXN (FRDA)</i>	0.900	0.989	0.950	0.953	1.000	0.910
<i>FXN (LOFA)</i>	0.100	0.999	0.625	0.929	0.775	0.908
<i>GAN</i>	1.000	1.000	1.000	0.996	1.000	0.975
<i>GBE1</i>	1.000	0.954	1.000	0.898	1.000	0.827
<i>GOSR2</i>	1.000	0.999	1.000	0.987	1.000	0.959
<i>GRM1</i>	0.800	0.988	1.000	0.956	1.000	0.920
<i>HSD17B4</i>	1.000	0.995	1.000	0.933	1.000	0.890
<i>KCNJ10</i>	0.000	0.998	1.000	0.972	1.000	0.950
<i>MRE11</i>	0.800	1.000	1.000	0.999	1.000	0.995
<i>NEU1</i>	0.769	0.996	1.000	0.967	1.000	0.939
<i>NPC1/NPC2</i>	0.895	1.000	0.965	0.994	0.965	0.988
<i>OPA1</i>	0.000	1.000	0.750	1.000	1.000	0.995
<i>OPA3</i>	0.900	0.987	1.000	0.964	1.000	0.927
<i>PEX10</i>	1.000	1.000	1.000	0.984	1.000	0.966
<i>PEX7</i>	0.900	1.000	0.900	0.994	1.000	0.985
<i>PHYH</i>	0.000	0.999	0.000	0.986	1.000	0.977

<i>PLA2G6</i>	0.909	0.966	0.909	0.770	1.000	0.588
<i>PMM2</i>	0.897	0.998	1.000	0.952	1.000	0.913
<i>PNKP</i>	0.909	0.995	1.000	0.908	1.000	0.781
<i>PNPLA6</i>	0.571	1.000	0.714	1.000	0.714	0.998
<i>POLG</i>	0.933	0.998	1.000	0.965	1.000	0.894
<i>POLR3A</i>	1.000	0.962	1.000	0.923	1.000	0.871
<i>POLR3B</i>	0.733	0.993	0.967	0.970	1.000	0.938
<i>SACS</i>	1.000	0.992	1.000	0.941	1.000	0.886
<i>SCARB2</i>	0.800	0.999	0.933	0.988	0.933	0.980
<i>SNX14</i>	1.000	1.000	1.000	0.998	1.000	0.987
<i>SPG7</i>	0.478	0.991	0.913	0.959	0.913	0.935
<i>STUB1</i>	0.444	0.995	0.556	0.924	0.667	0.827
<i>SYNE1</i>	0.500	0.990	0.692	0.968	0.769	0.936
<i>VLDLR</i>	0.867	0.998	1.000	0.989	1.000	0.975
<i>VWA3B</i>	1.000	0.999	1.000	0.981	1.000	0.936
<i>WDR73</i>	1.000	1.000	1.000	0.937	1.000	0.893
<i>ZNF592</i>	0.600	1.000	1.000	0.996	1.000	0.970
Average	0.771	0.993	0.924	0.954	0.968	0.911

RADIAL knowledgebase

Key

H - High frequency

L - Low frequency

S - Specific

0 - Not present

NK - Not known

*

Feature occurs in $\geq 50\%$ of patients with the entityFeature occurs in $< 50\%$ of patients with the entity. \Feature presents in $< 10\%$ of entities

Feature not considered to be associated with the er

Feature not reported with the entity, but with insuf

Denotes signs and symptoms that are considered sp

		Entity									
		Gene									
		Entity									
		Gene									
Age of onset	Age of onset of ataxia < 10 years	L	0	L	L	H	H	H	L	L	L
	Age of onset of ataxia ≥ 10 years	L	H	H	H	L	L	L	H	L	L
Speed of progression	Slow progression (can walk unaided 20 years after disease onset)	L	L	L	L	L	L	L	L	L	L
	Rapid progression (required assistance to walk 20 years after disease onset)	H	L	L	L	L	H	L	H	L	L
Ocular symptoms	Telangiectasia* (2)	0	0	0	0	0	HS	0	0	0	0
	Cataract (9)	0	0	0	0	0	0	0	0	0	0
	Retinitis pigmentosa / retinal degeneration / chorioretinal	0	0	0	L	L	0	0	0	0	0
	Optic atrophy (19)	L	L	L	0	NK	0	L	0	L	L
	Red cherry macula* (3)	0	0	0	0	0	0	0	0	HS	HS
	Retinal nerve fibre layer (RNLF) hypertrophy* (1)	0	0	0	0	0	0	0	0	0	0
Other symptoms	Diplopia / strabismus (21)	0	0	L	L	0	L	L	L	NK	NK
	Gaze evoked nystagmus	L	L	L	L	NK	H	H	H	NK	NK
	Hypometric saccades	L	L	L	L	NK	L	L	L	NK	NK

Oculomotor symptoms	Slow saccades	0	0	NK	0	NK	L	L	L	NK	NK
	Saccades of elevated latencies	0	0	0	0	0	LS	LS	LS	NK	NK
	Oculomotor apraxia/Oculocephalic dissociation (11)	0	0	0	0	0	H	H	H	NK	NK
	Vertical supranuclear gaze palsy* (6)	0	0	0	0	0	0	0	0	0	0
	Progressive external ophthalmoplegia (10)	0	0	H	0	0	0	0	0	0	0
	Tonic upgaze (2)	0	0	0	0	0	0	0	0	NK	NK
Movement disorders	Chorea (15)	0	0	L	0	NK	L	L	L	L	L
	Dystonia (26 !)	0	0	L	L	NK	H	L	L	H	H
	Myoclonus (17)	0	0	L	L	0	L	L	0	L	L
	Parkinsonism (10)	0	0	L	0	0	L	0	0	NK	NK
Cortico-spinal tract	Enhanced/diffused tendon reflexes (42)	L	L	L	L	NK	L	0	0	L	L
	Extensor plantar reflexes (44)	H	H	L	H	NK	L	L	L	L	L
	Spasticity (30)	L	L	0	L	NK	NK	0	NK	L	L
Cognitive & psychiatric	Hallucinations and/or delusions (7)	0	0	L	0	NK	0	0	0	L	L
	Cognitive Decline (26)	0	0	L	0	0	L	L	L	L	L
	Mental Retardation / Delayed Developmental Milestones (46)	0	0	L	0	0	L	H	L	L	L
	Treatment resistant psychiatric symptoms (6)	0	0	LS	0	0	0	0	0	NK	NK
	Disruptive/aggressive behaviour in childhood (9)	0	0	L	0	0	0	0	0	L	L
Neurological	Absence of tendon reflexes (27)	H	L	H	H	H	L	H	H	L	L
	Myopathy (skeletal) (11)	L	L	L	0	0	0	0	0	NK	NK
	Epilepsy (33)	0	0	L	0	0	0	0	0	L	L
	Deafness (19)	L	L	L	L	NK	0	0	0	NK	NK
	Cataplexia* (1)	0	0	0	0	0	0	0	0	NK	NK
	Anosmia (2)	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK

	Quadrupedal gait (2)	0	0	0	0	0	0	0	NK	NK
	Stridor (3)	0	0	0	0	0	0	0	0	0
	Stroke-like episodes (5)	0	0	LS	0	0	0	0	0	0
	Autonomic dysfunction (10)	NK	NK	L	0	0	NK	0	L	L
Musculo-skeletal	Pes cavus (25)	L	L	NK	L	NK	L	L	NK	NK
	Scoliosis (22)	L	L	0	L	NK	L	L	NK	NK
	Loss of the dorsal kyphosis (1)	0	0	0	0	NK	0	0	NK	NK
	Adducted thumbs (2)	0	0	0	0	0	0	0	NK	NK
	Oligodontia (2)	0	0	0	0	0	0	0	NK	NK
	Short Fourth metacarpal / metatarsal bones (3)	0	0	0	0	0	0	0	NK	NK
	Short fifth metacarpal / metatarsal bones (3)	0	0	0	0	0	0	0	NK	NK
	Osteoporosis (4)	0	0	0	0	0	0	0	NK	NK
	Coarsened facial features (4)	0	0	0	0	0	0	0	NK	NK
Visceral & gastrointestinal	Hepatomegaly (5)	0	0	0	0	NK	0	0	0	0
	Splenomegaly (4)	0	0	0	0	NK	0	0	NK	NK
	Cardiomyopathy / pericardial effusions / cardiac arrhythmia (8)	H	L	0	L	0	0	0	0	0
	Diabetes (8)	L	L	0	L	0	L	0	0	0
	Diarrhoea (4)	0	0	0	0	HS	0	0	0	0
	Malabsorption (1)	0	0	NK	0	HS	0	0	0	0
	Vomiting (5)	0	0	NK	0	LS	0	0	0	0
	Renal failure (7)	0	0	NK	0	0	0	0	NK	NK
	Achalasia (1)	0	0	0	0	0	0	0	NK	NK
	Cryptorchidism (1)	0	0	0	0	0	0	0	NK	NK
	Xanthoma (1)	0	0	0	0	0	0	0	0	0

Skin	Telangiectasias (1)	0	0	0	0	0	HS	0	0	0	0
	Café-au-lait spots (2)	0	0	0	0	0	LS	0	0	NK	NK
	Frizzly/kinky hair (1)	0	0	0	0	0	0	0	0	NK	NK
	Alopecia (1)	0	0	0	0	0	0	0	0	NK	NK
	xeroderma / ichthyosis (3)	0	0	0	0	0	0	0	0	NK	NK
Misc.	Recurrent infections* (2)	0	0	0	0	0	LS	0	0	NK	NK
	Malignancies* (2)	0	0	0	0	0	LS	0	0	0	0
	Immune system defects* (2)	0	0	0	0	0	LS	0	0	0	0
	Obesity (4)	0	0	0	0	0	0	LS	0	NK	NK
	Adrenal insufficiency (1)	0	0	0	0	0	0	0	0	NK	NK
	Alacrimia (1)	0	0	0	0	0	0	0	0	NK	NK
	Hypogonadotropic hypogonadism (delayed puberty) (11)	0	0	0	0	0	L	0	L	NK	NK
Neuroimaging data	Obvious cerebellar atrophy (56)	L	L	L	L	L	H	H	H	L	L
	No cerebellar atrophy (26)	H	H	L	H	H	L	0	0	NK	NK
	Spinal cord atrophy (12)	H	H	NK	H	NK	0	NK	NK	NK	NK
	Cerebellar white-matter changes (13)	0	0	L	0	0	NK	0	0	0	0
	Stroke-like lesions (4)	0	0	LS	0	0	0	0	0	0	0
	Anterior superior cerebellar atrophy (and not global cerebellar atrophy) (5)	0	0	0	0	NK	0	0	0	NK	NK
	Olivary nuclei hyperintensity (2)	0	0	LS	0	NK	0	0	0	0	0
	T2-weighted linear hypointensities in the pons (stripes) (specific sign) (1)	0	0	0	0	0	0	0	0	0	0
	Cerebral leucopathy (19)	0	0	L	0	0	L	0	0	NK	NK
	Brainstem atrophy (16)	0	0	0	0	NK	0	L	L	NK	NK
	Small pituitary (1)	0	0	0	0	NK	0	0	0	NK	NK
	Hyperintensities in the pons (8)	0	0	0	0	NK	0	0	0	NK	NK

	Hypointensity of basal ganglia (NBIA) (4)	0	0	0	0	NK	0	0	0	NK	NK
	Bilateral middle cerebellar peduncles hyperintensities (7)	0	0	LS	0	NK	0	0	0	NK	NK
	Simplified cerebral gyration (2)	0	0	0	0	NK	0	0	0	NK	NK
	Thin corpus callosum (15)	0	0	0	0	NK	0	0	0	NK	NK
Electro-myography	Axonal sensorimotor neuropathy (37)	0	0	L	0	L	H	H	H	L	L
	Pure sensory neuropathy (12)	H	H	H	H	H	L	0	0	0	0
	Demyelinating component of the neuropathy (13)	0	0	0	0	0	0	0	0	0	0
	No peripheral neuropathy (28)	0	L	L	L	0	NK	0	0	L	L
Bior	Elevated serum lactic acid level (5)	0	0	LS	0	0	0	0	0	0	0
	Decreased serum vitamin E level (specific sign) (2)	0	0	0	HS	HS	0	0	0	0	0
	Decreased serum cholesterol &/or triglycerides (1)	0	0	0	0	HS	0	0	0	0	0
	Decreased serum vitamin A, D and/or K (2)	0	0	0	0	HS	0	0	0	0	0
	Abetalipoproteinemia (specific sign) (1)	0	0	0	0	HS	0	0	0	0	0
	Acanthocytosis (1)	0	0	0	0	HS	0	0	0	0	0
	Elevated serum LDL cholesterol level (specific sign) (4)	NK	NK	NK	NK	NK	0	LS	0	NK	NK
	Elevated serum creatin kinase level (specific sign) (7)	NK	NK	NK	NK	NK	LS	LS	LS	NK	NK
	Decreased serum immunoglobulin level (specific sign) (2)	0	0	0	0	0	LS	0	0	0	0
	Decreased serum albumin level (specific sign) (3)	0	0	0	0	0	0	HS	0	0	0
	Elevated serum alpha-fetoprotein level (specific sign) (6)	0	0	0	0	0	HS	LS	HS	0	0
	Hexosaminidase A deficiency (2)	0	0	0	0	0	0	0	0	HS	LS
	Hexosaminidase B deficiency (specific sign) (1)	0	0	0	0	0	0	0	0	NK	HS
	Elevated serum phytanic acid level (specific sign) (4)	0	0	0	0	0	0	0	0	0	0
	Elevated serum cholestanol level (specific sign) (1)	0	0	0	0	0	0	0	0	0	0
	Decreased coenzyme Q10 level (muscle/fibros) (3)	NK	NK	NK	0	0	0	LS	0	0	0

marker evidence	Decreased ceruloplasmine serum level (2)	0	0	0	0	0	0	0	0	0
	Decreased iron serum level (1)	0	0	0	0	0	0	0	0	0
	Decreased copper serum level (2)	0	0	0	0	0	0	0	NK	NK
	Elevated 24 hours urinary copper (Wilson's disease) (specific sign) (1)	0	0	0	0	0	0	0	0	0
	Elevated serum oxysterol level (1)	0	0	0	0	0	0	0	0	0
	Altered urinary oligasaccharides (2)	0	0	0	0	0	0	0	NK	NK
	Elevated 3-methylglutaconic acid and/or elevated 3-methylglutaric acid	0	0	0	0	0	0	0	NK	NK
	Elevated aspartate transaminase and/or elevated alanine transaminase	0	0	L	0	H	0	0	NK	NK
	Anemia (4)	0	0	0	0	NK	0	0	0	NK
	Glycogen Branching Enzyme activity decreased in leukocytes (1)	0	0	0	0	0	0	0	NK	NK
	Serum biotinidase enzyme activity decreased (1)	0	0	0	0	0	0	0	0	0
	Elevated ferritin serum level (1)	0	0	0	0	0	0	0	0	0
	Decreased neuraminidase activity in fibroblasts (1)	0	0	0	0	0	0	0	NK	NK
	Karyotype translocations (1)	0	0	NK	NK	NK	HS	0	0	NK
	Type 1 transferrin isoform pattern and/or abnormal serum transferrin	0	0	NK	NK	NK	NK	NK	0	NK
	Decreased leukocytes phosphomannomutase activity (1)	0	0	0	0	0	0	0	0	0
	Elevated pristanic acid level (2)	0	0	0	0	0	0	0	NK	NK
	Coagulations anomalies and thrombotic events (1) ADDED	NK	NK	NK	NK	NK	NK	NK	NK	NK

ity
sufficient evidence to exclude association
specific

Spinocerebellar ataxia, autosomal recessive 22 (SCAR22)	VM/A3B	0	H	H	0	NK	NK	NK	NK	NK	NK	NK	H	NK
Spinocerebellar ataxia, autosomal recessive 23 (SCAR23)	TDP2	H	L	L	H	NK	NK	NK	NK	NK	NK	NK	NK	NK
Spinocerebellar ataxia, autosomal recessive 20 (SCAR20)	SNX14	H	0	L	L	0	NK	NK	0	0	NK	NK	H	NK
Lichtenstein-Knorr syndrome	SLC9A1	H	NK	NK	NK	NK	NK	NK	0	NK	NK	NK	NK	NK
Boucher-Neuhauser syndrome	PNPLA6	H	L	L	L	0	H	0	0	0	L	H	H	L
Spinocerebellar ataxia, autosomal recessive 16 (SCAR16)	STUB1	H	L	L	L	0	L	0	0	0	0	0	H	NK
Ataxia-oculomotor apraxia 4 (AOA4)	PNKP	H	L	L	H	0	0	0	0	0	0	0	NK	NK
Polynuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract	ABHD12	L	L	H	L	0	H	H	0	0	L	L	L	NK
Spinocerebellar ataxia plus neuropathy (SCAN1)	TDP1	L	L	L	L	0	0	0	0	0	0	0	NK	NK
Ataxia-telangiectasia-like disorder 1 (ATLD1)	MRE11	H	L	L	L	0	0	0	0	0	0	0	H	H
Marinesco-Sjogren syndrome (MSS)	SIL1	H	L	H	L	0	H	0	0	0	0	H	H	NK
Infantile onset spinocerebellar ataxia (IOSCA)	C10ORF2	H	L	L	H	0	0	0	H	0	L	L	L	NK
Spinocerebellar ataxia, autosomal recessive 10 (SCAR10) / ARCA3	ANO10	L	H	L	L	LS	0	NK	0	0	0	L	H	NK
Wilson disease (WD)	ATP7B	L	H	H	L	0	L	0	0	0	0	0	H	L
Niemann-Pick disease Type C (NP-C)	NPC1/ NPC2	L	L	L	L	0	0	0	0	0	0	0	NK	L
Coenzyme Q10 Deficiency, Primary, 4 / ARCA2	ADCK3	H	L	H	L	0	NK	0	0	0	0	L	NK	NK
Spinocerebellar ataxia, autosomal recessive 8 (SCAR8)	SYNE1	L	H	H	L	0	L	0	0	0	0	L	L	NK
Cerebrotendinous xanthomatosis (CTX)	CYP27A1	L	H	L	L	0	H	0	0	0	0	0	NK	NK
Refsum disease	PHYH	L	L	L	L	0	L	0	0	0	0	NK	NK	NK
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	SACS	H	L	H	L	0	0	0	0	0	LS	NK	H	NK
Congenital disorder of glycosylation, type 1a (CDG1a)	PMIM2	H	L	L	L	0	0	H	0	0	0	H	NK	NK

NK	NK	NK	NK	L	NK	L	NK	L	NK	NK	L	NK	NK	NK	L	NK	NK	NK	NK	NK
NK	NK	NK	NK	LS	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	NK	NK	NK
NK	0	NK	NK	0	0	0	0	0	NK	NK	H	NK	NK	H	L	0	NK	NK	NK	NK
0	LS	0	0	0	0	HS	0	0	0	0	0	0	0	0	LS	0	NK	NK	NK	NK
0	NK	0	0	L	L	0	0	0	L	0	0	0	0	0	NK	0	NK	NK	NK	NK
NK	NK	NK	0	0	0	0	LS	0	NK	0	0	NK	0	NK	NK	0	NK	NK	NK	NK
0	0	0	0	0	L	L	L	0	L	0	L	NK	0	NK	NK	L	NK	0	NK	NK
NK	0	0	L	L	L	H	H	0	L	0	L	NK	0	H	L	L	NK	0	NK	NK
NK	0	NK	L	L	L	L	L	0	L	0	L	NK	L	0	L	0	NK	0	NK	NK
0	0	0	L	0	NK	L	H	0	NK	0	0	NK	0	0	0	0	NK	0	NK	NK
0	L	0	L	L	L	L	L	H	NK	L	L	NK	L	NK	L	L	NK	0	NK	L
NK	H	NK	H	L	L	L	L	L	L	L	0	NK	L	L	L	L	NK	L	NK	L
NK	H	0	H	L	L	L	0	L	L	L	0	NK	L	NK	L	L	NK	L	NK	L
0	0	0	L	0	0	L	L	0	NK	0	0	NK	0	0	0	0	NK	NK	NK	NK
L	L	L	L	L	L	H	L	L	L	NK	NK	NK	L	H	H	H	NK	NK	NK	L
H	L	NK	L	L	L	H	L	L	L	H	L	NK	L	L	L	NK	NK	H	H	H
0	0	0	LS	0	0	LS	LS	0	LS	0	0	NK	0	0	0	0	NK	NK	NK	NK
L	0	0	L	0	0	L	L	0	NK	0	0	NK	0	0	L	0	NK	L	NK	NK
H	H	NK	L	0	0	0	0	0	H	NK	L	L	H	H	0	L	H	L	NK	NK
NK	0	NK	L	0	L	0	0	0	L	H	0	0	0	0	0	0	NK	NK	NK	NK
H	L	NK	L	0	H	L	L	L	L	L	0	L	L	L	L	0	NK	L	H	NK
0	L	H	0	0	NK	L	0	L	L	NK	0	NK	H	0	0	0	H	H	NK	NK
0	0	NK	0	0	0	LS	0	0	NK	NK	0	NK	0	0	0	0	NK	0	NK	NK
NK	NK	LS	NK	0	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	NK	0	NK	NK	NK	NK

0	0	NK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	LS	0	0	0	LS	0	0	0	0	0	0	0	0	0	0	0
LS	0	0	0	0	LS	0	0	0	LS	0	0	0	0	0	0	0	NK	0	0
NK	0	NK	0	0	0	0	L	0	L	NK	0	NK	0	NK	NK	0	NK	NK	NK
L	L	NK	0	L	L	0	0	L	L	NK	0	NK	H	0	0	NK	NK	L	NK
H	NK	NK	0	L	NK	L	0	0	L	L	0	NK	L	0	0	0	NK	L	NK
0	LS	NK	0	0	NK	0	0	0	NK	NK	0	NK	0	0	0	0	NK	NK	NK
NK	0	NK	0	0	0	0	0	0	NK	0	0	NK	0	NK	LS	0	NK	NK	NK
0	0	NK	0	0	0	0	0	0	NK	0	0	0	0	0	0	0	0	0	0
0	0	LS	0	0	0	0	0	0	NK	NK	0	NK	0	NK	NK	0	NK	LS	NK
NK	0	NK	0	0	0	0	0	0	NK	0	0	NK	0	NK	LS	0	NK	LS	NK
HS	0	NK	LS	0	0	0	LS	0	LS	NK	0	NK	0	NK	LS	0	NK	NK	NK
NK	0	NK	0	LS	0	0	0	0	NK	0	0	NK	0	NK	LS	0	NK	HS	NK
LS	0	0	0	0	0	HS	LS	0	NK	NK	0	NK	0	0	0	0	NK	LS	NK
NK	NK	NK	NK	0	NK	HS	LS	0	NK	NK	0	NK	0	0	0	0	NK	LS	NK
L	0	L	0	0	0	0	0	0	0	NK	0	NK	0	0	L	0	NK	NK	NK
0	0	NK	0	0	0	0	L	0	NK	NK	0	NK	0	0	L	0	NK	NK	NK
LS	0	0	HS	0	0	NK	0	0	NK	NK	0	NK	0	0	LS	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	NK	NK	0	NK	0	0	0	0	NK	NK	NK
LS	0	0	0	0	0	NK	0	0	HS	NK	0	NK	0	0	0	0	NK	NK	NK
LS	0	LS	0	0	0	0	LS	0	NK	0	0	NK	0	0	0	0	NK	NK	NK
0	0	NK	0	0	0	0	0	0	NK	0	0	NK	0	0	0	0	NK	NK	NK
0	0	NK	0	0	0	0	0	0	NK	0	0	NK	0	0	0	0	NK	NK	NK
0	0	0	HS	0	0	0	0	0	NK	NK	0	NK	0	0	0	0	NK	NK	NK

0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK	NK
0	0	NK	0	0	0	0	0	0	0	NK	0	0	NK	0	NK	NK	0	LS	NK	NK
0	0	NK	0	0	0	0	0	0	0	NK	0	0	NK	0	0	0	0	0	0	0
0	0	NK	0	0	0	0	0	0	0	NK	0	0	NK	0	NK	LS	0	NK	NK	NK
0	0	LS	0	0	0	0	0	0	0	NK	0	NK	NK	0	NK	NK	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	NK	NK	NK	NK	0	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	NK	NK	LS	NK	0	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	NK	NK	NK	NK	0	0	0	0	NK	NK	NK
NK	0	NK	0	0	0	0	NK	0	LS	0	0	NK	0	LS	0	0	0	NK	LS	NK
0	0	NK	0	0	0	0	0	0	0	NK	0	0	NK	0	0	0	0	0	0	0
0	0	NK	0	0	0	0	0	0	0	NK	0	0	NK	0	0	0	0	0	0	0
L	0	NK	0	0	0	0	NK	0	L	H	0	NK	0	NK	L	H	NK	NK	NK	NK
H	H	NK	H	H	H	L	L	H	H	H	H	H	L	H	H	H	L	H	NK	L
0	0	L	L	0	NK	L	L	0	NK	0	0	NK	L	0	0	0	0	L	NK	NK
NK	L	NK	NK	0	NK	0	0	NK	H	NK	0	NK	NK	0	0	0	0	NK	NK	NK
0	0	L	H	0	0	0	L	0	L	0	0	NK	NK	0	0	0	0	NK	NK	NK
NK	0	0	0	0	LS	0	0	0	LS	0	0	0	0	0	0	0	0	NK	NK	NK
LS	HS	NK	0	0	0	0	0	0	0	0	0	0	NK	NK	0	0	LS	NK	NK	NK
0	0	NK	LS	0	0	0	NK	0	NK	NK	0	NK	NK	0	0	0	0	NK	NK	NK
0	HS	0	0	0	0	0	0	0	0	NK	NK	0	NK	NK	0	NK	0	NK	NK	NK
L	NK	L	L	0	0	L	L	0	NK	NK	0	NK	NK	0	0	L	NK	NK	NK	NK
L	0	NK	L	0	0	NK	NK	L	H	NK	0	NK	L	L	H	L	NK	L	NK	NK
0	0	NK	0	0	0	0	0	0	0	NK	NK	0	NK	NK	0	NK	LS	NK	NK	NK
0	L	NK	L	0	0	0	L	0	NK	NK	0	NK	NK	0	0	L	NK	NK	NK	NK

0	0	NK	0	0	0	0	LS	0	NK	NK	0	NK	NK	0	0	0	0	0	0
NK	NK	NK	LS	0	0	0	LS	0	LS	0	0	NK	NK	NK	0	0	NK	NK	NK
0	0	NK	0	0	0	0	0	0	NK	0	0	NK	NK	0	0	0	0	0	0
0	0	NK	0	0	0	0	NK	0	NK	NK	0	NK	NK	0	H	0	NK	NK	NK
L	H	L	L	L	0	0	0	0	L	0	L	H	L	H	L	L	NK	NK	NK
0	0	0	0	0	0	0	0	0	H	0	L	NK	0	0	L	0	NK	NK	NK
H	H	H	H	0	0	0	0	0	0	0	NK	0	H	NK	0	0	NK	NK	NK
L	L	L	L	H	H	H	H	H	NK	H	L	0	0	0	H	L	NK	L	NK
0	0	0	0	0	LS	0	0	0	LS	NK	NK	NK	NK	0	LS	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	0	NK	NK	NK
0	0	0	LS	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	NK	NK	NK	0	NK	0	NK	NK	NK	NK	0	NK	NK	LS	LS	0	NK	NK	NK
0	NK	NK	NK	LS	LS	0	NK	NK	NK	HS	0	NK	NK	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	LS	LS	0	NK	NK	NK
0	0	0	0	0	0	0	0	LS	0	0	0	0	0	LS	0	0	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	HS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	0	HS	0	0	0	0	0	0	0	0	0	0	0	0	0	NK	NK	NK
0	0	0	0	0	LS	0	0	LS	NK	0	0	0	0	0	0	0	NK	NK	NK

0	0	0	0	0	0	0	HS	0	0	0	0	0	0	0	0	0	NK	NK	NK	NK
0	0	0	0	0	0	0	NK	0	0	0	0	0	0	0	0	0	NK	0	0	0
0	0	NK	0	0	0	0	HS	0	NK	0	0	0	NK	0	0	0	NK	0	0	0
0	0	0	0	0	0	0	HS	0	0	0	0	0	0	0	0	0	NK	NK	NK	NK
0	0	0	0	0	0	LS	0	0	0	0	0	0	0	0	0	0	NK	NK	NK	NK
NK	0	NK	0	0	0	0	0	0	NK	0	0	NK	0	NK	NK	0	NK	LS	NK	NK
NK	0	NK	0	0	0	0	0	0	NK	0	0	NK	0	NK	NK	0	NK	NK	NK	NK
L	0	L	0	0	0	L	L	0	NK	0	0	0	0	0	L	0	0	0	0	0
0	0	NK	0	0	0	0	LS	0	NK	0	0	0	0	0	LS	0	0	0	0	0
0	0	NK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	NK	0	0	0	0	0	NK	0	0	0	0	0	LS	0	0	0	0	0
0	0	NK	0	0	0	0	0	0	NK	0	0	0	0	0	0	0	0	0	0	0
0	NK	0	NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	NK	NK	NK	NK
HS	NK	0	NK	0	NK	0	NK	NK	NK	NK	0	NK	0	NK	NK	0	NK	NK	NK	NK
HS	0	0	0	0	0	0	0	0	NK	0	0	0	0	0	0	0	0	0	0	0
0	0	NK	0	0	0	0	0	0	NK	0	0	0	0	0	0	0	0	0	0	0
HS	NK	NK	NK	0	NK	NK	NK	NK	NK	NK	0	NK	NK	NK	NK	NK	NK	NK	NK	NK

with or without intracellular inclusions	ACID1	H	0	1	H
Progressive myoclonic epilepsy 4	SCARB2	0	H	0	H
Epilepsy progressive myoclonus 6	GOSR2	H	0	0	H

NK	NK	NK	NK	H	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
NK	NK	NK	NK	LS	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	NK	NK
NK	NK	NK	NK	H	NK	NK	NK	NK	NK	NK	NK	L	L	NK	NK	NK	0	NK	NK	NK
NK	NK	NK	NK	0	NK	NK	NK	LS	NK	NK	NK	NK	NK	NK	LS	LS	0	NK	NK	NK
NK	NK	NK	NK	0	NK	NK	NK	0	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	L	NK
NK	NK	NK	NK	NK	HS	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	0	NK
NK	0	0	0	NK	NK	NK	NK	0	NK	0	L	L	0	0	0	0	NK	0	0	H
NK	0	L	0	NK	NK	NK	NK	0	NK	H	L	L	H	0	L	L	L	0	L	L
H	H	H	0	NK	NK	NK	L	H	NK	0	0	NK	0	0	0	0	L	0	0	L
NK	0	0	0	NK	NK	NK	NK	0	NK	0	0	NK	0	0	0	0	0	0	0	NK
NK	L	L	0	0	L	NK	L	NK	NK	H	L	L	H	H	H	L	H	H	L	H
NK	0	L	L	0	L	NK	L	L	L	H	NK	L	H	L	H	L	L	H	L	H
NK	0	NK	NK	0	NK	NK	NK	NK	L	H	NK	L	H	L	L	L	0	H	L	H
NK	0	0	0	NK	NK	NK	NK	0	NK	0	NK	NK	0	0	0	0	L	0	0	0
L	L	H	NK	NK	NK	NK	L	L	NK	NK	NK	L	L	H	L	L	L	0	NK	L
NK	0	H	H	NK	H	L	H	NK	H	H	H	H	L	H	H	H	H	H	L	H
NK	0	0	0	NK	NK	NK	NK	0	NK	NK	NK	NK	0	0	0	NK	LS	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	NK	NK	NK	NK	0	0	0	NK	0	0	0	0
H	0	0	L	H	NK	NK	NK	NK	NK	0	L	NK	0	0	0	0	0	L	L	0
NK	0	0	0	0	NK	NK	NK	0	0	0	NK	NK	0	NK	0	0	0	0	0	0
H	H	H	0	0	NK	L	L	H	0	0	L	L	L	L	L	L	H	0	0	L
NK	0	0	H	0	L	NK	NK	0	0	L	L	NK	0	0	0	0	H	0	L	0
NK	0	0	0	0	NK	NK	NK	0	0	0	NK	NK	0	0	0	0	0	0	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK

0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	NK	NK
L	0	0	L	NK	NK	NK	NK	0	NK	0	NK	NK	0	0	0	0	0	0	0
H	0	0	NK	NK	NK	NK	NK	0	NK	L	L	NK	L	0	L	0	L	0	NK
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	NK	0	0	0	0	0	0	NK
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	NK	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	HS	HS	0	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	NK	NK	NK
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	NK	0	0	0	0	0	0	0
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	NK	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	LS	0
NK	HS	0	LS	NK	NK	NK	NK	0	NK	0	NK	HS	0	0	0	0	HS	0	0
NK	0	0	0	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	HS	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0

NK	0	0	0	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	NK	0	NK	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	LS	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	0	0	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	0	0	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	0	0	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	0	0	0	NK	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	NK	NK	NK	NK	0	0	0	NK	0	0	0	H	H	0	0	0
L	L	NK	H	H	H	NK	H	NK	H	H	L	H	H	H	H	H	NK	H	H
H	L	H	0	0	NK	NK	NK	H	NK	0	L	0	NK	0	0	NK	L	NK	L
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	H	0	0	0	L	NK	H
NK	0	NK	0	NK	NK	NK	NK	NK	NK	L	0	0	L	NK	H	H	L	NK	L
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	0	0	0	0	0	NK	0
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	0	0	LS	0	0	NK	0
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	0	0	0	0	0	NK	NK
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	0	0	0	0	0	NK	0
NK	0	NK	L	NK	NK	NK	NK	NK	NK	H	L	0	H	0	H	H	L	NK	0
NK	0	NK	0	NK	L	NK	NK	NK	NK	0	NK	L	H	L	L	L	L	NK	0
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	0	0	0	NK	0	NK	0
NK	0	NK	0	NK	NK	NK	NK	NK	NK	L	0	0	NK	0	L	NK	0	NK	0

0	0	0	0	0	0	0	0	0	0	0	0	0	LS	0	0	NK	0	NK	0	0
NK	0	NK	0	NK	NK	NK	NK	NK	NK	0	0	0	0	0	LS	LS	0	NK	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	LS	0	NK	0	0	0	0
NK	0	NK	0	NK	NK	NK	NK	NK	NK	L	L	L	H	0	H	H	L	NK	0	0
L	L	NK	H	H	NK	NK	NK	NK	NK	0	NK	NK	L	L	0	0	L	NK	L	0
L	0	NK	0	NK	NK	NK	NK	L	NK	0	NK	NK	0	NK	0	0	0	NK	L	0
L	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	L	NK	0	NK	0	0	L	NK	0	0
L	L	NK	NK	NK	NK	NK	NK	NK	NK	0	NK	H	H	H	H	H	H	NK	L	H
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	LS	0	0	0	0	0	0	0	0
LS	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	LS	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	LS	0	0	0	0	0	0	0	0
NK	0	0	0	HS	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	HS	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	NK	NK	NK	0	0	0	0	0	0	0	0

NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0
NK	0	0	0	NK	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0
NK	0	0	0	0	NK	NK	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0
NK	NK	NK	NK	NK	NK	HS	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	HS
0	0	L	0	0	0	L	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0
0	0	0	0	0	0	HS	NK	NK	NK	0	NK	LS	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	HS	0	NK	0	NK	NK	NK	0	NK	NK	0	0	0	0	0	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK

retardation, Optic atrophy and Skin Cerebellar hypoplasia and mental retardation with or without	VLDLR	H	0	L
Peroxisome biogenesis disorder 9B	PEX7	L	H	L

NK	NK	NK	NK	NK	NK	L	NK	L	NK	L	NK	NK	NK	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0
NK	NK	L	NK	NK	NK	NK	NK	NK	NK	NK	L	NK	NK	0
NK	NK	0	NK	NK	NK	NK	NK	NK	NK	LS	NK	NK	NK	0
L	NK	0	NK	NK	NK	L	NK	NK	L	NK	L	NK	NK	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	0
0	0	0	0	0	0	0	0	0	NK	L	L	0	H	0
0	0	L	0	0	0	L	0	0	NK	H	L	0	H	0
0	0	0	L	0	0	0	0	0	L	L	0	H	0	0
0	0	0	L	0	0	L	0	L	NK	L	0	0	L	0
L	L	H	H	L	H	H	0	L	L	L	L	L	NK	L
L	NK	L	H	NK	H	H	H	H	L	H	L	0	NK	NK
NK	NK	H	NK	NK	H	H	L	H	L	H	H	0	NK	NK
0	0	0	0	0	0	0	0	0	NK	L	0	0	NK	0
L	NK	L	L	NK	L	L	L	L	NK	H	L	L	H	0
L	H	H	NK	H	L	0	H	0	H	H	H	L	NK	L
0	0	0	0	0	0	0	0	0	NK	LS	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	L	0	0	NK	0
L	0	0	L	0	NK	0	H	L	NK	H	H	NK	NK	0
NK	0	0	0	0	0	L	0	L	L	0	0	0	NK	0
L	H	0	L	L	L	0	0	0	H	L	0	H	NK	0
L	0	0	0	0	0	0	0	L	H	0	H	L	L	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
LS	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK

0	LS	0	0	HS	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	HS	0	0	0	0	0
0	0	0	0	0	0	0	0	LS	0	0	0	0	0	0
NK	NK	L	H	0	NK	L	0	H	NK	L	0	0	NK	NK
L	L	0	L	0	L	L	L	0	NK	L	H	0	NK	0
0	0	0	L	0	0	0	L	0	NK	L	0	L	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	NK	NK	0
0	0	LS	0	0	0	0	0	0	NK	0	0	NK	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
LS	0	0	0	0	NK	0	0	0	NK	0	0	0	NK	NK
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
0	0	0	0	0	0	0	LS	0	NK	0	0	LS	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	LS	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	LS	NK	0
L	0	0	0	0	0	0	0	0	NK	0	0	L	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	L	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	LS	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	NK
0	0	0	HS	0	NK	0	0	0	NK	0	0	0	NK	NK
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	NK
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0

0	0	0	NK	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	HS	0	NK	0	0	0	NK	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	HS	NK	0	0	NK	NK
LS	0	0	0	0	NK	0	0	0	NK	0	0	0	NK	NK
0	0	0	0	0	0	0	0	0	HS	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	LS	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	HS	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	HS	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	NK	0	0	0	0	0	NK	0	H	0	NK	0
NK	H	H	L	H	L	H	L	H	H	H	H	L	NK	H
NK	0	0	L	NK	L	L	L	L	L	L	0	H	NK	L
NK	0	0	0	0	L	L	L	H	NK	0	0	0	NK	0
NK	0	0	0	0	H	L	L	H	L	L	NK	0	NK	0
NK	0	0	0	0	0	0	0	LS	NK	0	0	0	NK	0
NK	0	0	0	0	NK	0	NK	LS	NK	0	0	0	NK	0
NK	0	0	0	0	0	0	0	NK	NK	0	0	0	NK	0
NK	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
NK	0	0	0	0	H	0	L	H	NK	L	L	0	NK	0
NK	H	L	0	L	NK	NK	NK	H	NK	L	0	0	NK	0
NK	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
NK	0	0	0	0	H	0	0	H	NK	0	0	0	NK	0

NK	0	0	0	0	0	0	NK	0	NK	HS	0	0	HS	0
NK	0	0	0	0	0	0	0	LS	NK	0	0	0	0	0
0	HS	0	0	LS	0	0	0	0	NK	0	0	0	NK	0
NK	0	L	0	L	L	0	0	L	NK	L	L	0	NK	0
L	NK	0	H	0	L	L	H	H	L	H	H	L	NK	NK
NK	NK	0	0	0	0	0	NK	0	NK	0	0	0	NK	NK
L	NK	0	0	0	L	0	NK	L	NK	0	H	L	NK	NK
L	NK	H	NK	H	L	L	0	L	L	L	L	L	L	NK
0	0	0	0	0	0	0	0	0	HS	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
HS	0	0	0	0	0	0	0	0	NK	0	LS	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	NK	0	0	0	NK	0	0	0	NK	0

0	0	0	0	0	0	0	0	0	NK	0	0	0	HS	0
0	0	0	0	0	0	0	0	0	0	0	0	0	LS	0
0	0	0	0	0	0	0	0	0	0	0	0	0	LS	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	HS	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	L	NK	0
0	0	0	0	0	0	0	0	0	NK	0	0	0	HS	0
0	0	0	0	0	0	0	0	HS	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	HS	0	0	0	NK	0
0	0	0	0	0	0	0	0	0	0	0	0	0	HS	0
0	0	0	0	0	0	0	0	0	0	0	0	HS	0	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NK	0	0	0	0	0	0	0	0	NK	0	LS	0	NK	0
NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK

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